



## Clinical trial results:

### Autologous Stem cell Transplantation In refractory Crohn's disease - Low Intensity Therapy Evaluation

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2017-002545-30   |
| Trial protocol           | GB               |
| Global end of trial date | 29 November 2020 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 02 December 2021 |
| First version publication date | 02 December 2021 |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | IRAS220495 |
|-----------------------|------------|

##### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN17160440 |
| ClinicalTrials.gov id (NCT number) | -              |
| WHO universal trial number (UTN)   | -              |

Notes:

#### Sponsors

|                              |                                                                                                   |
|------------------------------|---------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Barts Health NHS Trust                                                                            |
| Sponsor organisation address | 5 Walden Street, London, United Kingdom, E1 2EF                                                   |
| Public contact               | Dr Mays Jawad, Queen Mary University of London, +44 020 7882 7252, research.governance@qmul.ac.uk |
| Scientific contact           | Dr Mays Jawad, Queen Mary University of London, +44 020 7882 7252, research.governance@qmul.ac.uk |

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 |

Notes:

## Results analysis stage

|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 27 July 2021     |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 29 November 2020 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 29 November 2020 |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this trial is to assess whether autologous haematopoietic stem cell transplantation (HSCT) with a low intensity treatment regimen (lite) is safe and effective in inducing regression of ileo-colonic ulceration in Crohn's Disease, where previous treatments have been unsuccessful, compared with standard care.

Definitions:

Autologous - cells or tissue obtained from the same individual

Hematopoietic - cells that give rise to blood cells

Protection of trial subjects:

Patients who were not randomised to receive HSCTlite (study intervention) were treated as per standard care. Patients who were randomised to receive HSCTlite received standard clinical haematology follow up during and following their stem cell transplant.

Patients were free to withdraw from the study at any time without giving a reason and without this affecting their ongoing treatment. Safety events were regularly reviewed by an independent Data Monitoring and Ethics Committee, and the decision to pause recruitment on safety grounds was taken following review of this safety data.

Participants were provided with a contact card and encouraged to get in touch with their local trial team if they had experienced any adverse events.

Background therapy:

The control group were permitted any current available treatment for Crohn's disease, except stem cell transplant.

Evidence for comparator:

The comparator included all treatments available to patients with Crohn's disease, under non-trial circumstances. These could include: (1) biologic therapy, (2) nutritional therapy, (3) corticosteroids and (4) conventional immune modulators. The study evaluated the intervention to investigate if this could potentially be offered as routine care in the future.

|                                                           |             |
|-----------------------------------------------------------|-------------|
| Actual start date of recruitment                          | 09 May 2018 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | Yes         |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 23 |
| Worldwide total number of subjects   | 23                 |
| EEA total number of subjects         | 0                  |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| 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)                 | 0  |
| Adults (18-64 years)                      | 23 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

#### Recruitment details:

The study opened to recruitment on 9th May 2018 and the last patient was randomised on 26th September 2019. The decision was made by the TSC and DMEC to pause recruitment on 30th December 2019 and no further patients were recruited to the study after this time. In total 49 patients were consented, with 23 randomised.

### Pre-assignment

#### Screening details:

Potentially eligible patients were asked for consent to be discussed at the trial MDT. Once MDT had confirmed the patient seemed appropriate for the trial, full consent was taken and screening investigations completed.

Referral to trial MDT – 77

MDT confirmed could proceed – 74

Screening completed – 49

Baseline completed - 27

Randomised - 23

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Not blinded                    |

### Arms

|                              |            |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes        |
| <b>Arm title</b>             | Usual care |

#### Arm description:

Standard care for Crohn's disease

|                                                           |          |
|-----------------------------------------------------------|----------|
| Arm type                                                  | Control  |
| No investigational medicinal product assigned in this arm |          |
| <b>Arm title</b>                                          | HSCTlite |

#### Arm description:

Autologous stem cell transplant

|                                        |                                                               |
|----------------------------------------|---------------------------------------------------------------|
| Arm type                               | Experimental                                                  |
| Investigational medicinal product name | Cyclophosphamide, Fludarabine, Rabbit ATG, G-CSF (filgrastim) |
| Investigational medicinal product code |                                                               |
| Other name                             |                                                               |
| Pharmaceutical forms                   | Powder and solvent for solution for infusion                  |
| Routes of administration               | Intravenous drip use                                          |

