ANIMATE Amendments Log

Amend No & date *All amendments are logged and numbered sequentially*	**Details of amendment** *Includes list of documents amended e.g. CTA, labels, protocol, etc and reason for amendment.*	**Substantial or Non-Substantial?**	**Regulatory Body**	**Date Submitted** *(dd/mm/yy)*	**Date categorisation email & amend pack sent to site** *(dd/mm/yy)*	**Implementation date** *(dd/mm/yy)*	**Date of approval** *(dd/mm/yy)*	**Date approvals sent to sites** *(dd/mm/yy)*	**Date sent to third parties if relevant** *(dd/mm/yy)*
1 13.03.2018	**Details of Amendment:** Changes agreed to address initial Grounds for Non-Acceptance from MHRA submitted to REC for approval Main change: - Rationale given for dose and regimen of nivolumab used **Documents Amended:** **Protocol v1.1 21.02.18** **Risk Assessment Reviewed (SA only): N/A, Incorporated into initial Risk Assessment for trial**	Substantial – decision made by Pip Patrick, Senior Trial Coordinator as essential trial documents had been amended.	**MHRA** **REC** **HRA**	n/a 13.03.18 13.03.18	22.06.18 – sent with initial site setup pack	17.04.18	n/a 10.04.18 17.04.18	22.06.18 – sent with initial site setup pack	PET core lab: 23.11.18 HMDS: 23.11.18 WIMM lab, Oxford: 23.11.18 MRC-Glasgow University Centre for Virus Research : pending
2 13.04.2018	**Details of Amendment:** Main changes: - Change of central laboratory from UCL Cancer Institute to Weatherall Institute of Molecular Medicine, Oxford - Minor change to PV reporting requirements - Minor change to eligibility criteria & investigations **Documents Amended:** **Protocol v2.0 10.04.2018** **PIS v2.0 10.04.2018** **ICF v2.0 10.04.2018** Addition of new sites: - Nottingham University Hospitals NHS Trust - University Hospital Southampton NHSFT - Royal Marsden NHSFT **Risk Assessment Reviewed (SA only): N/A, Incorporated into initial Risk Assessment for trial**	Substantial – decision made by Pip Patrick, Senior Trial Coordinator as essential trial documents had been amended.	**MHRA** **REC** **HRA**	13.04.18 13.04.18 13.04.18	22.06.18 – sent with initial site setup pack	18.05.2018	20.04.2018 30.04.2018 08.05.2018	22.06.2018 –sent with initial site setup pack	PET core lab: 23.11.2018 HMDS: 23.11.2018 WIMM lab, Oxford: 23.11.2018 MRC-Glasgow University Centre for Virus Research : pending

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3 14.06.2018	**Details of Amendment:** Main changes: - Addition of new central laboratory – MRC-Glasgow University Centre for Virus Research - Additional blood samples for TARC analysis - Updates to reflect implementation of GDPR/Data Protection Act 2018 - Clarification of eligibility criteria with relation to hepatitis B serology - Clarification about use of national registries for follow up of patients - Optional consent introduced for storage of left-over blood samples for use in future research. **Documents Amended:** **Protocol v2.1 12.06.2018** **PIS v3.0 12.06.2018** **ICF v3.0 12.06.2018** **Pregnancy Monitoring IS v2.0 12.06.2018** **Pregnancy Monitoring ICF v2.0 12.06.2018** **Risk Assessment Reviewed (SA only): Y - Risk assessment v1.1, 15.06.2018**	Substantial – decision made by Pip Patrick, Senior Trial Coordinator as essential trial documents had been amended.	**MHRA** **REC** **HRA**	14.06.2018 14.06.2018 14.06.2018	14.06.2018	19.07.2018	09.07.18 13.08.18, reissued 30.08.18 13.08.18	13.08.18	PET core laboratory: 23.11.2018 HMDS: 23.11.2018 WIMM lab, Oxford: 23.11.2018 MRC-Glasgow University Centre for Virus Research : pending

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4 04.02.2019	**Details of amendment:** Change of IMP QP release site. Was Clinical Management Supplies Europe (CSM) Belgium as being responsible for QP release. This was changed prior to trial activation and CSM's German manufacturing site was contracted for final QP relase. QC check identified the CTA was never amended and a Substantial amendment was therefore submitted to update the CTA to the correct QP sign off.	Substanial – amendment to CTA required	**MHRA only**	04.02.2019	n/a	n/a	20.02.19	n/a	CTA amended, no other trial docs changed therefore not circulated

