## Southampton Clinical Trials Unit

**REMoDL-A**

REMoDL-A

# eCRF Completion Guidelines

IRAS: 266600

REC: 21/SC/0122

Protocol Number: 3

A Randomised Phase II Evaluation of Molecular Guided Therapy for Diffuse Large B-Cell Lymphoma with Acalabrutinib

| Version number | V1 |
|---|---|
| Effective Date | 06-Oct-21 |

| Role | Name | Signature | Date |
|---|---|---|---|
| **Author** | Robert Waugh | RJWaugh | 08-Sep-21 |
| **TM Approved** | Nicole Keyworth | E-mail approval | 15-Sep-21 |

For general enquiries or access issues relating to Medidata Rave, please contact a Southampton Clinical Trials Unit representative via email at: REMoDLA@soton.ac.uk or by telephone on 02381 205154.

For technical problems relating to Medidata Rave, please contact the Medidata help desk via email at: helpdesk@mdsol.com or by telephone on 0800 001 5212.

## Table of Contents

## 1. DOCUMENT HISTORY

| Version number | Effective date | Summary of changes | Author |
|---|---|---|---|
| V1 | 06-Oct-21 | New Document | Robert Waugh |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

## 2. GENERAL INSTRUCTIONS

Once logged on via www.imedidata.com using your unique username and password, you will be directed to the Rave EDC home page where you will have access to the REMoDL-A study once all pre-requisite e-learning has been completed.

### 2.1 Answering queries

You can respond to queries in two ways:

1.  Modify the data in the data entry field and click save. No additional response is required.



2.  Include an additional response in the user response field. Once an answer is entered click save.



> **Important Note: Please do not record <u>any</u> person's name or identifiable information in the eCRF pages, item comments or query responses, as it will be permanently stored in the audit trail. Please refer to the person's role or group if necessary, e.g. Research Nurse, Investigator, Clinical Study Manager etc.**

## 2.2 Icon Keys

1. Icon keys are available at site, subject, form and question level. A table of common icons is shown below.

2. Some Icons can be used to show the current status of an entry (e.g. the "Complete" icon) or show that corrective action is required on an entry (e.g. the "Query Open" icon), or to use as an "Action" button to make entries (e.g. the "Edit" icon).

Icon Key
CRF Version 66 - Page Generated: 17 Aug 2015 10:47:03 GMT Daylight Time

| | | | | | |
|---|---|---|---|---|---|
| 👥 | Site | ◯ | Never Touched | ⊙ | Incomplete |
| 🞂 | Studies | ✅ | Complete | 🗋 | Requires Verification |
| 🗋 | Study | 🖤 | Locked | 👁 | Requires Review |
| 👤 | Subject | ⊙ | Entry Lock | ❓ | Query Open |
| 👤 | Subject in doubt | ⚠ | Not Conformant | ⊙ | Answered Query |
| 📄 | Form | ⊘ | Inactive | 🟡 | Requires Coding |
| 🔍 | Site Group | ⊙ | Overdue | ✏ | Requires Signature |
| 🏠 | Home | 🟨 | Sticky Notes | ✚ | Out of Range High |
| ▭ | Comments | ▴ | Data Changed | ▬ | Out of Range Low |
| ✒ | Edit | 🗋 | Protocol Deviation | 🌐 | Requires Translation |
| ⧗ | Study Status Deferred | ⧗ | Site Status Deferred | 1 | Requires First Pass DDE |
| ▤ | Folder not available to the user | ▤ | Add Marking | 2 | Requires Second Pass DDE |
| ▱ | Task Summary Pop Up | ▭ | Folder | ⧉ | Requires Reconciliation DDE |
| 🌐 | Requires Coder Coding | | | | |

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**Important Note: Only some of these icon keys will be visible depending on your role.**

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## 2.3 Task Summary

After entering data it is a good idea to go into the "Task Summary" to see if any "Open Queries" can be resolved. The "Task Summary" can be accessed in two ways:

1. <u>Subject ID</u>   Click on an individual Subject ID to generate an individual "Task Summary".

| 🏠 | 🗋 Hatric | 👥 Emma Test Site | 👤 1111112 | |
|---|---|---|---|---|

Grid View

🗐 Primary Record

| Visit | Date | ▽ Task Summary: Subject | Pages |
|---|---|---|---|
| | | 🞂 ✏ Requiring Signature | 10 ▱ |
| | | 🞂 ⚠ NonConformant Data | 0 ▱ |
| | | 🞂 ❓ Open Queries | 6 ▱ |
| | | 🞂 🟨 Sticky Notes | 0 ▱ |

