ANIMATE Monitoring Plan

Overview	
Phase of trial	Phase IIb (Therapeutic exploratory)
Overall outcome of risk assessment	Medium
IMP type	B (Nivolumab)

Version History			
Version number	Date	Summary of changes made *(include rationale for significant changes)*	Changes made by
1.0	25.07.2018	N/A – initial version	Oliver Schofield & Pip Patrick

Site Initiation			
	Trial specific plan	**MMR** *(See Appendix 1)*	**Rationale (if different)**
Format	Teleconference preferred, on-site visit if required (for example if a site has not participated in a CTC haematology trial in the last 12 months).	On-site visit or Teleconference	N/A
Occurs at what point?	Prior to activation		
Responsible role (s)	Trial Coordinator or Senior Trial Coordinator		
Trigger for re-initiation	If a site does not recruit any patients within 8 months of their trial initiation, a re-initiation teleconference should be considered. The decision about whether or re-initiation will be performed should be documented and filed in the TMF/eTMF. Sites may also be re-initiated if there is evidence of non-compliance indicating a lack of understanding the protocol.		
Ongoing Training	Ongoing training for site staff not present at the site initiation will be performed by other trained site staff in the first instance; the protocol, initiation slides and guidance documents provided by UCL CTC should be used as the basis of this training. Evidence of training should be filed in the ISF. If the site does not have their own training log the UCL CTC will provide a training log for this purpose. If a site requests further training or there is a lack of understanding of the trial protocol, further training will be provided by the CTC via teleconference as described above. If required, an on-site visit will be booked. For significant protocol amendments where there are major changes of process, additional training may be provided by the CTC by teleconference. It will be the responsibility of the PI at each site to ensure that all relevant staff are fully aware of updates to the protocol and study requirements. Evidence of understanding/training (e.g. via a training log or meeting minutes) should be filed in the ISF.		
Initiation report	The initiation report will be distributed to sites within 2 weeks of the initiation and if a response is required the date this is required by will be detailed in the report.		

Central Monitoring Requests and Site Quality Control			
Central monitoring introduction	Central monitoring encompasses checks of documents and information submitted by participating sites to UCL CTC or another central location. Sites will be sent routine requests to submit documents for central monitoring according to the timelines outlined below. Additional documents may be collected at appropriate other time points (e.g. CRFs should be submitted following each patient visit, according to the protocol specifications). This section outlines the documents to be collected for this trial, and the nature of the reviews that will be conducted of those documents (for full details of checks to be undertaken refer to the Central Monitoring TSP, Data Management Plan and Registration/Randomisation TSP). Where applicable checks have been undertaken at an on-site monitoring visit, it will not be necessary to repeat these centrally unless otherwise indicated. Routine requests will be sent throughout the recruitment and maintenance stage of the trial, and may be extended into the follow-up stage if deemed necessary.		
	Trial specific plan	**MMR** *(See Appendix 1)*	**Rationale (if different e.g. risk assessment highlighted need for increased monitoring)**
Frequency of routine document requests	Requests sent biannually Sites may not be included in the request if they were activated within the preceding 3 months. On-site monitoring triggered for non-compliant sites	Requests sent biannually On-site monitoring triggered for non-compliant sites	N/A
Trigger for routine document requests	Requests will be sent to active sites biannually from the anniversary of the activation of the first site, as per above criteria.		
Documents/ information collected at the time of routine requests	**Documents Collected:** • Site staff delegation log (delegation logs will also be collected when UCL CTC staff become aware of a change of staff at the site) • Nivolumab stock balance log		
Quality control checklists provided to sites	• Investigator Site File document version checklist • Pharmacy Site File document version checklist		
Additional documents/ information collected for central monitoring (as required)	**Documents collected:** • Case Report Forms (CRFs) including registration form and post-salvage treatment form, as per timelines in the protocol – to be collected throughout recruitment and treatment phase. • Screening Logs: will be requested as required throughout the recruitment phase, typically prior to TMG meetings. • Biological samples inventory log • Online sample tracker • Principal Investigator's CV and/or evidence of GCP training: PI's CV will be collected at site set up, when there is a change of PI and at site closure. PI's GCP certificates will be collected every 2 years unless local policy differs. • Patient-specific drug accountability logs will be collected when each patient completes trial treatment. When a Treatment Summary Form is received, the Trial Coordinator or Data Manager will check whether the corresponding patient accountability log has been		