#### Dosage and administration details:

##### Mobilisation

Cyclophosphamide, 1 hour infusion 1g/m<sup>2</sup> on day 1, G-CSF (filgrastim) 5mcg/kg subcutaneously 4 days following cyclophosphamide until the day of stem cell harvest

##### Conditioning

Fludarabine: IV fludarabine 25mg/m<sup>2</sup>, given on days -6, -5, -4, -3 and -2. Reduced doses in the presence of impaired renal function, cyclophosphamide 60mg/kg/day IV over 1 hour, given in 500ml of normal saline on days -3 and -2. Rabbit ATG IV 2.5mg/kg was given on days -3, -2 and -1. A test dose was given as per standard local practice. G-CSF: Stem cells were re-infused at day 0. G-CSF 5mcg/kg/day (to the nearest vial) began on day +5 and continued until absolute neutrophil counts reached >1.0x10<sup>9</sup>/L for two consecutive days.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Usual care | HSCTlite |
|-----------------------------------------------------|------------|----------|
| Started                                             | 9          | 13       |
| Completed                                           | 9          | 9        |
| Not completed                                       | 0          | 4        |
| Adverse event, serious fatal                        | -          | 1        |
| Consent withdrawn by subject                        | -          | 1        |
| Withdrawn due to early study closure                | -          | 2        |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One person was withdrawn post-randomisation after being found ineligible and therefore didn't make the ITT criteria.

## Baseline characteristics

### Reporting groups

|                                   |            |
|-----------------------------------|------------|
| Reporting group title             | Usual care |
| Reporting group description:      |            |
| Standard care for Crohn's disease |            |
| Reporting group title             | HSCTlite   |
| Reporting group description:      |            |
| Autologous stem cell transplant   |            |

| Reporting group values                             | Usual care | HSCTlite | Total |
|----------------------------------------------------|------------|----------|-------|
| Number of subjects                                 | 9          | 13       | 22    |
| Age categorical                                    |            |          |       |
| Units: Subjects                                    |            |          |       |
| In utero                                           | 0          | 0        | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0          | 0        | 0     |
| Newborns (0-27 days)                               | 0          | 0        | 0     |
| Infants and toddlers (28 days-23 months)           | 0          | 0        | 0     |
| Children (2-11 years)                              | 0          | 0        | 0     |
| Adolescents (12-17 years)                          | 0          | 0        | 0     |
| Adults (18-64 years)                               | 9          | 13       | 22    |
| From 65-84 years                                   | 0          | 0        | 0     |
| 85 years and over                                  | 0          | 0        | 0     |
| Gender categorical                                 |            |          |       |
| Units: Subjects                                    |            |          |       |
| Female                                             | 5          | 7        | 12    |
| Male                                               | 4          | 6        | 10    |
| Smoking status                                     |            |          |       |
| Units: Subjects                                    |            |          |       |
| Never smoked                                       | 7          | 7        | 14    |
| Current smoker                                     | 1          | 2        | 3     |
| Previous smoker (stopped 5+ years)                 | 1          | 3        | 4     |
| Not recorded                                       | 0          | 1        | 1     |
| Presence of perianal Crohn's disease               |            |          |       |
| Units: Subjects                                    |            |          |       |
| Yes                                                | 5          | 3        | 8     |
| No                                                 | 4          | 10       | 14    |
| Stoma                                              |            |          |       |
| Units: Subjects                                    |            |          |       |
| Yes - ileostomy                                    | 2          | 3        | 5     |
| Yes - end ileostomy                                | 0          | 3        | 3     |
| Yes - loop colostomy                               | 0          | 1        | 1     |
| No                                                 | 7          | 6        | 13    |
| Disease location                                   |            |          |       |
| Units: Subjects                                    |            |          |       |
| L1 - ileal                                         | 0          | 3        | 3     |
| L2 - colonic                                       | 1          | 1        | 2     |