2. <u>Site Page</u> Click on the Site to generate a site "Task Summary".

| 🏠 | 🗋 Hatric | 👥 Emma Test Site | |
|---|---|---|---|

| Subject | | ▽ Task Summary: Site | Subjects |
|---|---|---|---|
| | 🔍 | 🞂 ✏ Requiring Signature | 4 ▱ |
| Advanced Search  ⊕ Add Subject | | 🞂 ⚠ NonConformant Data | 1 ▱ |
| Subject | | 🞂 ❓ Open Queries | 4 ▱ |
| 👤 1111111 | | 🞂 🟨 Sticky Notes | ▱ |

## 3. OVERVIEW OF TRIAL VISITS

3.1 Screening and Treatment Visits

```
┌──────────────┐
│  Screening   │
└──────────────┘
       ↓
┌──────────────┐
│   Baseline   │
└──────────────┘
       ↓
┌──────────────┐
│   Cycle 1    │
└──────────────┘
       ↓
┌──────────────┐
│Randomisation │
└──────────────┘
       ↓
┌──────────────┐
│   Cycle 2    │
└──────────────┘
       ↓
┌──────────────┐
│Interim PET scan│
└──────────────┘
       ↓
┌──────────────┐
│   Cycle 3    │
└──────────────┘
       ↓
┌──────────────┐
│   Cycle 4    │
└──────────────┘
       ↓
┌──────────────┐
│   Cycle 5    │
└──────────────┘
       ↓
┌──────────────┐
│   Cycle 6    │
└──────────────┘
       ↓
┌──────────────┐
│End Of Treatment│
└──────────────┘
```

## 3.2 Follow-Up Visits

Has the patient experienced disease progression?

Did the patient withdraw from trial follow-up? If Yes, did the patient consent to annual follow-up data collection?

No → Standard Follow-up

Yes → Survival Follow-up

No → End of Study

**Standard Follow-up branch (No):**

Standard Follow-up

↓

3 Month Follow-up

↓

6 Month Follow-up

↓

9 Month Follow-up

↓

12 Month Follow-up

↓

16 Month Follow-up

↓

20 Month Follow-up

↓

24 Month Follow-up

↓

Annual Survival Follow-up Until End of Study Criteria Is Met

**Survival Follow-up branch (Yes):**

Survival Follow-up

↓

Annual Survival Follow-up Until End of Study Criteria Is Met

**End of Study branch (No):**

End of Study

### 3.3 Unscheduled Visits

For any hospital visits not included in 3.1 Screening and Treatment Visits and 3.2 Follow-Up Visits, Unscheduled Visit folders should be completed, which can be added with the 'Add Event' drop down list on the subject home page.



## 4. REMoDL-A SPECIFIC FORMS

Not all forms available within the database have been explained here, only those which have specific data requirements, or a high likelihood of non-conformant data, have been explained below.

- At each visit, please ensure the Adverse Events form and Concomitant Medications forms in the AECM folder are updated as applicable.

- Adverse events that occur prior to the start of therapy, but following receiving consent, should be recorded on the Adverse Events form in the AECM folder only if related to trial procedures. Any other adverse events that occur prior to the start of therapy should be recorded on the Medical History form in the Baseline folder and listed as ongoing. Any adverse events that occur following the end of therapy should only be on the Adverse Events form if deemed related to IMPs.

- Dates should be entered in the format DD MMM YYYY unless specified otherwise. In the case of an unknown date, 'UN UNK 0001' can be entered for the date, month or year respectively. Unknown dates may only be entered for medical history start dates, concomitant medication start dates or expected delivery date on the Pregnancy Notification form.

- Help boxes are denoted by the [?] icon. These support data entry by indicating what data format certain data items should be in or they provide guidance on how to complete log lines where applicable. To view the help text, click on the [?] icon.

- When using a log table, new log lines can be added through the 'Add a new Log line' button at the bottom of the table.