	submitted. If not yet received, a reminder will be sent to Pharmacy. A triggered warning will appear on the CRF tracking log when the Treatment Summary Form and patient-specific drug accountability log is due to ensure both are collected on time. • Drug Request Forms (including forms with completed 'Acknowledgement of Receipt' section) • PET-CT scan central review reports (sent by the PET core laboratory at St Thomas' Hospital)
Checks undertaken through central monitoring – *full details are provided in the Central Monitoring TSP / Data Management Plan & Registration/Randomisation TSP*	***Trial Logs/Reports*** The site staff delegation log and screening log will be checked for consistency and completeness.
	Patient Eligibility Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). Checks of the criteria listed on the registration form will be undertaken by an appropriately trained UCL CTC staff member prior to registration. Registration for the ANIMATE trial may be performed before or during first or second line salvage treatment, but must be no later than 14 days after completing the second cycle of first or second line salvage. Appropriately trained UCL CTC staff members will review the registration form to confirm patient eligibility. If further information is required, UCL CTC will contact the person requesting registration to discuss the patient and request updated forms to be sent. Eligibility for trial treatment will be confirmed centrally at UCL CTC after two cycles of first or second line salvage chemotherapy (four cycles if receiving treatment with brentuximab vedotin). This will be based on both the central review report on the patient's end of salvage PET-CT scan (PET0) and clinical eligibility criteria reported in the Post Salvage Treatment CRF.
	Informed Consent Details relating to the informed consent process will be collected on the registration form and are subject to review by CTC as part of patient eligibility checks. ***Optional Consent*** The following aspects of the trial are optional: • ***Undergoing a repeat tumour biopsy if PET-positive after 8 cycles of nivolumab (biopsy sample to be sent to HMDS).*** Details of whether the patient has consented to this will be collected via the Registration CRF. Changes of consent will be collected via the Lost to Follow Up CRF. • ***Donating left over biopsy material for use in future ethically approved research*** – Details of whether the patient has consented to this will be collected via the Registration CRF. Changes of consent will be collected via the Lost to Follow Up CRF. From implementation of Protocol v2.0/PIS v3,0/ICF v3.0: ***Donating left over blood samples & derivatives for use in future ethically approved research*** – Details of whether the patient has consented to this will be collected via the Registration CRF. Changes of consent will be collected via the Lost to Follow Up CRF. When a new patient registered into the trial, a member of CTC staff will set up a patient record for them on the sample tracking website. Details of optional consent will be transcribed from the Registration CRF onto the tracking website. This information will be visible viewable by staff at the CTC, central labs and sites. Where consent is not given, fields will be deactivated so sites are unable to send and track samples, and the lab will know not to expect samples. • ***Pregnancy monitoring of female patients of childbearing potential*** – Details of whether a patient has consented to this aspect of the trial will be collected on the Registration form. This will be used to inform whether follow up pregnancy reports are requested if the patient becomes pregnant at any point between commencement of nivolumab and 6 months post last nivolumab administration.

	• ***Pregnancy monitoring in female partners of trial patients*** - this will be monitored via the trial-specific pregnancy report form if a patient's partner becomes pregnant between the start of trial treatment and 8 months post last nivolumab administration. **Re-consent** UCL CTC will provide sites with re-consent logs for all patients who need to re-consent. These will be collected and reviewed centrally to ensure that re-consent has been undertaken in a timely fashion.
	Drug Accountability Logs Copies of drug accountability logs must be returned to UCL CTC for all trial patients. Sites will be required to submit patient-specific logs following completion of the patient's treatment. When a Treatment Summary Form is received, the Trial Coordinator or Data Manager will check whether the corresponding patient accountability log has been submitted. If not yet received, a reminder will be sent to Pharmacy. A triggered warning will appear on the CRF tracking log when the patient-specific drug accountability log is due to ensure both are collected on time.Nivolumab balance logs will also be collected as part of regular central monitoring requests. Balance logs, patient specific logs and completed drug request forms will be reviewed to confirm that all supplied drug has been dispensed only to trial patients and that the quantity of supplied drug dispensed/quarantined/destroyed can be reconciled with the quantity supplied to the site.
	Data Management Data received at UCL CTC will be checked for legibility, completeness, accuracy and consistency, including checks for missing or unusual values in accordance with the trial Data Management Plan. If any problems are identified data queries will be issued to the site as per UCL CTC SOPs.
	Site Quality Control Checklists Completed site quality control checklists returned by sites will be reviewed and any documents that are missing from the site files will be provided. If a checklist is not returned to UCL CTC it will be assumed that documents contained within the files at that site are up-to-date.
	PET-CT scan central review reports Central review reports provided by the PET core laboratory will be cross-checked against CRFs to confirm: - Eligibility for trial treatment (PET0) - Eligibility to continue with cycles 5-8 of treatment (PET4) - Indication for a repeat biopsy after 8 cycles of treatment (PET8)
	Biological sample log / Sample tracking database The biological samples inventory log will be cross-checked against the online sample tracking database and data collected on CRFs to ensure that samples have been sent as per protocol requirements and in line with patient consent.
Central monitoring summary	Where central monitoring of data and/or documentation submitted by a site identifies any discrepancies, a query will be raised with the site and followed up until resolution. If the discrepancy is significant, this will be discussed with the STC/TGL and, where possible, review of additional documents will be undertaken (for example, accountability logs may be reviewed for additional patients). If there is concern of serious or systematic failure, or evidence that a patient may have been placed at risk e.g. indication that stopping rules for nivolumab were not observed following an adverse reaction, evidence of an overdose having been administered, etc.), the matter will be discussed urgently with site staff. An incident will be raised and the matter will be escalated appropriately according to relevant UCL CTC SOPs.

Serious Non-Compliance / Triggers for On-site monitoring visits

Monitoring visits may be triggered following review of data from each site by the trial team. Trigger review meetings will take place in line with TMG and/or IDMC meetings and at least annually during the recruitment and treatment phase of the trial, but may be carried out more often if there are concerns. During the review meetings, data in relation to the triggers below will be reviewed per site to determine whether an on-site visit is necessary.

- High rates of late reported SAEs
- High rates of outstanding data
- High rates of data queries or unresolved queries
- Concern by the trial physician or trial management staff raised by central review
- Inappropriate drug administration
- Rate of site incidents
- Lower than expected AE/SAE rate, in proportion to the number of patients recruited, in the time the site has been open and in comparison to other open sites
- Any other evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements.

Sites will be sent a letter in advance outlining the reason(s) for the visit. The letter will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities, who will be performing the visit and when the visit is likely to occur.

Sites who are persistently non-compliant or who persistently do not return data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC.

Triggered On-site Monitoring

Patients to be reviewed during triggered visits may be selected by using an algorithm and/or based on the issues and/or triggers identified for the site.

For each triggered visit the nature of the reviews will be led by the triggers that have been identified e.g. if a visit triggered for suspected underreporting of SAEs then SDR for SAEs will be prioritised. Reviews for the areas of concern will be monitored as a priority during the visit.

Once the priority reviews have been completed the following reviews in order of priority should take place for the patients selected (refer to 'On-site Monitoring review section for SDV/SDR/CRF/data to be reviewed per patient):

- Patient consent
- Patient eligibility
- Patient Safety / SAE reporting
- Safety assessments, e.g. autoimmune tests
- Secondary/other endpoints
- Drug accountability/IMP administration compliance

Specific arrangements will be made for each individual on-site monitoring visit of this kind to account for the nature of the trigger and, in the case of a 'for cause' visit, the areas reviewed will cover details specific to the area of suspected/actual non-compliance.

Site Closure

	Trial specific plan	**MMR** *(See Appendix 1)*	**Rationale (if different)**
Format	Central collection & review of required documents	Central collection & review of required documents	N/A

Review and Authorisation		
Oliver Schofield		25/07/2018
Trial Coordinator Name	**Signature**	**Date**
Pip Patrick		25/7/2018.
Senior Trial Coordinator Name	**Signature**	**Date**
Krista Wills		25th 2018.
Monitoring Coordinator Name	**Signature**	**Date**