|                                      |         |         |    |
|--------------------------------------|---------|---------|----|
| L3 - ileocolonic                     | 3       | 5       | 8  |
| L4 - isolated upper disease          | 1       | 0       | 1  |
| L1 L4                                | 2       | 3       | 5  |
| L3 L4                                | 2       | 1       | 3  |
| Previous surgery for Crohn's disease |         |         |    |
| Units: Subjects                      |         |         |    |
| Intestinal surgery                   | 5       | 8       | 13 |
| Perianal surgery                     | 1       | 0       | 1  |
| Both intestinal and perianal surgery | 3       | 4       | 7  |
| No previous surgery                  | 0       | 1       | 1  |
| Duration of disease                  |         |         |    |
| Units: years                         |         |         |    |
| arithmetic mean                      | 14.1    | 13.6    |    |
| standard deviation                   | ± 7.8   | ± 6.7   | -  |
| Baseline CDAI                        |         |         |    |
| Units: score                         |         |         |    |
| arithmetic mean                      | 271.5   | 381.5   |    |
| standard deviation                   | ± 115.2 | ± 209.1 | -  |
| Baseline SES-CD                      |         |         |    |
| Units: score                         |         |         |    |
| arithmetic mean                      | 10.1    | 11.8    |    |
| standard deviation                   | ± 5.7   | ± 8.7   | -  |
| Number of previous biologics         |         |         |    |
| Units: number                        |         |         |    |
| arithmetic mean                      | 3.33    | 3.08    |    |
| standard deviation                   | ± 0.50  | ± 0.76  | -  |

## End points

### End points reporting groups

|                                                                   |            |
|-------------------------------------------------------------------|------------|
| Reporting group title                                             | Usual care |
| Reporting group description:<br>Standard care for Crohn's disease |            |
| Reporting group title                                             | HSCTlite   |
| Reporting group description:<br>Autologous stem cell transplant   |            |

### Primary: Absence of ulceration

|                                                                                                                                                                                                                                                     |                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| End point title                                                                                                                                                                                                                                     | Absence of ulceration <sup>[1]</sup> |
| End point description:<br>Treatment success at week 48 defined as mucosal healing (no endoscopic ulceration (SES CD ulcer size sub score = 0, assessed by adjudication panel blind to allocation and time of assessment)) without surgery or death. |                                      |
| End point type                                                                                                                                                                                                                                      | Primary                              |
| End point timeframe:<br>at 48 weeks                                                                                                                                                                                                                 |                                      |

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the early study closure and low numbers, the original statistical analysis plan was amended and an addendum to the SAP was written, in which it was decided that a mixed effects logistic regression model would be used for the primary outcome, however upon receiving the data and fitting the model, the model did not converge. Therefore, it was decided only descriptive statistics were to be reported for the primary endpoint.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical remission (CDAI<150)

|                                     |                               |
|-------------------------------------|-------------------------------|
| End point title                     | Clinical remission (CDAI<150) |
| End point description:              |                               |
| End point type                      | Secondary                     |
| End point timeframe:<br>At 48 weeks |                               |



### Statistical analyses

No statistical analyses for this end point

### Secondary: Steroid free clinical remission (CDAI <150)

|                 |                                             |
|-----------------|---------------------------------------------|
| End point title | Steroid free clinical remission (CDAI <150) |
|-----------------|---------------------------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At 48 weeks

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical remission (Harvey Bradshaw Index <4)

|                 |                                               |
|-----------------|-----------------------------------------------|
| End point title | Clinical remission (Harvey Bradshaw Index <4) |
|-----------------|-----------------------------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At 48 weeks

### Statistical analyses

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No statistical analyses for this end point

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**Secondary: Clinical remission (PRO2 - abdominal pain <1 and stool frequency <1.5)**

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|                 |                                                                        |
|-----------------|------------------------------------------------------------------------|
| End point title | Clinical remission (PRO2 - abdominal pain <1 and stool frequency <1.5) |
|-----------------|------------------------------------------------------------------------|

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End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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End point timeframe:

At 48 weeks

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Complete endoscopic remission (SES-CD score=0)**

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|                 |                                                |
|-----------------|------------------------------------------------|
| End point title | Complete endoscopic remission (SES-CD score=0) |
|-----------------|------------------------------------------------|

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End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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End point timeframe:

At 48 weeks

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the point of patient consent to the trial, until patients completed their participation in the trial. Ongoing adverse events at trial completion were followed up where possible until the study database was frozen.