- Log lines can be inactivated through the 'Inactivate' button at the bottom of the table, selecting the appropriate log line from the left-hand dropdown box and clicking the 'Inactivate' button.

| # | If 'Yes', continue below<br>2. Which test was performed? | 3. On what date was the test performed? | 4. If 'ECG', is the result abnormal? | 5. If 'ECG', is the result clinically significant? | 6. If ECHO or MUGA what was the LVEF? | 7. If ECHO or MUGA, what is the lower limit of the LVEF normal range? | 8. If ECHO or MUGA, is the LVEF result clinically significant? | |
|---|---|---|---|---|---|---|---|---|
| 1 | ... | ... | | | | | | |
| | Add a new Log line  Inactivate | | | | | | | |

| # | If 'Yes', continue below<br>2. Which test was performed? | 3. On what date was the test performed? | 4. If 'ECG', is the result abnormal? | 5. If 'ECG', is the result clinically significant? | 6. If ECHO or MUGA what was the LVEF? | 7. If ECHO or MUGA, what is the lower limit of the LVEF normal range? | 8. If ECHO or MUGA, is the LVEF result clinically significant? | |
|---|---|---|---|---|---|---|---|---|
| 1 | ... | ... | | | | | | |
| 2 | ... | ... | | | | | | |
| | 2  INACT_L - Log line not required  Inactivate  Cancel | | | | | | | |

- Inactivated log lines can then be reactivated through the 'Reactivate' button at the bottom of the table, selecting the appropriate log line from the left-hand dropdown box and clicking the 'Reactivate' button.

| # | If 'Yes', continue below<br>2. Which test was performed? | 3. On what date was the test performed? | 4. If 'ECG', is the result abnormal? | 5. If 'ECG', is the result clinically significant? | 6. If ECHO or MUGA what was the LVEF? | 7. If ECHO or MUGA, what is the lower limit of the LVEF normal range? | 8. If ECHO or MUGA, is the LVEF result clinically significant? | |
|---|---|---|---|---|---|---|---|---|
| 1 | ... | ... | | | | | | |
| 2 | | | | | | | | |
| | Add a new Log line  Inactivate  Reactivate | | | | | | | |

| # | If 'Yes', continue below<br>2. Which test was performed? | 3. On what date was the test performed? | 4. If 'ECG', is the result abnormal? | 5. If 'ECG', is the result clinically significant? | 6. If ECHO or MUGA what was the LVEF? | 7. If ECHO or MUGA, what is the lower limit of the LVEF normal range? | 8. If ECHO or MUGA, is the LVEF result clinically significant? | |
|---|---|---|---|---|---|---|---|---|
| 1 | ... | ... | | | | | | |
| 2 | | | | | | | | |
| | 2  ACT_L - Log line required  Reactivate  Cancel | | | | | | | |

- If a patient or their partner becomes pregnant whilst taking part in the trial or in the 12 months following the last dose of treatment, then the Pregnancy Report folder **must** be completed within 24 hours of your site becoming aware. This folder can be added with the 'Add Event' drop down list on the subject home page.

- Unscheduled Visit folders can be added with the 'Add Event' drop down list on the subject home page.

### 4.1 Primary Record Form

Please click on 'Add Subject', which will generate the Primary Record Form.



The subject initials should be entered in the format XXX or X-X, where there is no middle initial. All other combinations will cause a non-conformance query to fire.

Once 'save' has been clicked, a patient ID in a ten digit format will be generated. The first 3 letters represent the study, the next four numbers represent the site number and the last three numbers represent the unique subject identity number e.g. RMA-8778123, where RMA represents REMoDL-A, 8778 is the site number and 123 is the subject identity number.

### 4.2 Screening Folder

4.2.1 Subject Characteristics

If Q2. "What is the sex of the subject?" has been answered 'Female' then Q2.1 "Is the subject of childbearing potential?" **must** be answered. If Q2.1 is answered 'Yes' then the Pregnancy Test form will be available in the Screening, Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 5 Day 1, Cycle 6 Day 1, End of Treatment, 3 Month Follow Up, 6 Month Follow Up, 9 Month Follow Up and 12 Month Follow Up folders.

For Q3. "What is the subject's height?", the height in cm should entered in the format xx.x, xxx.x, xxx or xx.

4.2.2 Eligibility

For Q2. "What was the version of protocol used to assess the eligibility?", the version number should be entered in the format x, with no decimal places.

If Q3. "Were all eligibility criteria met?" has been answered 'Yes', then the Screening and Baseline folders will be populated with the forms required for completion prior to treatment, and the Cycle 1 and Randomisation folders will be available.

4.2.3 Disease Assessment Screening

For the log table (Q4-9), the lesion with the longest axis **must** be entered in log line 1.

If Q1. "In addition to the six largest measurable sites reported below, are there any other extranodal sites (including measurable and non-measurable)?" has been answered 'Yes' then the Additional Non-Target Extranodal Sites form in the Screening folder should be completed.