Appendix 1 – Minimum Monitoring Requirements

Risk factor	Phase I	Phase IIa	Phase IIb	Phase III
High	**Site initiation:** • On-site visit	**Site initiation:** • On-site visit	**Site initiation:** • On-site visit	**Site initiation:** • On-site visit or telecon
	Trial monitoring: ***Onsite (SDV)*** • Consent & eligibility: 100% SDV for all pts • SAE /AE reporting: 100% SDV for all pts • Primary endpoint(s): 100% SDV for all pts • Secondary endpoints: Trial specific • Drug accountability: 100% SDV for all pts • Key Safety Assessments: 100% SDV for all pts • Other trial data: 100% SDV for all pts ***Central Monitoring and site quality control*** • Frequency determined per trial	**Trial monitoring:** ***Onsite (SDV)*** • Consent & eligibility: 100% SDV for all pts • SAE reporting: 100% SDV for all pts • AE reporting: 100% SDV or SDR for all pts • Primary endpoint(s): 100% SDV for all pts • Secondary endpoints: Trial specific • Drug accountability: 100% SDV for 1st pt enrolled at each site & 50% of pts thereafter. 100% for all supplied drugs • Key Safety Assessments: 100% for all pts • Other trial data: 100% SDV for 1st pt enrolled at each site & 10% of pts thereafter ***Central Monitoring and site quality control*** • Frequency determined per trial	**Trial monitoring:** ***Onsite (SDV)*** • Consent & eligibility: 100% SDV for 50% of pts • SAE reporting: 100% SDV for 50% of pts • AE reporting: 100% SDV or SDR for 50% of pts • Primary endpoint(s): 100% SDV for 50% of pts • Secondary endpoints: Trial specific • Drug accountability: 100% SDV for 1st pt enrolled at each site. 100% for all supplied drugs • Key Safety Assessments: 100% for 1st pt enrolled at each site • Other trial data: 100% SDV for 1st pt enrolled at each site ***Central Monitoring and site quality control*** • Request sent biannually	**Trial monitoring:** ***Onsite (SDV)*** • Some on-site monitoring required if trial incorporates an unlicensed product (per risk assessment may also be required for unlicensed indications and newly licenced products) – level to be determined per trial ***Central Monitoring and site quality control*** • Request sent biannually • On-site monitoring visits triggered for non-compliant sites
	Site closure: • On-site visit	**Site closure:** • On-site visit or teleconference	**Site closure:** • On-site visit or teleconference	**Site closure:** • Central collection & review of required docs
Medium	**Site initiation:** • On-site visit	**Site initiation:** • On-site visit	**Site initiation:** • On-site visit or telecon	**Site initiation:** • On-site visit, telecon or Investigator Meeting
	Trial monitoring: ***Onsite (SDV)*** • Consent & eligibility: 100% SDV for all pts • SAE reporting: 100% SDV for all pts • AE reporting: 100% SDV or SDR for all pts • Primary endpoint(s): 100% SDV for all pts • Secondary endpoints: Trial specific, • Drug accountability: 100% SDV for all pts • Key Safety Assessments: 100% SDV for all pts • Other trial data: 100% SDV for 1st pt enrolled at each site & 10% of pts thereafter ***Central Monitoring and site quality control*** • Frequency determined per trial	**Trial monitoring:** ***Onsite (SDV)*** • Consent & eligibility: 100% SDV for 50% of pts • SAE reporting: 100% SDV for 50% of pts • AE reporting: 100% SDV or SDR for 50% of pts • Primary endpoint(s): 100% SDV for 50% of pts • Secondary endpoints: Trial specific • Drug accountability: 100% SDV for 1st pt enrolled at each site. 100% for all supplied drugs • Key Safety Assessments: 100% SDV for 1st pt enrolled at each site • Other trial data: 100% SDV for 1st pt enrolled at each site ***Central Monitoring and site quality control*** • Request sent biannually	**Trial monitoring:** ***Onsite (SDV)*** • Some on-site monitoring required if trial incorporates an unlicensed product (per risk assessment may also be required for unlicensed indications and newly licenced products) – level to be determined per trial ***Central Monitoring and site quality control*** • Request sent biannually • On-site monitoring visits triggered for non-compliant sites	**Trial monitoring:** ***Onsite (SDV)*** • Some on-site monitoring required if trial incorporates an unlicensed product (per risk assessment may also be required for unlicensed indications and newly licenced products) – level to be determined per trial ***Central Monitoring and site quality control*** • Request sent annually • On-site monitoring visits triggered for non-compliant sites
	Site closure: • On-site visit	**Site closure:** • On-site visit or teleconference	**Site closure:** • Central collection & review of required docs	**Site closure:** • Central collection & review of required docs

Risk factor	Phase I	Phase IIa	Phase IIb	Phase III
Low	**Site initiation:** • On-site visit	**Site initiation:** • On-site visit or telecon	**Site initiation:** • On-site visit or telecon	**Site initiation:** • On-site visit, telecon or Investigator Meeting
	Trial monitoring: ***Onsite (SDV)*** • Consent & eligibility: 100% SDV for all pts • SAE reporting: 100% SDV for all pts • AE reporting: 100% SDV or SDR for all pts • Primary endpoint(s): 100% SDV for all pts • Secondary endpoints: Trial specific • Drug accountability: 100% SDV for all pts • Key Safety Assessments: 100% SDV for all pts • Other trial data: 100% SDV for 1st pt enrolled at each site & 10% of pts thereafter ***Central Monitoring and site quality control*** • Frequency determined per trial	**Trial monitoring:** ***Onsite (SDV)*** • Some on-site monitoring required if trial incorporates an unlicensed product (per risk assessment may also be required for unlicensed indications and newly licenced products) level to be determined per trial ***Central Monitoring and site quality control*** • Request sent biannually • On-site monitoring visits triggered for non-compliant sites	**Trial monitoring:** ***Onsite (SDV)*** • Some on-site monitoring required if trial incorporates an unlicensed product (per risk assessment may also be required for unlicensed indications and newly licenced products) – level to be determined per trial ***Central Monitoring and site quality control*** • Request sent biannually • On-site monitoring visits triggered for non-compliant sites	**Trial monitoring:** ***Onsite (SDV)*** • Some on-site monitoring required if trial incorporates an unlicensed product (per risk assessment may also be required for unlicensed indications and newly licenced products) – level to be determined per trial ***Central Monitoring and site quality control*** • Request sent annually • On-site monitoring visits triggered for non-compliant sites
	Site closure: • On-site visit	**Site closure:** • Central collection & review of required docs	**Site closure:** • Central collection & review of required docs	**Site closure:** • Central collection & review of required docs