CORRELATIVE SCIENCE PROCEDURE MANUAL

1. Purpose

This document describes the procedures required for the collection, shipping, and processing of biospecimens from all patients enrolled or registered on A041702. This document also describes the procedures that will be followed subsequent to the receipt of biospecimens by the Alliance Hematologic Biorepository (HEME) prior to their use for protocol-specified and future, unspecified correlative science research studies. This document should be used by staff involved with any aspect of the A041702 biospecimen collection, processing, and submission, including staff at satellite institutions.

2. Scope

This document applies to all biospecimens collected specifically for A041702 only. Please refer to the trial protocol-specific language for additional details regarding eligibility, participant enrollment, data submission, and specific procurement procedures. **Please ensure that you are reading the most updated version of this document. This document may experience minor updates, revisions, and clarifications independent of a formal protocol amendment. The most recent version of this document may be found on the Alliance website and CTSU.**

3. Definitions

Term	Definition
HEME	Alliance Hematologic Biorepository

4. Contact Information

4.1 For questions and problems related to protocol administration, eligibility, patient registration, and data submission, relevant contact information is listed on protocol pages 1 and 2.

4.2 For information on using the BioMS system, please refer to the 'Help' links on the BioMS webpage to access the online user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: 1-855-55-BIOMS or bioms@alliancenctn.org. For assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS or bioms@alliancenctn.org.

4.3 For all other questions regarding biospecimen procurement and shipping procedures, please contact the Alliance Biorepository Program Manager: 1-314-747-4402 or alliance@email.wustl.edu.

5. Site Preparation

5.1 Please refer to A041702 protocol document for any specific requirements related to patient enrollment, registration, and regulatory compliance.

5.2 Please ensure that you have appropriate log on credentials and can successfully access the BioMS application. The BioMS application is used for logging the collection and shipment of biospecimens to HEME. For training and assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS or bioms@alliancenctn.org.

6. Collection Schema

The following biospecimens are to be collected at each of the time points. Please refer to biospecimen collection and processing methods and specific shipping procedures below.

Time Point	Biospecimen	Kit	Quantity	Form Required	Collection / Processing Method	Shipping	Notes
Mandatory for <u>all</u> patients registered to A041702							
Prior to Registration	Bone Marrow Aspirate (EDTA / lavender top)	N	10 ml	N	Bone Marrow Aspirate- EDTA (9.1)	Ambient	1
Prior to Registration	Peripheral Blood (Acid Citrate Dextrose / ACD-A)	N	40 ml	N	Peripheral Blood – ACD-A (10.1)	Ambient	1
Prior to Registration	Peripheral Blood (Sodium Heparin)	N	5 ml	Y	Peripheral Blood- Sodium Heparin (10.2)	Ambient	1, 2
Prior to Registration	Buccal Cell Sample (Sterile Conical – provided by HEME upon request)	Y	1 sample	N	Buccal Cell Sample (11.1)	Ambient	1
Day 1, Cycle 15	Bone Marrow Aspirate (EDTA / lavender top)	N	10 ml	Y	Bone Marrow Aspirate- EDTA (9.1)	Ambient	1, 3, 4, 7
Day 1, Cycle 15	Peripheral Blood (Acid Citrate Dextrose / ACD-A)	N	40 ml	N	Peripheral Blood – ACD-A (10.1)	Ambient	1, 3, 7
Day 1, Cycle 15	Peripheral Blood (Sodium Heparin)	N	5 ml	Y	Peripheral Blood- Sodium Heparin (10.2)	Ambient	1, 3, 7
Day 1 q 6 Cycles Beginning C22 until 6 Years from Registration (Step 1), then q 12 Cycles	Peripheral Blood (Acid Citrate Dextrose / ACD-A)	N	40 ml	N	Peripheral Blood – ACD-A (10.1)	Ambient	1, 5
Day 1 q 6 Cycles Beginning C22 until 6 Years from Registration (Step 1), then q 12 Cycles	Peripheral Blood (Sodium Heparin)	N	5 ml	N	Peripheral Blood- Sodium Heparin (10.2)	Ambient	1, 5
Discontinuation of Treatment	Bone Marrow Aspirate (EDTA / lavender top)	N	10 ml	Y	Bone Marrow Aspirate- EDTA (9.1)	Ambient	1, 6, 7