4.2.4 LB Chemistry Renal/Liver, LB Haematology and LB Immunoglobulins

Please note that "Is the result clinically significant?" should be completed for **all** laboratory assessments regardless of whether they are considered abnormal or not. All clinically significant results should be added to the Medical History form in the Baseline folder as currently ongoing.

On the LB Chemistry Renal/Liver form, Q11.5 and Q12.5 "What is the upper limit of normal?" should be answered with the applicable upper limit of normal value for your site according to the specific lab range values.

4.2.5 Cardiac Assessment

Any clinically significant findings should be added to the Medical History form in the Baseline folder as currently ongoing.

### 4.3 Baseline Folder

4.3.1 Physical Examination

Any abnormal findings should be added to the Medical History form in the Baseline folder as currently ongoing.

### 4.3.2 Vital Signs

For Q3. "Systolic Blood Pressure", Q4. "Diastolic Blood Pressure", Q5. "Heart Rate" and Q6. "Respiratory Rate", the data should be entered in the format xx or xxx.

For Q7. "Temperature" and Q8. "Weight", the data should be entered in the format xx, xxx, xx.x or xxx.x, in the units °C and kg, respectively.

### 4.3.3 LB Chemistry Additional

Please note that "Is the result clinically significant?" should be completed for **all** laboratory assessments regardless of whether they are considered abnormal or not. All clinically significant results should be added to the Medical History form in the Baseline folder as currently ongoing.

Q5.5 "What is the upper limit normal?" should be answered with the applicable upper limit of normal value for your site according to the specific lab range values.

### 4.3.4 Pre-Planned Radiotherapy

If Q1. "Do you plan to give radiotherapy at conclusion of the subject's 6 cycles of R-CHOP?" is answered with 'Yes', then the Consolidation form in the Protocol-specified Consolidation Therapy folder should be completed following trial treatment.

### 4.4 Cycle Folders

### 4.4.1 Date of Visit

If Q1. "Did the visit take place?" is answered with 'Yes', then the folder will populate with the forms required for completion for that visit. For Cycle 6, once Q1. has been answered the End of Treatment folder will be available.

### 4.4.2 Physical Examination

Any abnormal findings should be added to the Adverse Events form in the AECM folder.

### 4.4.3 Vital Signs

For Q3. "Systolic Blood Pressure", Q4. "Diastolic Blood Pressure", Q5. "Heart Rate" and Q6. "Respiratory Rate", the data should be entered in the format xx or xxx.

For Q7. "Temperature" and Q8. "Weight", the data should be entered in the format xx, xxx, xx.x or xxx.x, in the units °C and kg, respectively.

### 4.4.4 LB Chemistry, LB Haematology and LB Immunoglobulins

Please note that "Is the result clinically significant?" should be completed for **all** laboratory assessments regardless of whether they are considered abnormal or not. All clinically significant results should be added to the Adverse Events form in the AECM folder.

On the LB Chemistry Renal/Liver form, Q11.5 and Q12.5, and the LB Chemistry Additional form, Q5.5 "What is the upper limit of normal?" should be answered with the applicable upper limit of normal value for your site according to the specific lab range values.

### 4.4.5 Cardiac Assessment

Any clinically significant findings should be added to the Adverse Events form in the AECM folder.

### 4.4.6 R-CHOP

For Q2. "What was the Body Surface Area (BSA) used to calculate this dose of R-CHOP?", the data should be entered in the format x.xx.

If there was a dose delay for any of the individual components of R-CHOP, then the respective "How long was the delay?" question should be answered with the number of days between when that component of R-CHOP should have been administered and the day on which it was administered. For example, if R-CHOP treatment was due on 01-Jan-21, and all components, except Prednisolone, were administered on 08-Jan-21 and Prednisolone was administered on 09-Jan-21, then the length of the delay would be 7 days for all components, except Prednisolone, with the delay for Prednisolone being 8 days.

If Q8.1 "Was any intrathecal chemotherapy given?" is answered with 'Yes', then once the form is saved, a log table containing questions Q8.2-8.5 will be available and should be completed.

### 4.4.7 Acalabrutinib Diary

The Acalabrutinib Diary form should contain the details of the lost or spoiled capsules from that cycle, as well as the acalabrutinib dosage regime taken by the patient, as documented by the patient on the acalabrutinib patient diary.