Adverse event reporting additional description:

During this follow up of ongoing adverse events, it was discovered that a participant had died following completion of their participation in the trial. This death has been included in the figures reported here.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Usual care |
|-----------------------|------------|

Reporting group description:

All participants randomised to usual care (control group), including one participant found to be ineligible post randomisation.

|                       |          |
|-----------------------|----------|
| Reporting group title | HSCTlite |
|-----------------------|----------|

Reporting group description:

All participants randomised to HSCTlite (trial intervention).

| Serious adverse events                            | Usual care      | HSCTlite          |  |
|---------------------------------------------------|-----------------|-------------------|--|
| Total subjects affected by serious adverse events |                 |                   |  |
| subjects affected / exposed                       | 4 / 10 (40.00%) | 13 / 13 (100.00%) |  |
| number of deaths (all causes)                     | 0               | 2                 |  |
| number of deaths resulting from adverse events    | 0               | 2                 |  |
| Investigations                                    |                 |                   |  |
| C-reactive protein abnormal                       |                 |                   |  |
| subjects affected / exposed                       | 0 / 10 (0.00%)  | 1 / 13 (7.69%)    |  |
| occurrences causally related to treatment / all   | 0 / 0           | 1 / 1             |  |
| deaths causally related to treatment / all        | 0 / 0           | 1 / 1             |  |
| Nervous system disorders                          |                 |                   |  |
| Optic neuritis                                    |                 |                   |  |
| subjects affected / exposed                       | 0 / 10 (0.00%)  | 1 / 13 (7.69%)    |  |
| occurrences causally related to treatment / all   | 0 / 0           | 1 / 1             |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0             |  |
| Blood and lymphatic system disorders              |                 |                   |  |
| Thrombotic microangiopathy                        |                 |                   |  |

|                                                      |                |                 |  |
|------------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 10 (0.00%) | 3 / 13 (23.08%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 4 / 4           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Anaemia                                              |                |                 |  |
| subjects affected / exposed                          | 0 / 10 (0.00%) | 1 / 13 (7.69%)  |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Methaemoglobinaemia                                  |                |                 |  |
| subjects affected / exposed                          | 0 / 10 (0.00%) | 1 / 13 (7.69%)  |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| General disorders and administration site conditions |                |                 |  |
| Adverse reaction                                     |                |                 |  |
| subjects affected / exposed                          | 0 / 10 (0.00%) | 1 / 13 (7.69%)  |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Pyrexia                                              |                |                 |  |
| subjects affected / exposed                          | 0 / 10 (0.00%) | 1 / 13 (7.69%)  |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Adverse drug reaction                                |                |                 |  |
| subjects affected / exposed                          | 0 / 10 (0.00%) | 2 / 13 (15.38%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 2 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Immune system disorders                              |                |                 |  |
| Anaphylactic reaction                                |                |                 |  |
| subjects affected / exposed                          | 0 / 10 (0.00%) | 2 / 13 (15.38%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 2 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Gastrointestinal disorders                           |                |                 |  |
| Vomiting                                             |                |                 |  |
| subjects affected / exposed                          | 0 / 10 (0.00%) | 1 / 13 (7.69%)  |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |

|                                                 |                 |                |  |
|-------------------------------------------------|-----------------|----------------|--|
| Diarrhoea                                       |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 13 (7.69%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Colitis                                         |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 13 (7.69%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Gastrointestinal disorder                       |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 13 (7.69%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Intestinal obstruction                          |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 13 (7.69%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Crohn's disease                                 |                 |                |  |
| subjects affected / exposed                     | 3 / 10 (30.00%) | 0 / 13 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Enterocutaneous fistula                         |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 13 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                 |                |  |
| Respiratory failure                             |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 13 (7.69%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1          |  |
| Pulmonary veno-occlusive disease                |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 13 (7.69%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1          |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Dyspnoea                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 13 (7.69%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 13 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 13 (7.69%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 3 / 13 (23.08%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Infections and infestations                     |                 |                 |  |
| Herpes zoster                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 13 (7.69%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 1 / 13 (7.69%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cytomegalovirus infection                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 13 (7.69%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumocystis jirovecii pneumonia                |                 |                 |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 13 (7.69%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                |  |
|-------------------------------------------------|-----------------|----------------|--|
| Abdominal abscess                               |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 1 / 13 (7.69%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Infection                                       |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 1 / 13 (7.69%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Urinary tract infection                         |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 13 (7.69%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Influenza                                       |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 1 / 13 (7.69%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Sepsis                                          |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 1 / 13 (7.69%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Neutropenic sepsis                              |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 13 (7.69%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Anal abscess                                    |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 1 / 13 (7.69%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Abdominal sepsis                                |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 13 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | Usual care      | HSCTlite         |  |
|-------------------------------------------------------|-----------------|------------------|--|
| Total subjects affected by non-serious adverse events |                 |                  |  |
| subjects affected / exposed                           | 3 / 10 (30.00%) | 11 / 13 (84.62%) |  |
| Vascular disorders                                    |                 |                  |  |
| Thrombosis                                            |                 |                  |  |
| subjects affected / exposed                           | 0 / 10 (0.00%)  | 1 / 13 (7.69%)   |  |
| occurrences (all)                                     | 0               | 1                |  |
| Hypertension                                          |                 |                  |  |
| subjects affected / exposed                           | 0 / 10 (0.00%)  | 1 / 13 (7.69%)   |  |
| occurrences (all)                                     | 0               | 1                |  |
| Hypotension                                           |                 |                  |  |
| subjects affected / exposed                           | 0 / 10 (0.00%)  | 1 / 13 (7.69%)   |  |
| occurrences (all)                                     | 0               | 1                |  |
| General disorders and administration site conditions  |                 |                  |  |
| Pyrexia                                               |                 |                  |  |
| subjects affected / exposed                           | 1 / 10 (10.00%) | 1 / 13 (7.69%)   |  |
| occurrences (all)                                     | 1               | 1                |  |
| Catheter site discharge                               |                 |                  |  |
| subjects affected / exposed                           | 0 / 10 (0.00%)  | 1 / 13 (7.69%)   |  |
| occurrences (all)                                     | 0               | 1                |  |
| Influenza                                             |                 |                  |  |
| subjects affected / exposed                           | 1 / 10 (10.00%) | 0 / 13 (0.00%)   |  |
| occurrences (all)                                     | 1               | 0                |  |
| Respiratory, thoracic and mediastinal disorders       |                 |                  |  |
| Pleural effusion                                      |                 |                  |  |
| subjects affected / exposed                           | 0 / 10 (0.00%)  | 1 / 13 (7.69%)   |  |
| occurrences (all)                                     | 0               | 1                |  |
| Hypoxia                                               |                 |                  |  |
| subjects affected / exposed                           | 0 / 10 (0.00%)  | 1 / 13 (7.69%)   |  |
| occurrences (all)                                     | 0               | 1                |  |
| Psychiatric disorders                                 |                 |                  |  |
| Depression                                            |                 |                  |  |
| subjects affected / exposed                           | 0 / 10 (0.00%)  | 1 / 13 (7.69%)   |  |
| occurrences (all)                                     | 0               | 1                |  |



|                                                                                                 |                     |                      |  |
|-------------------------------------------------------------------------------------------------|---------------------|----------------------|--|
| Hallucination<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 10 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1  |  |
| Mental disorder<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 10 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1  |  |
| Investigations                                                                                  |                     |                      |  |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 10 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1  |  |
| Oxygen saturation<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 10 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1  |  |
| Investigation<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 10 (0.00%)<br>0 | 2 / 13 (15.38%)<br>2 |  |
| Gamma-glutamyltransferase increased<br>subjects affected / exposed<br>occurrences (all)         | 0 / 10 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1  |  |
| Blood glucose increased<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 10 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1  |  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 10 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1  |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)          | 0 / 10 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1  |  |
| Liver function test abnormal<br>subjects affected / exposed<br>occurrences (all)                | 0 / 10 (0.00%)<br>0 | 2 / 13 (15.38%)<br>3 |  |
| Antimicrobial susceptibility test resistant<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1  |  |
| Mycobacterium tuberculosis complex test positive                                                |                     |                      |  |