Discontinuation of Treatment	Peripheral Blood (Acid Citrate Dextrose / ACD-A)	N	40 ml	N	Peripheral Blood – ACD-A (10.1)	Ambient	1, 6, 7
Discontinuation of Treatment	Peripheral Blood (Sodium Heparin)	N	5 ml	N	Peripheral Blood- Sodium Heparin (10.2)	Ambient	1, 6, 7
Relapse / Progression	Peripheral Blood (Acid Citrate Dextrose / ACD-A)	N	40 ml	N	Peripheral Blood – ACD-A (10.1)	Ambient	1, 8
Relapse / Progression	Peripheral Blood (Sodium Heparin)	N	5 ml	N	Peripheral Blood- Sodium Heparin (10.2)	Ambient	1, 8

Notes:

1. Submission is mandatory for **all** patients registered to A041702.
2. Peripheral whole blood for central FISH testing is required for all patients at the pre-registration assessment and within 36 business days prior to registration. Blood should be submitted as soon as possible after pre-registration so that FISH can be performed centrally. The Central FISH Review Form must be submitted along with the peripheral blood. Failure to submit this form with the specimen may delay turnaround time for central review. The Central FISH Review Form can be located on the A041702 protocol-specific page on the CTSU and the Alliance websites.
3. For patients who have completed 14 cycles of treatment, bone marrow and peripheral blood may be submitted +/- 7 business days from Cycle 15 Day 1.
4. MRD assessment will be performed, and the specimen MUST be submitted no later than 7 business days after Day 1 of Cycle 15 to allow for re-registration by Cycle 15 Day 21 and for agent ordering and provision by CTEP. See sections 10.1 and 4.6 of study protocol for more information.
5. Submit +/- 7 business days.
6. For patients who have discontinued treatment during Cycles 1-14 for reasons other than clinical disease progression to CLL, 1, blood and bone marrow must be submitted within +/- 14 business days of discontinuation of therapy.
7. At Cycle 15 Day 1 (+/- 7 days) and/or discontinuation of treatment, the Central Bone Marrow and Peripheral Blood MRD Form must be submitted along with the bone marrow aspirate and peripheral blood to HEME. Failure to submit this form with the specimens may delay turnaround time for central review. The Central Bone Marrow and Peripheral Blood MRD Form can be located in **Appendix 1** of this manual and on the A041702 protocol-specific page on the CTSU and Alliance websites. Patient DOB and Gender must be included on form for MRD analysis.
8. The relapse/progression specimen is not required if the discontinuation of therapy specimen submissions were submitted within the previous 2 months.

7. Biospecimen Collection Kits

7.1 Blood and Bone Marrow Specimens

7.1.1 There is no independent "kit" for submission of peripheral blood or bone marrow aspirates. Sites are responsible for acquiring materials for collection and shipping of these specimens.

7.1.2 Please see **Section 12 – Biospecimen Shipping** for specific instructions on shipping to HEME.

7.2 Buccal Cell Samples

7.2.1 To facilitate the proper collection and shipping of buccal cell samples, biospecimen collection kits and materials will be provided. The cost of the kit and shipping the kit to the site will be paid for. The institution is expected to pay for shipping the kit with the specimen back to HEME via **FedEx priority overnight shipping.**

7.2.2 Kits should be requested at least 10 working days in advance of the anticipated collection date. All kits must be requested by using the BioMS system.

7.2.3 In the event that a buccal cell sample needs to be collected and a sample kit is not available on site, instructions for collection using site-supplied materials are found in **section 11.1.**

7.2.4 Buccal collection sample can be collected and shipped to HEME after Prior to Registration.

8. Biospecimen Labeling and Tracking

8.1 All research biospecimens (vacutainer tubes, buccal cell samples) MUST be labeled with the protocol number (A041702), Alliance patient number, patient initials (Last, First, Middle), the date and time (if applicable) of collection and specimen type (e.g. bone marrow, peripheral blood, buccal).

8.2 Label all containers and vials with an indelible, solvent-resistant marker when they are at ambient temperature.

8.3 Do not affix any labels to vials or tubes. Label the collection containers directly with the marking pen.

8.4 All biospecimens that are collected and sent to HEME must be **logged and tracked in BioMS**. The BioMS system is a web-based application that tracks the collection and shipping of biospecimens. Once individual biospecimens are logged and 'shipped' in the BioMS system, a packing manifest will be created by the system. This manifest must be printed out and must accompany all biospecimen shipments. To become familiar with the BioMS system and for further information about training, access, and use, please contact the BioMS Help desk at: 1-855-55-BIOMS or bioms@alliancenctn.org.