If the A.M. dose was missed, then Q5. "Time Taken A.M." should be left blank, and Q7. "A.M. dose missed?" and its relevant counterparts should be completed. If the P.M. dose was missed, then Q6. "Time Taken P.M." should be left blank, and Q8. "P.M. dose missed?" and its relevant counterparts should be completed.

For Q5. "Time Taken A.M." and Q6. "Time Taken P.M.", the times should be entered in a 24-hour format.

If the P.M. dose is taken outside of the 11-13 hour post-A.M. dose time window, the automated query "PM dose is not between 11 and 13 hours after AM dose" will be added to Q6. "Time Taken P.M.". This query should be answered to confirm that this is correct.

If the P.M. dose is taken after midnight, Q6. "Time Taken P.M." should be completed on the same log line as the A.M. dose for that day. The automated query "Time of PM dose is not after time of AM dose" will be added to Q6., which should be answered to confirm that this was taken the following day.

If further log lines are required, the data should remain in chronological order.

Please note that there are multiple pages in the log table by default, which can be changed between using the numbers in the bottom right of the table. All log lines can be displayed on one page by changing the dropdown list, shown below, from 'Paginate' to 'Show All Lines'.



### 4.4.8 Acalabrutinib Compliance

The Acalabrutinib Compliance form should contain the details of the number of acalabrutinib tablets prescribed to and returned by the patient, as well as the dosage regime of acalabrutinib that should have been followed by the patient, as documented in the patient medical notes.

If there were no remaining capsules for the patient to return, Q2. "Did the subject return the remaining capsules at the end of this cycle?" should be answered with 'Yes' and Q2.1 "If Yes, how many capsules were returned?" should be answered with '0'.

For the log table (Q3-7.3), the whole cycle should be recorded without gaps in the dates or overlapping dates. Where the dose has been changed or the treatment withheld, this should be added onto a separate log line. Please see below for an example.



The log table (Q3-7.3) should detail the Acalabrutinib dosing schedule that was intended, and therefore should not include any missed doses, which should be detailed in the Acalabrutinib Diary form.

### 4.4.9 Subject Continuing

Following Cycle 1, once Q1. "Was the subject randomised?" on the Randomisation form in the Randomisation folder is answered with any response other than 'Not Randomised for other reason', then the Cycle 2 folder will be available. For Cycles 2-5, if Q1. "Is the subject continuing on treatment?" is answered with 'Yes', then the next visit folder will be available.

If Q1. "Is the subject continuing on treatment?" is answered with 'No', then no further visit folders will be visible, and the End of Treatment folder should be completed.

### 4.5 Randomisation Folder

If Q1. "Was the subject randomised?" is answered with any response other than 'Not Randomised for other reason', then the Cycle 2 folder will be available. If 'Not Randomised for other reason' is answered, then the End of Treatment folder should be completed.

### 4.6 End of Treatment Folder

4.6.1 Date of Visit

If Q1. "Did the visit take place?" is answered with 'Yes', then the folder will populate with the forms required for completion for that visit.

4.6.2 Vital Signs

For Q3. "Systolic Blood Pressure", Q4. "Diastolic Blood Pressure", Q5. "Heart Rate" and Q6. "Respiratory Rate", the data should be entered in the format xx or xxx.

For Q7. "Temperature" and Q8. "Weight", the data should be entered in the format xx, xxx, xx.x or xxx.x, in the units °C and kg, respectively.

4.6.3 LB Chemistry, LB Haematology and LB Immunoglobulins

Please note that "Is the result clinically significant?" should be completed for **all** laboratory assessments regardless of whether they are considered abnormal or not. All clinically significant results should be added to the Adverse Events form in the AECM folder.

4.6.4 Response Assessment

If Q3. "Overall Response" is answered with 'Progressive disease', then the Disease Progression/Recurrence form in the Disease Prog/Recur folder should be completed.

If Q3. "Overall Response" is **not** answered with 'Complete response', then the Biopsy form will be available in the End of Treatment folder. Please note that whilst it is not mandatory to conduct a biopsy to confirm residual disease following a scan, if a biopsy was conducted, then the result should be recorded in the Biopsy form.

4.6.5 Physical Examination

Any abnormal findings should be added to the Adverse Events form in the AECM folder.

4.6.6 End of Treatment

If Q3. "What is the primary reason for ending treatment?" is answered with 'Progression', then the Disease Progression/Recurrence and New/Progressed Lesion Assessment forms in the Disease Prog/Recur folder should be completed.