|                                                                                                                                                                                                                                                        |                                                                           |                                                                            |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                       | 0 / 10 (0.00%)<br>0                                                       | 1 / 13 (7.69%)<br>1                                                        |  |
| Cardiac disorders<br>Tachycardia<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                   | 0 / 10 (0.00%)<br>0                                                       | 1 / 13 (7.69%)<br>1                                                        |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)<br><br>Pineal gland cyst<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0<br><br>0 / 10 (0.00%)<br>0<br><br>0 / 10 (0.00%)<br>0 | 2 / 13 (15.38%)<br>2<br><br>1 / 13 (7.69%)<br>1<br><br>1 / 13 (7.69%)<br>1 |  |
| Blood and lymphatic system disorders<br>Neutropenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                                                                    | 0 / 10 (0.00%)<br>0<br><br>0 / 10 (0.00%)<br>0                            | 1 / 13 (7.69%)<br>1<br><br>1 / 13 (7.69%)<br>1                             |  |
| Ear and labyrinth disorders<br>Tinnitus<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                            | 0 / 10 (0.00%)<br>0                                                       | 1 / 13 (7.69%)<br>1                                                        |  |
| Eye disorders<br>Vision blurred<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                    | 0 / 10 (0.00%)<br>0                                                       | 1 / 13 (7.69%)<br>1                                                        |  |
| Gastrointestinal disorders<br>Mouth ulceration<br>subjects affected / exposed<br>occurrences (all)<br><br>Gastrointestinal haemorrhage                                                                                                                 | 0 / 10 (0.00%)<br>0<br><br>                                               | 1 / 13 (7.69%)<br>1<br><br>                                                |  |

|                                        |                 |                 |  |
|----------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed            | 0 / 10 (0.00%)  | 1 / 13 (7.69%)  |  |
| occurrences (all)                      | 0               | 1               |  |
| Abdominal pain                         |                 |                 |  |
| subjects affected / exposed            | 0 / 10 (0.00%)  | 2 / 13 (15.38%) |  |
| occurrences (all)                      | 0               | 2               |  |
| Diarrhoea                              |                 |                 |  |
| subjects affected / exposed            | 0 / 10 (0.00%)  | 2 / 13 (15.38%) |  |
| occurrences (all)                      | 0               | 3               |  |
| Nausea                                 |                 |                 |  |
| subjects affected / exposed            | 0 / 10 (0.00%)  | 2 / 13 (15.38%) |  |
| occurrences (all)                      | 0               | 2               |  |
| Vomiting                               |                 |                 |  |
| subjects affected / exposed            | 0 / 10 (0.00%)  | 2 / 13 (15.38%) |  |
| occurrences (all)                      | 0               | 2               |  |
| Rectal haemorrhage                     |                 |                 |  |
| subjects affected / exposed            | 1 / 10 (10.00%) | 0 / 13 (0.00%)  |  |
| occurrences (all)                      | 2               | 0               |  |
| Crohn's disease                        |                 |                 |  |
| subjects affected / exposed            | 2 / 10 (20.00%) | 0 / 13 (0.00%)  |  |
| occurrences (all)                      | 2               | 0               |  |
| Skin and subcutaneous tissue disorders |                 |                 |  |
| Rash                                   |                 |                 |  |
| subjects affected / exposed            | 1 / 10 (10.00%) | 2 / 13 (15.38%) |  |
| occurrences (all)                      | 1               | 2               |  |
| Rash papular                           |                 |                 |  |
| subjects affected / exposed            | 0 / 10 (0.00%)  | 1 / 13 (7.69%)  |  |
| occurrences (all)                      | 0               | 1               |  |
| Contusion                              |                 |                 |  |
| subjects affected / exposed            | 0 / 10 (0.00%)  | 1 / 13 (7.69%)  |  |
| occurrences (all)                      | 0               | 1               |  |
| Seborrhoeic dermatitis                 |                 |                 |  |
| subjects affected / exposed            | 0 / 10 (0.00%)  | 1 / 13 (7.69%)  |  |
| occurrences (all)                      | 0               | 1               |  |
| Renal and urinary disorders            |                 |                 |  |
| Acute kidney injury                    |                 |                 |  |

