

Supplementary Material 7

Trial Recruitment

D.6 Trial Recruitment

The trial received initial MHRA and ethics approval on 16th December 2014 and 8th December 2014, respectively.

Six sites were opened for recruitment. Table S5 provides further details on site activation. Throughout the trial, more sites were opened to improve recruitment efforts.

Table S5: Sites opened for recruitment in the BUTEO Trial.

Site	Site Activation Date	Date First Patient Recruited	Date Last Patient Recruited
Queen Elizabeth Hospital, Birmingham	14 Apr, 2015	8 Sept, 2015	2 Mar, 2018
Queen's Medical Centre, Nottingham	26 Oct, 2015	20 May, 2016	18 May, 2018
Royal Victoria Infirmary, Newcastle	8 Aug, 2016	-	-
John Radcliffe Hospital, Oxford	31 Jan, 2017	11 May, 2017	29 Dec, 2017
Addenbrooke's Hospital, Cambridge	15 Aug, 2017	-	-
The Royal Free Hospital, London	8 Mar, 2018	19 Jun, 2018	19 Jun, 2018

Note: The Royal Victoria Infirmary, Newcastle was only a clinical site in the BUTEO trial with the corresponding trial management site being the Freeman Hospital, Newcastle.

Seven patients were recruited in total to the dose confirmatory stage as one patient (TNO2) withdrew and discontinued treatment. As per version 5.0 of the protocol, as the individual had not completed visit 7, they were replaced. The resulting six patient cohort were included in the safety analysis for the initial Data Monitoring Committee (DMC), meeting dated 16th November 2016. It was confirmed at this meeting that recruitment could continue at the confirmed dose of 8mg/kg, moving the trial into phase II, for which recruitment restarted on 5th December 2016.

The trial's last-patient-last-visit was on 23rd October 2018, with the trial closing on 2nd January 2019 following the interim analyses (stage one of the Simon's two-stage trial design) findings and subsequently agreed recommendation of both the independent DMC and the Trial Steering Committee (TSC). Twenty three patients were recruited in total to the BUTEO Trial.

Figure S3 shows the trial's recruitment both per month and cumulatively. On figure S3, the vertical dashed blue lines indicate the opening of a new site.