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5 10.12.2019	**Details of Amendment:** Main changes: - Timings of patient registration/inclusion criteria amended and clarified - Change in PET0 scanning time 14 days (±3 days) (i.e. day 11-17 inclusive) after last treatment administration in cycle 2 of first or second line salvage chemotherapy (cycle 3 or 4 if being treated with brentuximab vedotin) - Guidance on immune related diarrhoea and hepatitis updated in the light of October 2019 MHRA safety advice regarding CMV infection & reactivation reported in patients treated with nivolumab and ipilimumab - Lipase testing removed from the trial - Amylase and ACTH testing changed from being required prior to every cycle to only prior to cycle 5 during trial treatment - Thyroid Function Tests changed from being required prior to cycles 4 and 7 to cycles 3, 5 and 7 - Timings for pregnancy tests amended to 3 days prior to registration, confirmation of eligibility and trial treatment - References to the Sample Tracking Website Manual added to prompt sites to track all samples and scans online, previously omitted in error - Clarification added that repeat biopsies should be performed as per standard local procedures - Adverse Event form added to list of CRFs, previously omitted in error - Minor changes made to Pharmacovigilance section to make it consistent with new UCL CTC template	Substantial	**MHRA** **REC** **HRA**	10.12.2019 10.12.2019 10.12.2019	12.12.2019	17.02.2020	10.01.2020 15.01.2020 07.02.2020	11.02.2020	PET core laboratory: NK HMDS: NK WIMM lab, Oxford: NK MRC-Glasgow University Centre for Virus Research: NK

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5 10.12.2019 continued	- References to Central monitoring changed to centralised monitoring in Trial monitoring and oversight section to make it consistent with new UCL CTC template - Dosage unit amended to g/l for haemoglobin, previously given incorrectly as g/dl - Reference to MRC-University of Glasgow Centre for Virus Research added to Funding section - ceCT, cycle 3 or 4 for BV and more detailed follow up schedule added to Trial Schema - ceCT added to reference guide to patient visits - Change of Trial Coordinator- Tesha Suddason - Position and site updated for Dr Beth Phillips - BMS logo removed								

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6 28.05.2020	Details of amendment: Various changes made, see protocol summary of changes table for details: S:\BNLI\Trials\Open\ANIMATE\03 PROTOCOL\d Protocol Drafts and Reviews\Protocol v4.0\Table of protocol changes v4.0.docx **The following documents were amended:** • **ARSAC form updated** • **Protocol from v3.0 to v4.0** • **PIS from v4.0 to v5.0** • **ICF from v4.0 to v4.1** • **PMIS for patient v1 created (missed in error)** • **PMICF for patient v1 created (missed in error)** Addition of new sites: - Lincoln County Hospital, PI Dr Gamal Sidra - Derriford Hospital, PI Dr Patrick Medd - Sandwell General Hospital, PI Dr Syeda Yasmin Hasan - Clatterbridge Cancer Centre, based at Royal Liverpool Hospital, PI Dr Nagesh Kalakonda - Aberdeen Royal Infirmary, PI Dr Dominic Culligan Change in PI at following sites: - Christie – Dr Beth Phillips - Nottingham – Dr Nicolas Martinez-Calle **Risk Assessment reviewed?: Y – Risk Assessment v2.0 under review**	Substantial – agreed by Rich Jenner STC. Essential trial documents amended.	MHRA	28.05.2020	18.06.2020	27.07.2020	10.06.2020	10.07.2020	PET core laboratory: 13.07.2020 HMDS: 13.07.2020 WIMM lab, Oxford: 13.07.2020 MRC-Glasgow University Centre for Virus Research:13.07.2020
			REC	29.05.2020			07.07.2020		
			HRA	29.05.2020 (emailed to REC who submit to HRA)			09.07.2020		
			ARSAC	01.06.2020			n/a ARSAC confirmed their review is not required.		

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7 26.06.2020	Pause to recruitment and collection of translational samples for ANIMATE: • Due to the COVID-19 pandemic and subsequent closure of the central laboratories, the CI/TMG made the decision on 30/03/20 to temporarily close the trial to recruitment. The consensus was that the impact of not collecting the samples would weaken the scientific credibility of the trial. • For those patients who had already been given a PIS, it was up to the PI and local team as to whether the patient proceeded to registration. • Future translational samples were not taken from patients already on trial. Permitting lung function tests to be omitted. Reopening to recruitment and the collection of translational samples for ANIMATE Assessment carried out via teleconsultation	Non-substantial – agreed by Rich Jenner. No trial documents amended.	MHRA REC HRA ARSAC	n/a n/a n/a n/a	n/a	29.06.2020	n/a n/a n/a n/a	29.06.2020	PET core laboratory: n/a HMDS: n/a WIMM lab, Oxford: n/a MRC-Glasgow University Centre for Virus Research:n/a0