|                                                  |                     |                      |  |
|--------------------------------------------------|---------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0 | 2 / 13 (15.38%)<br>2 |  |
| Infections and infestations                      |                     |                      |  |
| Tonsillitis                                      |                     |                      |  |
| subjects affected / exposed                      | 0 / 10 (0.00%)      | 1 / 13 (7.69%)       |  |
| occurrences (all)                                | 0                   | 1                    |  |
| Respiratory tract infection                      |                     |                      |  |
| subjects affected / exposed                      | 0 / 10 (0.00%)      | 1 / 13 (7.69%)       |  |
| occurrences (all)                                | 0                   | 1                    |  |
| Eye infection                                    |                     |                      |  |
| subjects affected / exposed                      | 0 / 10 (0.00%)      | 1 / 13 (7.69%)       |  |
| occurrences (all)                                | 0                   | 1                    |  |
| Epstein-Barr virus infection                     |                     |                      |  |
| subjects affected / exposed                      | 0 / 10 (0.00%)      | 2 / 13 (15.38%)      |  |
| occurrences (all)                                | 0                   | 2                    |  |
| Fungal infection                                 |                     |                      |  |
| subjects affected / exposed                      | 0 / 10 (0.00%)      | 1 / 13 (7.69%)       |  |
| occurrences (all)                                | 0                   | 1                    |  |
| Herpes zoster                                    |                     |                      |  |
| subjects affected / exposed                      | 0 / 10 (0.00%)      | 1 / 13 (7.69%)       |  |
| occurrences (all)                                | 0                   | 1                    |  |
| Anal abscess                                     |                     |                      |  |
| subjects affected / exposed                      | 0 / 10 (0.00%)      | 1 / 13 (7.69%)       |  |
| occurrences (all)                                | 0                   | 2                    |  |
| Bronchitis viral                                 |                     |                      |  |
| subjects affected / exposed                      | 0 / 10 (0.00%)      | 1 / 13 (7.69%)       |  |
| occurrences (all)                                | 0                   | 1                    |  |
| Cystitis                                         |                     |                      |  |
| subjects affected / exposed                      | 0 / 10 (0.00%)      | 1 / 13 (7.69%)       |  |
| occurrences (all)                                | 0                   | 1                    |  |
| Pharyngitis                                      |                     |                      |  |
| subjects affected / exposed                      | 1 / 10 (10.00%)     | 0 / 13 (0.00%)       |  |
| occurrences (all)                                | 1                   | 0                    |  |
| Urinary tract infection                          |                     |                      |  |
| subjects affected / exposed                      | 1 / 10 (10.00%)     | 0 / 13 (0.00%)       |  |
| occurrences (all)                                | 2                   | 0                    |  |

|                                                                                                          |                      |                     |  |
|----------------------------------------------------------------------------------------------------------|----------------------|---------------------|--|
| Viral infection<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 10 (10.00%)<br>1 | 0 / 13 (0.00%)<br>0 |  |
| Metabolism and nutrition disorders<br>Fluid overload<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0  | 1 / 13 (7.69%)<br>1 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 27 February 2018  | <ul style="list-style-type: none"><li>• Clarity added to protocol around procedures relating to mechanistic studies</li><li>• Corrections/tipos where required</li><li>• Increased window for some screening investigations prior to randomisation, and timing of CDAI in relation to colonoscopy</li><li>• Inclusion of the use of the IBD BioResource to identify potential participants</li><li>• Addition of HBI between mobilisation and conditioning, CDAI and HBI at both screening and baseline, added stoma version of IBDQ for participants where this is required</li><li>• Updates to PIS on advice from TSC – timing of discussion with both specialties, noted that most common side effects likely to occur in almost all patients</li><li>• Submitted reformatted versions of the validated participant questionnaires</li><li>• Minor updates to formatting for healthcare resource use questionnaire, symptom diary and vaccination proforma</li></ul>                                                                                                                                                                                                                                                                                                                              |
| 01 June 2018      | <ul style="list-style-type: none"><li>• Changes to PI at Edinburgh and Nottingham sites</li><li>• Secondary outcome added in relation to MRI and MaRIA score</li><li>• Additional mechanistic serum sample added at week 40 visit</li><li>• Addition of potential storage of stem cell samples for use in future research</li><li>• Added Karnofsky performance status at screening and week 48 for all participants</li><li>• Information added in relation to press release to aid recruitment, and potential use of a study Twitter account</li><li>• Participant allocation letter submitted which can be used to follow up informing participants of their allocation where face to face is not possible</li><li>• Addition of a vaccination advice sheet for GPs</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 05 June 2018      | <ul style="list-style-type: none"><li>• To allow the use of PICs, and to add Nottingham NHS Treatment Centre as a PIC for the Nottingham site</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 02 August 2018    | <ul style="list-style-type: none"><li>• The removal of details of MA holder for each IMP in section D2-1 of the application. The intention has always been for sites to use any brand of the IMPs in this study, and whilst the correct section of the application was completed to reflect this, details from the sample SmPCs submitted originally was also included, which implied that those brands were specified.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 05 September 2018 | <ul style="list-style-type: none"><li>• To add King's College Hospital London as a non-recruiting site, and to change the site type for Guy's &amp; St Thomas' to a non-treatment site.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 02 November 2018  | <ul style="list-style-type: none"><li>• Administrative changes to the protocol to update the organisations for two collaborators, Sponsor contact email address, CI deputy details</li><li>• Increase the window for screening investigations from within 4 weeks to 8 weeks of randomisation</li><li>• Provided clarity on how the primary outcome will be assessed for patients who have had ileo and/or colonic resection, but are still eligible to take part in the trial</li><li>• Correction to DMEC meeting frequency in line with the DMEC Charter</li><li>• Correction to treatment section in the PIS to note that mobilisation cyclophosphamide will be given on one day, rather than two.</li><li>• Clarification in the PIS that endoscopy might be undertaken if the bowel cannot be examined using ileocolonoscopy.</li><li>• The SmPC for filgrastim has been updated since the start of the study; the revised version has been submitted with this amendment to update the RSI.</li><li>• The SmPC for cyclophosphamide has been updated since the start of the study; although there have been no changes to the safety aspects, the updated version has been included with this amendment so that sites can have access to the latest information relating to the IMP.</li></ul> |