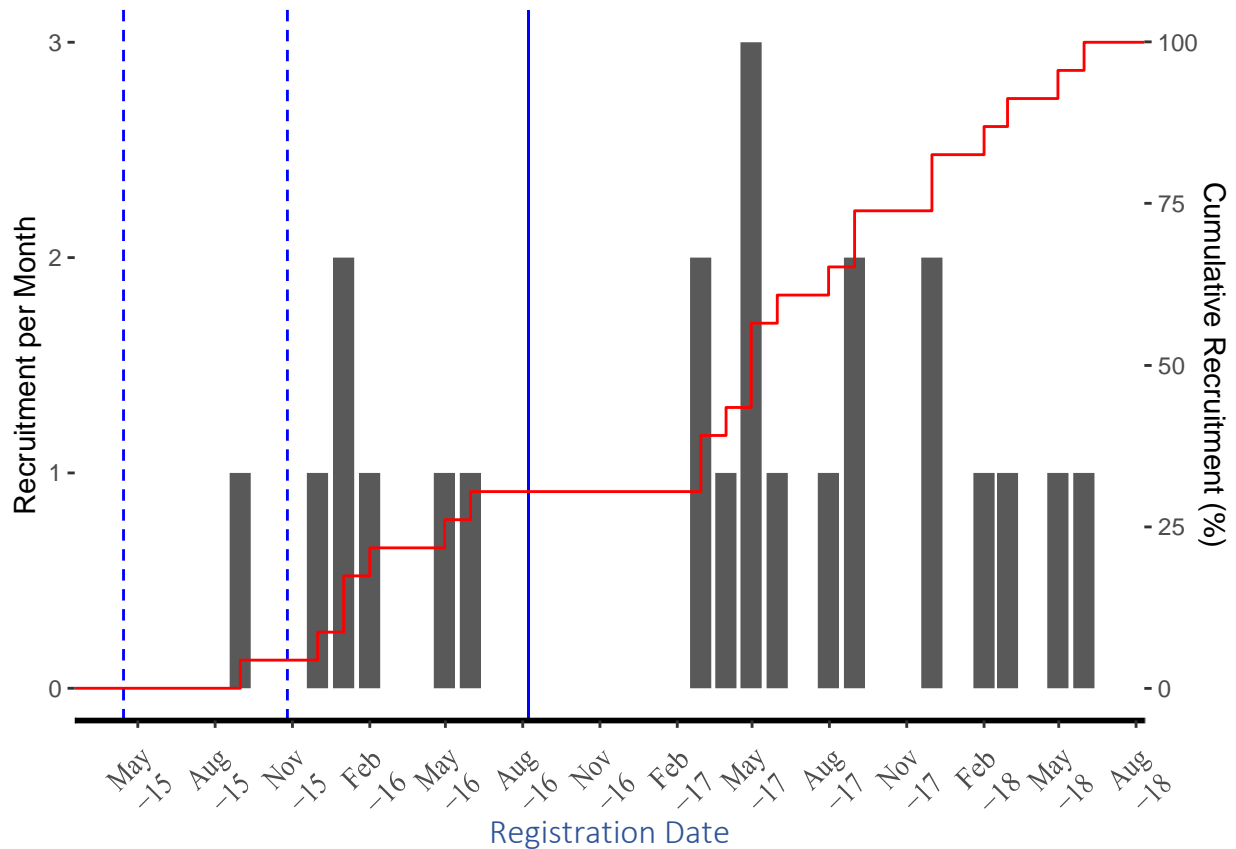


Figure S3: BUTEO Trial recruitment. Dashed blue lines indicate the opening of a new site.

Table S6 presents the numbers of patients who were recruited by site, while table S7 shows the number of patients screened for the trial, and the number of those who went on to fail screening and the number who went on to be registered and recruited. Figure S4 depicts recruitment in relation to hospital trial opening times. On figure S4 the blue shading illustrates that the centre was open and recruiting, whereas the grey shading illustrates the centre was not yet open. The Queen Elizabeth Hospital, Birmingham (QEH) was the first site to open and as such recruited 13 patients out of 22 consented and screened. This represented the highest number of either consent and screening, or recruitment from a single site. The Queen Medical Centre, Nottingham (QMC) opened 207 days after trial opening and recruited 5 of the 7 patients that consented and were screened. Subsequent sites that opened and recruited patients were: the John Radcliffe Hospital, Newcastle (JRH) opened after 670 days and recruited 4 patients out of 4 consented and screened; the Royal Free Hospital, London (RFH) opened after 1014 days recruiting 1 (4.4%) of 1 (2.7%) consented and screened

patient. Sites not depicted on figure S4, (the Royal Victoria Infirmary, Newcastle; and Addenbrooke's Hospital, Cambridge) failed to recruit any patients.

Recruitment was slower than anticipated due to the need for a dose confirmation stage, and its subsequent DMC. While the two screening visits did not slow recruitment upfront, it did result in a number of patients failing the second screening visit due to a change in LFTs that then made them ineligible. Although PSC is a rare disease, many potential participants live normal lives and have full time jobs, therefore involvement in a trial such as BUTEO requires a substantial time commitment from them.

Table S6: Recruitment information by site.

Site	Number of Patients Recruited	Principal Investigator Name
Queen Elizabeth Hospital, Birmingham	13	Dr Gideon Hirschfield
Queen's Medical Centre, Nottingham	5	Dr Guruprasad Aithal
Royal Victoria Infirmary, Newcastle	0	Dr Mark Hudson
John Radcliffe Hospital, Oxford	4	Professor Eleanor Barnes
Addenbrooke's Hospital, Cambridge	0	Dr George Mells
The Royal Free Hospital, London	1	Dr Douglas Thorburn

Table S7: Recruitment information by centre

Site	Number of Patients Screened	Number of Screening Failures	Number of Patients Recruited
Queen Elizabeth Hospital, Birmingham	22 (62.86%)	10 (76.92%)	13 (56.52%)*
Queen's Medical Centre, Nottingham	7 (20.00%)	2 (15.38%)	5 (21.74%)
Royal Victoria Infirmary, Newcastle	1 (2.86%)	1 (7.69%)	0 (0.00%)
John Radcliffe Hospital, Oxford	4 (11.43%)	0 (0.00%)	4 (17.39%)
Addenbrooke's Hospital, Cambridge	0 (0.00%)	0 (0.00%)	0 (0.00%)
The Royal Free Hospital, London	1 (2.86%)	0 (0.00%)	1 (4.35%)
Total	35 (100.00%)	13 (100.00%)	23 (100.00%)

Note:

*One patient was registered at Birmingham and then found to be ineligible. They are therefore counted as both a screen failure and as a patient recruited.



Figure S4: BUTEO Trial centre openings and patient recruitment.