If Q4. "Is the subject going to receive IV CNS Prophylaxis?" is answered with 'Yes', Q5. "Is the subject going to receive consolidative Rituximab (up to 2 doses only)?" is answered with 'Yes', or Q6. "Is the subject going to receive consolidative radiotherapy?" is answered with 'Yes – Consolidative Pre-planned' or 'Yes, Consolidative Not Pre-planned' then the Consolidation form in the Protocol-specified Consolidation Therapy folder should be completed.

If Q7. "Is the subject going to receive any additional anti-lymphoma therapy?" is answered with 'Yes', then the Additional Anti-Lymphoma Therapy folder should be completed.

If it is indicated that the patient has had disease progression and is continuing in follow-up, then Q8. "Is subject continuing in follow-up?" should be answered with 'Yes – Annual Survival Follow-up'.

If Q8. "Is subject continuing in follow-up?" is answered with 'Yes – Standard Follow-up', then the 3 Month Follow Up folder will be available. If Q8. is answered with 'Yes – Annual Survival Follow-up', then the Annual Survival Follow-up 1 folder will be available. If Q8. is answered with 'No', then the End of Study folder should be completed. Please note, 'No' should only be answered where patients have withdrawn consent for collection of any follow-up data.

### 4.7 Follow-up Folders

4.7.1 Date of Visit FU

If Q1. "Did the visit take place?" is answered with 'Yes', then the folder will populate with the forms required for completion for that visit.

4.7.2 Physical Examination

Any abnormal findings should be added to the Adverse Events form in the AECM folder.

4.7.3 Response Assessment

A contrast enhanced CT scan should be conducted at the 12 and 24 month follow-up visits; therefore, Q2.2. "Response Assessment by PET:" and Q2.3. "Response Assessment by PET Deauville Score:" should be answered with 'Not Done', and Q2.2.1. "If 'Not Done/Not Available', give reason" and Q2.3.1. "If 'Not Done/Not Available', give reason" should be answered with 'Not Required'.

If Q3. "Overall Response" is answered with 'Progressive disease', then the Disease Progression/Recurrence and New/Progressed Lesion Assessment forms in the Disease Prog/Recur folder should be completed.

If Q3. "Overall Response" is **not** answered with 'Complete response', then the Biopsy form will be available in the same folder as the Response Assessment form. Please note that whilst it is not mandatory to conduct a biopsy to confirm residual disease following a scan, if a biopsy was conducted, then the result should be recorded in the Biopsy form.

4.7.4 LB Chemistry, LB Haematology and LB Immunoglobulins

Please note that "Is the result clinically significant?" should be completed for **all** laboratory assessments regardless of whether they are considered abnormal or not. Clinically significant results related to IMPs **only** should be added to the Adverse Events form in the AECM folder.

4.7.5 Further Treatment

If Q1. "Has the subject received any additional anti-lymphoma therapy since last visit?" is answered with 'Yes', then the Additional Anti-Lymphoma Therapy folder should be completed.

### 4.7.6 Disease Status

If Q1. "Has the subject had disease progression or recurrence since the last visit?" is answered with 'Yes', then the Disease Progression/Recurrence and New/Progressed Lesion Assessment forms in the Disease Prog/Recur folder should be completed.

If a scan has been carried out to confirm disease progression, other than at the 12 and 24 month follow-up visits, an Unscheduled visit should be added, and the Disease Assessment and Response Assessment forms completed.

### 4.7.7 Continuing Follow-up

If Q1. "Is subject continuing in follow-up?" is answered with 'Yes – Standard Follow-up', then the next standard follow-up folder will be available. If Q1. is answered with 'Yes – Annual Survival Follow-up', then the Annual Survival Follow-up 1 folder will be available. If Q1. is answered with 'No', then the End of Study folder should be completed.

### 4.7.8 Continuing Annual Survival Follow-up (only available in the 24-month Follow-Up folder)

If Q1. "Is subject continuing in Annual Survival Follow-up?" is answered with 'Yes', then the Annual Survival Follow-up 1 folder will be available. If Q1. is answered with 'No', then the End of Study folder should be completed.

## 4.8 Protocol-specified Consolidation Therapy Folder

### 4.8 Consolidation

If any of the questions are answered with 'Yes', then the corresponding form in the Protocol-specified Consolidation Therapy folder should be completed.