8.5 In the event that BioMS cannot be accessed, please complete a BioMS Specimen Log and Shipping Manifest form which can be found here- **http://tinyurl.com/alliance-bioms-contingency**.

9. Bone Marrow Collection

9.1 Aspirate- EDTA tube

9.1.1 Collect 10 ml of bone marrow following standard institutional protocol into a EDTA tube. Invert tube 10 times.

9.1.2 Store EDTA tube with bone marrow at ambient temperature. Do not freeze or refrigerate the tube. The tube must be shipped on the same day it is collected and must be received at HEME within 24 hours of collection. **Saturday, Sunday, or holiday collections are NOT permitted.** Ensure that the EDTA tube is shipped at ambient temperature to avoid freezing.

9.1.3 At Cycle 15 Day 1 (+/- 7 days) and/or discontinuation of treatment, the Central Bone Marrow and Peripheral Blood MRD Form must be submitted along with the bone marrow aspirate to HEME. The form may also be emailed to AllianceLTB@osumc.edu. Failure to submit this form with the specimen may delay turnaround time for central review. The Central Bone Marrow and Peripheral Blood MRD Form can be located in Appendix 1 of this manual or on the A041702 protocol-specific page on the CTSU and Alliance websites.

9.1.3.1 Patient demographics (date of birth and gender) must be included on the Central Bone Marrow and Peripheral Blood MRD Form. If omitted, result turnaround time will be increased as the information needs verified by HEME.

10. Blood Collection

10.1 Peripheral blood (ACD-A Tubes—no processing)

10.1.1 Collect 40 ml of peripheral blood by standard venous phlebotomy technique into ACD-A tubes. Invert tubes 10 times.

10.1.2 Store ACD-A tubes with peripheral blood at ambient temperature. Do not freeze or refrigerate the tubes. The tubes must be shipped on the same day they are collected and must be received at HEME within 24 hours of collection. **Saturday, Sunday, or holiday collections are NOT permitted.** Ensure that the ACD-A tubes are shipped at ambient temperature to avoid freezing.

10.1.3 At Cycle 15 Day 1 (+/- 7 days) and/or discontinuation of treatment, the Central Bone Marrow and Peripheral Blood MRD Form must be submitted along with the peripheral blood to HEME. The form may also be emailed to AllianceLTB@osumc.edu. Failure to submit this form with the specimen may delay turnaround time for central review. The Central Bone Marrow and Peripheral Blood MRD Form can be located in Appendix 1 of this manual or on the A041702 protocol-specific page on the CTSU and Alliance websites.

10.1.3.1 Patient demographics (date of birth and gender) must be included on the Central Bone Marrow and Peripheral Blood MRD Form. If omitted, result turnaround time will be increased as the information needs verified by HEME.

10.2 Peripheral blood (Sodium Heparin Tube—no processing)

10.2.1 Collect 5 ml of peripheral blood by standard venous phlebotomy technique into a sodium heparin tube. Invert tube 10 times.

10.2.2 Store sodium heparin tube with peripheral blood at ambient temperature. Do not freeze or refrigerate the tube. The tube must be shipped on the same day it is collected and must be received at HEME within 24 hours of collection. **Saturday, Sunday, or holiday collections are NOT permitted.** Ensure that the sodium heparin tube is shipped at ambient temperature to avoid freezing.

10.2.3 Prior to registration: The heparin tube must be submitted as soon as possible after pre-registration so that FISH can be performed centrally. The Central FISH Review Form must be submitted along with the peripheral blood to HEME and should also be emailed to Cecelia Miller at cecelia.miller@osumc.edu. Failure to submit this form with the specimen may delay turnaround time for central review. The Central FISH Review Form can be located on the A041702 protocol-specific page on the CTSU and the Alliance websites.

10.2.4 At Cycle 15 Day 1 (+/- 7 days) and/or discontinuation of treatment, the Central Bone Marrow and Peripheral Blood MRD Form must be submitted along with the peripheral blood to HEME. The form may also be emailed to AllianceLTB@osumc.edu. Failure to submit this form with the specimen may delay turnaround time for central review. The Central Bone Marrow and Peripheral Blood MRD Form can be located in Appendix 1 of this manual or on the A041702 protocol-specific page on the CTSU and Alliance websites.

