UKALL14 Monitoring Plan

Overview	
Phase of trial	Phase III
Overall outcome of risk assessment	Medium
IMP type(s)	Rituximab (Mabthera®), Pegaspargase (Oncaspar®), Nelarabine (Atriance®) and Palifermin (Kepivance®)

Version History			
Version number	Date	Summary of changes made	Changes made by
v4	18/10//2016	Clarification of triggers for on-site monitoring. Added further details of on-site monitoring activities to be performed during triggered visits. Note it was not deemed necessary to transfer monitoring plan to template v7 at this stage in the trial.	Krista Wills
v3	28/04/2015	Transfer to the new CTC Monitoring Plan Template Changes to frequency of document collection as agreed with CTC monitoring coordinator (some documents previously collected annually now collected on an *ad hoc* basis) Change to oversight of consent process Change to drug accountability process from per-drug to per-patient logs	Nadjet El-Mehidi
v2	02/12/2011	Transfer to the new CTC Monitoring Plan Template Removal of requirement for site self-assessment monitoring Introduction of site file QC checklists and collection of documents for central monitoring at UCL CTC	Simon Purnell
v1	05/01/2011	Initial version	Jo Gambell

Site Initiation			
	Trial specific plan	**MMR** *(See Appendix 1)*	**Rationale (if different)**
Format	On site visit or teleconference	On site visit, teleconference or investigator meeting	N/A
Occurs at what point?	Prior to activation		
Responsible person(s)	Trial Coordinator, Senior Trial Coordinator		

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. Where applicable checks have been undertaken at an on-site monitoring visit, it will not be necessary to repeat these centrally. Routine requests will be sent throughout the recruitment 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	Request sent annually. On-site monitoring visits triggered for non-compliant sites.	Request sent annually. On-site monitoring visits triggered for non-compliant sites.	N/A
Trigger for routine document requests	Requests will be sent to sites annually according to their month of activation. The first request will be sent to each site one year following their activation, and annually thereafter until site closure. Where site closure document requests are planned within 4 months of the central monitoring due date, this will replace the annual central monitoring request.		
Documents/ information collected at the time of routine requests	**Documents Collected:** • Site staff delegation log (unless site confirms no changes are necessary; delegation logs may also be collected on an *ad hoc* basis if UCL CTC become aware of a change of staff at the site) • Informed Consent Form Log (where details of the consent process have not been collected on the patient registration CRF)		
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/randomisation form • 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. • Drug Accountability Logs: patient specific logs and balance logs will be used and will be requested at the end of each cycle • Screening logs: will be requested as required, typically prior to TMG meetings and when annual reports are due (e.g. to REC or funder)		
Central monitoring duties delegated by UCL CTC to core laboratory	Minimal residual disease (MRD) reports are to be requested by, and sent directly from sites to, the core laboratory at the Royal Free Hospital. The core lab will provide UCL CTC with updates on any outstanding reports on request.		
Checks undertaken through central monitoring	***Trial Logs/Reports*** The site staff delegation log, screening log and informed consent form log will be checked for consistency and completeness.		

Checks undertaken through central monitoring cont.	***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.
	Informed Consent Details relating to the informed consent process will be collected on the registration form from implementation of registration form v5.0. Details relating to the informed consent process prior for patients registered prior to the implementation of registration form v5.0 will be recorded on the Informed Consent Log and are subject to review by CTC as part of patient eligibility.
	Drug Accountability Logs Copies of drug accountability logs must be returned to UCL CTC for all trial patients. Sites will be required to submit logs following completion of each phase of a patient's IMP treatment. At least 10% of the logs, (including one log for a patient on arm B2, one log for a patient on arm T2, and, at transplant sites, one log for a patient treated on either arm P1 or P2), will be monitored centrally to ensure completeness and correlation with data collected in the CRF. In addition, drug accountability records for Rituximab (Mabthera®), Pegylated asparaginase (Oncaspar®), Nelarabine (Atriance®) and Palifermin (Kepivance®) 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. (Where possible, this will be conducted by review of the stock accountability log).
	Data Management Data received at UCL CTC will be checked for legibility, completeness, accuracy and consistency, including checks for missing or unusual values. 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.
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 an IMP were not observed following an adverse reaction, evidence of an overdose having been administered), 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

On-site monitoring visits may be scheduled where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements. The following may also trigger an on-site monitoring visit):

- In response to TSC request
- Lower than expected number of SAEs reported (*to be assessed statistically periodically*)
- Poor quality, delays with or concerns regarding SAE reporting
- Poor CRF / query return rate or significant delays in submitting data or responding to queries
- Poor data quality
- Important incidents and/or breaches
- Significant site staff turnover (particularly for pivotal staff e.g. investigator, research nurse, trial coordinator, lead pharmacy staff)

Note the trial team will review the above factors regularly to determine whether an on-site visit is necessary; taking into account the nature and frequency of issues at each site.

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

Should an on-site monitoring visit be required in response to non-compliance, site request or other trigger, the patients for review will be selected on a site by site basis according to the risk identified (e.g. transplant patients at transplant centres). The following source data verification/ review (SDV/SDR) checks will be prioritised:

- Patient consent for all patients selected for review
- Patient eligibility for a proportion of patients selected for review
- SAE reporting (SDR for unreported SAEs) for all patients selected for review
- Transplant data where applicable

In addition, at least one patient per site visit will be selected for detailed review (SDV and/or SDR), to evaluate site compliance with other aspects of the protocol, GCP and confirm adequacy of source documentation.

The following will only be reviewed if there is an indication that there is an issue in these areas:

- Primary endpoints
- Secondary/other endpoints
- Drug accountability

The algorithm may be utilised in the selection of patients to review see section below.

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

Algorithms

Where data are to be reviewed for a specific percentage of patients, prior to each monitoring activity a programme for random number generation will provide details of the *n*th patient(s) to be reviewed. This will be cross checked with the master subject list (or other document which gives a chronological record of patients enrolled at site) to establish the trial number of the patient(s) to be reviewed.

The algorithm will be based on:

- Number of patients enrolled at site
- Percentage of patients required
- The number(s) generated in any previous algorithm requests

Review and Authorisation

Emma Lawrie		20 OCT 2016
Supporting Trial Coordinator	**Signature**	**Date**
Pip Patrick		20 October 2016
Senior Trial Coordinator	**Signature**	**Date**
Krista Wills		24 Oct 2016
Monitoring Coordinator	**Signature**	**Date**

Appendix 1 – Minimum Monitoring Requirements

Risk factor	Phase I	Phase II (single arm)	Phase II (randomised controlled)	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 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 • 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 • Primary endpoint(s): 100% SDV for all pts • Secondary endpoints: Trial specific • Drug accountability: 100% SDV for 1st pt enrolled at each site & 10% of pts thereafter • 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 • Primary endpoint(s): 100% SDV for 50% of pts • Secondary endpoints: Trial specific • Drug accountability: 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 – 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 • Primary endpoint(s): 100% SDV for all pts • Secondary endpoints: Trial specific • Drug accountability: 100% SDV for 1st pt enrolled at each site & 10% of pts thereafter • 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 • Primary endpoint(s): 100% SDV for 50% of pts • Secondary endpoints: Trial specific • Drug accountability: 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 – 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 – 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
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 • Primary endpoint(s): 100% SDV for all pts • Secondary endpoints: Trial specific • Drug accountability: 100% SDV for 1st pt enrolled at each site & 10% of pts thereafter • 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 – 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 – 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 – level to be determined per trial ***Central Monitoring and site quality control*** • Request sent annually • On-site monitoring visits triggered for non-compliant sites
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