## 4.9 Annual Survival Follow-up Folders

If progression has previously been recorded, in the Disease Progression/Recurrence form in the Disease Prog/Recur folder, then Q3. "Has the subject had disease recurrence or progression from trial treatment induction since last visit?" should be answered with 'No'.

If Q3. "Has the subject had disease recurrence or progression from trial treatment induction since last visit?" has been answered with 'Yes' and no previous progression has been recorded, then the Disease Progression/Recurrence form in the Disease Prog/Recur folder should be completed.

If Q4. "Has the subject received any additional anti-lymphoma therapy since the last visit?" has been answered with 'Yes', then the Additional Anti-Lymphoma Therapy folder should be completed.

If Q2. "Is the subject alive?" is answered with 'Yes' and Q6. "Is the subject continuing in Annual Survival Follow-up?" is answered with 'Yes', then the next annual survival follow-up folder will be available. If Q2. or Q6. are answered with 'No', then the End of Study folder should be completed.

### 4.10 Disease Prog/Recur Folder

4.10.1 New/Progressed Lesion Assessment

If Q1. "Does the subject have a new lesion or a progressed pre-existing non-target lesion that meets the progression criteria?" is answered with 'Yes' and Q2. "Please confirm if this a new lesion or a progressed pre-existing non-target lesion" is answered with 'Progressed Pre-existing Non-Target Lesion', then the Progressed Non-Target Lesions Baseline form in the Disease Prog/Recur folder should be completed.

4.10.2 Progressed Non-Target Lesions Baseline

Baseline measurements should be provided, where possible, for non-target lesions that were **not** one of the six target lesions recorded at baseline.

For Q5.1 "Please provide longest axis for this site" and Q5.2 "Please provide shortest axis for this site", the Baseline measurements for the progressed pre-existing non-target lesions should be provided.

### 4.11 Unscheduled Visit Folder

4.11.1 Unscheduled Visit

If "Consolidation Therapy" is answered with 'Yes', then the Consolidation form in the Protocol-specified Consolidation Therapy folder should be completed.

If "Additional Anti-lymphoma Therapy?" is answered with 'Yes', then the Additional Anti-lymphoma Therapy form in the Additional Anti-lymphoma Therapy folder should be completed.

If any other question is answered with 'Yes', then the relevant form with be available in the same folder as the Unscheduled Visit form.

## 4.11.2 Physical Examination

Any abnormal findings should either be added to the Medical History form in the Baseline folder (if the unscheduled visit was conducted prior to treatment, but following receiving consent); to the Adverse Events form in the AECM folder (if the unscheduled visit was conducted following the start of cycle 1 and up to the end of treatment); or to the Adverse Events form in the AECM folder (if the unscheduled visit was conducted following end of treatment, but **only** if the adverse event is deemed related to IMPs).

## 4.11.3 Vital Signs

For Q3. "Systolic Blood Pressure", Q4. "Diastolic Blood Pressure", Q5. "Heart Rate" and Q6. "Respiratory Rate", the data should be entered in the format xx or xxx.

For Q7. "Temperature" and Q8. "Weight", the data should be entered in the format xx, xxx, xx.x or xxx.x, in the units °C and kg, respectively.

## 4.11.4 Response Assessment

If Q3. "Overall Response" is answered with 'Progressive disease', then the Disease Progression/Recurrence and New/Progressed Lesion Assessment forms in the Disease Prog/Recur folder should be completed.

If Q3. "Overall Response" is **not** answered with 'Complete response' and a non-mandatory biopsy was conducted to confirm residual disease following a scan then the result should be recorded in the Biopsy form, which can be added via the Unscheduled Visit form in the same folder.

## 4.11.5 LB Chemistry, LB Haematology and LB Immunoglobulins

Please note that "Is the result clinically significant?" should be completed for **all** laboratory assessments regardless of whether they are considered abnormal or not. All clinically significant results should either be added to the Medical History form in the Baseline folder (if the Unscheduled Visit was conducted prior to treatment, but following receiving consent);

to the Adverse Events form in the AECM folder (if the Unscheduled Visit was conducted following the start of Cycle 1 and up to the end of treatment); or to the Adverse Events form in the AECM folder (if the Unscheduled Visit was conducted following end of treatment, but **only** if the AE is deemed related to IMPs).

Q5.5 "What is the upper limit normal?" should be answered with the applicable upper limit of normal value for your site according to the specific lab range values.