10.2.4.1 Patient demographics (date of birth and gender) must be included on the Central Bone Marrow and Peripheral Blood MRD Form. If omitted, result turnaround time will be increased as the information needs verified by HEME.

11. Buccal Cell Sample Collection

11.1 The buccal cell sample should be collected prior to the initiation of treatment.

11.1.1 Buccal cell sample can be collected and shipped to HEME after Prior to Registration.

11.2 The buccal cell sample must be collected before brushing teeth or at least 2 hours after brushing teeth, eating or drinking. The specimen collection tube should be stored at room temperature until ready for use.

11.3 In the event that you need to collect a sample but do not have a biospecimen collection kit, instruct patient to rinse their mouth with 10 ml of mouthwash (e.g. Scope or similar) for 30 to 60 seconds and then spit the mouthwash back into a sterile 50 ml tube.

11.4 Securely tighten the cap on the tube and label the tube as instructed in **section 8**. Place the tube in a biohazard bag and seal.

11.5 Store buccal cell sample at room temperature if shipping immediately or in the refrigerator (4 degrees Celsius) if planning to ship the next day. Do not freeze the sample. The sample must be shipped on the same day it is collected or on the day following collection. **Collection on Saturdays or on the day before holidays is NOT permitted.** Ensure that the sample is shipped at ambient temperature to avoid freezing.

12. Biospecimen Shipping

12.1 Overview

12.1.1 Peripheral blood and bone marrow aspirate specimens should be packaged to avoid breakage in a padded envelope or preferably a Styrofoam cooler. In warm weather months, a cold gel pack should be included to regulate temperature.

12.1.2 Buccal cell samples should be enclosed within a sealed biohazard bag and returned within the biospecimen collection kit.

12.1.3 Place the original, completed copy of the BioMS packing manifest in the shipment. Do not send specimens without a completed BioMS Packing Manifest or substitute "BioMS Downtime Form." Biospecimens cannot be accepted without this completed form.

12.1.4 The Central Bone Marrow and Peripheral Blood MRD Form must be submitted along with the bone marrow aspirate and peripheral blood specimens at the timepoints indicated in the collection schema (section 6) and in section 10. This form can be located in Appendix 1 of this manual or is available for download on the A041702 protocol-specific page on CTSU and on the Alliance website.

12.1.5 For sodium heparin specimens collected at pre-registration, the Central FISH Review Form must be submitted. A copy of the Central FISH Review Form must also be electronically submitted to Cecelia Miller, cecelia.miller@osumc.edu. This form is available for download on the A041702 protocol-specific page on CTSU and on the Alliance website.

12.1.6 Specimens should be sent according to IATA guidelines. All biospecimens should be shipped on the same day that they are collected (Monday – Friday). Biospecimens must be received by the recipient lab within 24 hours of collection. If collected biospecimens cannot be shipped on the same day that they are collected (e.g. Saturday, Sunday or holiday collections), please contact the Alliance Biorepository Program Manager: 1-314-747-4402 or alliance@email.wustl.edu for further instructions, **at least** 24 hours prior to anticipated collection.

12.1.7 Do not ship on Saturday, Sunday or on the day before a nationally recognized holiday.

12.1.8 All specimens should be shipped via priority overnight shipping.

12.1.9 Shipping to HEME

Ship container for PRIORITY OVERNIGHT DELIVERY according to IATA guidelines and standard institutional policies and using the preferred vendor.
Ship to:
Alliance Hematologic Malignancy Biorepository (HEME)
The Arthur G. James Cancer Hospital and Solove Research Institute
300 West Tenth Avenue, Lobby
Columbus, OH 43210
Phone: 614-366-6295
Fax: 614-688-4755

13. Biospecimen Receipt and Quality Assurance Measures

13.1 Upon receipt, all physical biospecimens received will be reconciled with what is recorded on the BioMS packing manifest. Any discrepancies noted will be communicated to the Program Manager who will contact the submitting site for reconciliation.

13.2 Upon receipt, any biospecimen received that is not in appropriate physical condition (broken vials, frozen samples that are thawed, ambient samples that are frozen) will be reported to the Program Manager, who will contact the submitting site for reconciliation.

