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
V6	01/06/2023	Drug accountability review - only stock balance logs to be reviewed to ensure that all supplied drug has been accounted for at each site. Justification- trial in follow up and likely to end in 2023, monitoring focused on critical areas only. - Final central monitoring request timeline clarified; at the latest, prior to site closure. - Review process clarified, & locations via hyperlinks provided, to assist in documenting review. - The monitoring plan has not been updated to the current version of the CTC monitoring plan template due to the current status of the trial.	Krista Wills & Emma Lawrie
V5	16/11/2017	Update to include actions going forward for 'registration only' sub-study patients. Updated to reflect move of MRD core laboratory from the Royal Free Hospital to UCL Cancer Institute	Amy Douglas
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 N.B. where there are significant amendments to the protocol, re-training will be provided via teleconference and provision of written training materials.		
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. **New 'Registration only' sub-study:** With the release of protocol v11, B-cell patients can enter a 'registration only' sub-study, as recruitment to the B-cell randomisation is complete. The sub-study serves predominantly to address laboratory endpoints, supplemented by minimal outcome and survival data. Patients will be able to enter the sub-study and receive standard treatment as per their local clinician's choice. Any drugs given will be sourced from hospital stock and will not be regarded as IMPs. There is no requirement for safety reporting or drug accountability in 'registration only' sub-study patients.		
	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	The central monitoring requests for all sites will be combined and sent to all sites annually, 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: (balance logs will be collected and will be requested at the latest, prior to site closure. • Screening logs: will be requested as required, typically prior to TMG meetings and when annual reports are due (e.g. to REC or funder) • Document receipts for amended documents and other important communications
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 UCL Cancer Institute. 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. Central reviews of randomisation CRFs will also be performed.
	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. Central reviews of informed consent via registration CRFs will also be performed to ensure consent for sample collection.

	Drug Accountability Logs Stock balance records for Rituximab (Mabthera®), Pegylated asparaginase (Oncaspar®), Nelarabine (Atriance®) and Palifermin (Kepivance®) will be reviewed to confirm that supplied drug has been dispensed only to randomised trial patients and that the quantity of supplied drug dispensed/quarantined/destroyed can be reconciled with the quantity supplied to the site. Patient drug accountability logs will be reviewed only when issues noted with the stock balance log that cannot be reconciled. N.B. Accountability logs are not required for 'registration only' sub-study patients, who are receiving standard hospital stock treatment of their clinician's choice, and none of the drugs given are classed as IMPs.
	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. Site QC checklists are supplemented by the *ad hoc* collection of document receipts when amendments and other important trial-related communications are issued to sites.

Review process	**Stock balance logs Pegylated asparaginase** • Each entry has been completed in full. • IMP dispensed (include batch number) match those dispensed to the patients which were recruited to the site. • Only drug within its expiry date has been dispensed. • Confirm that all unused/expired drug has been recorded as destroyed/disposed of, with record of drug destruction certificates received if applicable. **Stock balance logs Rituximab** • Each entry has been completed in full. • IMP dispensed (include batch number) match those dispensed to the patients recruited to the site. • Only drug within its expiry date has been dispensed. • Confirm that all unused/expired drug has been recorded as destroyed/disposed of, with record of drug destruction certificates received if applicable. Rituximab destruction records per site is recorded here; S:\BNLI\Trials\Open\UKALL14\TMF\12 IMP\g Drug destruction records\Leftover rituximab destruction per site.xlsx **Stock balance logs Nelarabine** • Each entry has been completed in full. • IMP dispensed (include batch number) match those dispensed to the patient recruited to the site. • Only drug within its expiry date has been dispensed.	Primary: TC Secondary: /DM/STC

	• Confirm that all unused/expired drug has been recorded as destroyed/disposed of, with record of drug destruction certificates received if applicable. **Stock balance logs palifermin** • Each entry has been completed in full. • IMP dispensed (include batch number) match those dispensed to the patient recruited to the site. • Only drug within its expiry date has been dispensed. • Confirm that all unused/expired drug has been recorded as destroyed/disposed of, with record of drug destruction certificates received if applicable. For all logs, confirm completed pages have been signed by delegated pharmacy personnel. Accountability logs to be filed in the eTMF under the relevant site folder within the pharmacy section, for example S:\BNLI\Trials\Open\UKALL14\TMF\10 LOCAL SITES\b CTC sites files\Aberdeen Royal Infirmary\Pharmacy Paper logs to be held in the corresponding paper site file.	
Documents to be cross checked against accountability logs	In order to perform accountability review, ensure the logs are reviewed against the following; Patient list (copy located here; S:\BNLI\Trials\Open\UKALL14\TMF\12 IMP\d Supplies accountability) Destruction logs (located per site here; S:\BNLI\Trials\Open\UKALL14\TMF\12 IMP\g Drug destruction records) Delegation Logs	Primary: TC Secondary: DM/STC
Record of review	Follow up with the site for any queries or discrepancies noted until resolution. File all email correspondence in the TMF and track receipt and review. Where sites are using the UCL CTC template the 'For UCL CTC Use Only' section must be completed each time an accountability log is reviewed. Utilise docusign if performing remotely. Where sites are using their own in-house logs, the reviewer should use the 'UCL CTC use only' review label. The template can be found on the intranet associated with T13 Standard Operating Procedure for Monitoring and Oversight of Clinical Studies. Evidence of review will be recorded on the trial 'Centralised Monitoring' spreadsheet. This is located here; S:\BNLI\Trials\Open\UKALL14\TMF\01 TRIAL MANAGEMENT\cRA - MP\Monitoring\Central Monitoring\UKALL14 - Central monitoring tracking log.xls All correspondence regarding central review to be filed in the TMF/eTMF under the relevant site file.	Primary: TC Secondary: DMSTC
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	DocuSigned by: Emma Lawrie C97CF5B5063D48B...	09-Jun-2023
Trial Manager	**Signature**	**Date**
Charlotte Tyson	DocuSigned by: Charlotte Tyson 26C2DE649ADE473...	09-Jun-2023
Senior Project Manger	**Signature**	**Date**
Krista Wills	DocuSigned by: Krista Wills A3FCF43F9BD6446...	12-Jun-2023
Clinical Trials Operations Manager	**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 telecom	**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
	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

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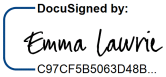
Emma Lawrie e.lawrie@ucl.ac.uk Trial Manager CRUK and UCL Cancer Trials Centre Security Level: Email, Account Authentication (None)	DocuSigned by:  C97CF5B5063D48B... Signature Adoption: Pre-selected Style Using IP Address: 128.40.163.112	Sent: 09 June 2023 | 08:49 Viewed: 09 June 2023 | 08:49 Signed: 09 June 2023 | 08:49
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Krista Wills k.wills@ucl.ac.uk Monitoring Coordinator CRUK and UCL Cancer Trials Centre Security Level: Email, Account Authentication (None)	DocuSigned by:  A3FCF43F9BD6446... Signature Adoption: Pre-selected Style Using IP Address: 128.40.163.112	Sent: 09 June 2023 | 08:49 Viewed: 12 June 2023 | 14:45 Signed: 12 June 2023 | 14:45
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In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	09 June 2023 | 08:49
Certified Delivered	Security Checked	12 June 2023 | 14:45
Signing Complete	Security Checked	12 June 2023 | 14:45
Completed	Security Checked	12 June 2023 | 14:45

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