### 4.11.6 Cardiac Assessment

Any clinically significant findings should either be added to the Medical History form in the Baseline folder (if the unscheduled visit was conducted prior to treatment, but following receiving consent); to the Adverse Events form in the AECM folder (if the unscheduled visit was conducted following the start of cycle 1 and up to the end of treatment); or to the Adverse Events form in the AECM folder (if the unscheduled visit was conducted following end of treatment, but **only** if the adverse event is deemed related to IMPs).

## 4.12 AECM

### 4.12.1 Adverse Events

If the adverse event is serious and therefore Q5. "Is the adverse event serious?" is answered with 'Yes', then the SCTU **must** be contacted within 24 hours of your site being made aware of the SAE by emailing (ctu@soton.ac.uk) or faxing (0844 774 0621) a copy of the SAE form to SCTU.

Each time there is change in grade of an adverse event, this should be recorded on a separate log line ensuring that Q10. "What was the outcome of this adverse event?" is answered with '2 = Resolved with sequelae' or '4 = Worsening' if the adverse event decreases or increases in grade, respectively, and there are no gaps in the dates or overlapping dates.

For patients exposed to acalabrutinib, ventricular arrhythmias (e.g. ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, etc.) are AEs of special interest, which **must** be reported within 7 days by answering Q11. "Is this an AE of special interest (as per protocol)?" with 'Yes'.

### 4.12.2 Concomitant Medications form

If there were more than two indications for one concomitant medication, the additional indication should be entered on an individual log line.

For Q3.2, "If taken for an adverse event or medical history condition please enter the corresponding Adverse event log number of Medical history number", each number should be proceeded with AE or MH, depending on the indication type, e.g. MH01. Where two indications have been added, Q3.2 should be answered in the format 'AE01, MH02', where the order of the numbers match the order of the indications for that log line.

For Q5. "Generic Name of Medicine", if the concomitant medication is a combination drug/therapy then each drug/therapy should be entered on an individual log line.

For Q8. "What was the individual dose of the medication/therapy?", the dose of combination drugs should be entered in the format xx/xx and for topical formulations the dose entered should be the number of applications per administration.

## 4.13 EOS

If the end of study is caused by death or withdrawal, Q1. "What was the date of end of study?" should be answered with the date of death or withdrawal, respectively.

## 5. eCRF SIGN-OFF

Once all required data has been entered and cleaned for a subject, the eCRF is ready for sign-off. SCTU will advise when this should take place and provide instructions at the same time.

## 6. DATA ENTRY GUIDELINES

The following table contains guidance on entering data that will be coded, such as adverse event descriptions. This will help to reduce queries raised during the coding process. It will also contain any data entry guidelines created in response to future protocol amendments or data input issues identified on the eCRF.

| Guidance on data entered by sites that will be coded – Adverse Events, Concomitant Medications, Medical History, End of Study forms | | |
|---|---|---|
| **Coding Guidance** | **Issue** | **Example (if applicable)** |
| A | Input a medical term | 'Study disease area' whilst is obvious in context it is not a medical term. |
| B | Avoid using '/' as the terms used will often not be considered synonymous in the coding dictionary | 'Shivering/shaking' is two terms |
| C | Only enter a single term | Fever and chills are two different medical concepts so cannot be coded as one individual event |
| D | Avoid 'describing' an event | 'Patient attended visit with a runny nose, cough, aching limbs and sore throat.' This contains four different medical events and each should be entered separately |
| E | Avoid uncommon acronyms or acronyms that could mean different things in different contexts | 'PE' for pulmonary embolism or pleural effusion, or pre-eclampsia for example |
| F | Surgery in medical history can contain two separate events | 'Surgery on foot due to broken foot' contains two events, 'Broken foot' and 'Foot surgery' |
| G | Queries raised by the coder are an open dialogue and sites should respond accordingly | 'Would >>TERM<< accurately reflect the Medical History as entered in this field?' – sites can respond to this with 'no' and/or provide further information that may help with |

| | | | |
|---|---|---|---|
| | | | finding an appropriate medical term. Clinician decision should be sought |
| H | Clarify any potentially ambiguous term | | 'Canal stenosis' could be 'ear canal' or 'spinal canal'. 'Cold' could refer to a common cold or feeling cold |
| I | Ensure drug-related reactions are stated explicitly | | 'Patient took paracetamol and developed a headache' does not confirm that this was a 'drug-induced headache' |

| Data Entry Guidelines (*to be added if and when required*) | | | | |
|---|---|---|---|---|
| **Number** | **Form** | **Issue** | **Resolution** | **Effective Date** |
| | | | | |