13.3 Aliquoted biofluids will be stored under liquid nitrogen vapor.

13.4 All biospecimens will remain in storage until additional processing or review is requested in writing by the appropriate protocol PI.

14. Document History

Version	Description and Justification of Change	Author	Effective Date
4.1	Updated HEME contact info	KL	01/15/2024
4.0	Updated collection schema footnotes to align with protocol amendment Relapse/Progression is in protocol as timepoint now so updated schema accordingly	PAA	05/23/2022
3.0	Updated nomenclature to be consistent with protocol Revised biospecimen collection timelines Added bone marrow collection to discontinuation of treatment timepoint New HEME forms included	PAA	12/15/2021
2.2	Updated instructions for buccal cell collection	PAA	06/21/2021
2.1	Updated collection instructions to allow for Friday collections / delivery on Saturdays	PAA	05/21/2021
2.0	Clarified footnotes with collection schema Updated biospecimen collection schedule Added HEME forms in Appendix Fixed minor grammatical errors and typos	PAA	05/20/2021
1.0	New	PAA	01/25/2021

Appendix 1- CENTRAL Bone Marrow and Peripheral Blood MRD Forms

ALLIANCE A041702

CENTRAL Bone Marrow and Peripheral Blood MRD FORM

CYCLE 15 DAY 1

Instructions: At Cycle 15 Day 1 (+/- 5 days), this form must be submitted along with the bone marrow aspirate or peripheral blood to the Alliance HEME Biorepository at OSU. The form must be completed by typing; ***do not handwrite. Failure to submit this form with the specimen may delay turnaround time for central review.***

Sample Type: _____

Patient Initials: _____ Patient Sex: ____ Patient DOB: _____ Patient ID: _____

Institution:_____ Institution ID: _____

Responsible CRA Name: _____

E-mail Address: _____

EMAIL ADDRESS FOR RESULTS: _____

Phone Number: _____Emergency Contact Number*: _____

**Please provide a pager or cell phone number for questions outside of regular business hours.*

Alternate Contact Information: _____

BioMS Tracking Number: _____Lab Accession #: _____Volume: ____

Comments (unusual circumstances during collection/processing of samples):

Shipped by: _____

Ship samples at room temperature to:

Alliance HEME Biorepository
300 West Tenth Avenue, Lobby
Attn: Chris Manring/Robin Taxier
Columbus, OH 43210

Email notification at time of shipment via BioMS:

Christopher.Manring@osumc.edu; AllianceLTB@osumc.edu; Rebecca.Pearson@osumc.edu

After receiving the central review results form via e-mail, the institution must forward the form to random01@mayo.edu in order to re-register the patient. The site will also be required to upload this form as Supporting Documentation using a report type of "Other" in Rave.

ALLIANCE A041702

CENTRAL Bone Marrow and Peripheral Blood MRD FORM

DISCONTINUATION OF TREATMENT

Instructions: At Early Termination, this form must be submitted along with the bone marrow aspirate or peripheral blood to the Alliance HEME Biorepository at OSU. The form must be completed by typing; ***do not handwrite. Failure to submit this form with the specimen may delay turnaround time for central review.***

Sample Type: _____

Patient Initials:_____ Patient Sex: _____ Patient DOB: _____ Patient ID:_____

Institution:_____ Institution ID:_____

Responsible CRA Name: _____

E-mail Address: _____

EMAIL ADDRESS FOR RESULTS: _____

Phone Number:_____ Emergency Contact Number*: _____

**Please provide a pager or cell phone number for questions outside of regular business hours.*

Alternate Contact Information: _____

BioMS Tracking Number:_____ Lab Accession #: _____

Comments (unusual circumstances during collection/processing of samples):

Shipped by: _____

Ship samples at room temperature to:

Alliance HEME Biorepository
300 West Tenth Avenue, Lobby
Attn: Chris Manring/Robin Taxier
Columbus, OH 43210

Email notification at time of shipment via BioMS:

Christopher.Manring@osumc.edu; AllianceLTB@osumc.edu; Rebecca.Pearson@osumc.edu

After receiving the central review results form via e-mail, the institution must forward the form to random01@mayo.edu in order to re-register the patient. The site will also be required to upload this form as Supporting Documentation using a report type of "Other" in Rave.