|                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 25 July 2019      | <ul style="list-style-type: none"> <li>• Addition of genetic and or functional tests during screening to exclude monogenic cause of intestinal inflammation in patients with predictive clinical phenotype</li> <li>• To allow possibility of second attempt at mobilisation with reduced or no cyclophosphamide in patients who fail to mobilise first time</li> <li>• Admin changes and updates to protocol</li> <li>• Clarified definition of SES-CD ulcer size subscore for eligibility and outcomes</li> <li>• Updates to PIS for GDPR requirements, and genetic testing as above</li> <li>• Additional two flowcharts to help explain trial to participants</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 12 August 2019    | Increase in dose of methylprednisolone (NIMP) from 1mg/kg/day to 2mg/kg/day, with scope to increase further up to 500-1000mg in the setting of an ATG reaction. Amendment in response to Urgent Safety Measure (July 2019).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 08 February 2020  | Administrative changes to reflect change in trial manager and research assistant. Removal of the circle Nottingham as this is now part of Nottingham University Hospitals NHS Trust. Allow the use of an alternative to MRI such as a CT scan for screening if patients are unable to have an MRI. Addition that MRI will not be carried out at week 4, week 24 or week 48 if this is contraindicated. At week 24 an assessment of whether anti-TNF therapy is indicated will be based on endoscopic evidence and if needed, abdominal ultrasound. Addition that any laboratory test result which is out of range, and clinically significant, will be recorded as an adverse event, unless it is expected as part of the patient's disease presentation, or reflects the status of their baseline disease. Consideration about reintroducing anti-TNF at week 24 for patients with multiple sclerosis. Anti-TNF therapy may not be appropriate for these patients therefore it will be reviewed on a case by case basis and discussed at MDT. Suitable alternative such as vedolizumab may be offered. Changes to the SmPC for filgrastim and thymoglobulin. |
| 30 March 2020     | Temporary Halt following fatal SUSAR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 22 September 2020 | Addition of letter to update patients on the closure to the ASTIClite trial.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date             | Interruption                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Restart date |
|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 30 December 2019 | <p>The trial was paused in December 2019 whilst a number of SUSARs were investigated. Two further SUSARs were reported in May 2020. In June 2020, the DMEC and TSC held a joint meeting to discuss the events, the outcomes of investigations and the impact of the coronavirus pandemic. The DMEC and TSC agreed that recruitment to the trial should stop. Patients already in follow up, either having completed the intervention, or in the control group, were followed up as normal. Patients randomised to the intervention who had not yet received this, were withdrawn from the study.</p> <p>In addition, the coronavirus pandemic affected the ability of trial sites to conduct all aspects of patient visits. Some visits were delayed, and some procedures had to be omitted.</p> | -            |

Notes:

## Limitations and caveats

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

Due to the early closure of the trial, participant numbers included in the final analysis are lower than anticipated. An addendum was written for the Statistical Analysis Plan to document the changes to the planned analyses given the reduced numbers.

Notes: