RAMPART (RE06)
SAMPLE COLLECTION MANUAL

An international investigator-led phase III multi-arm multi-stage multi-centre randomised controlled platform trial of adjuvant therapy in patients with resected primary renal cell carcinoma (RCC) at high or intermediate risk of relapse

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INDEX

1 INTRODUCTION

The aim of this study is to evaluate changes in multiple molecular factors in relation to treatment response and prediction of immunotoxicity.

The expression of biomarkers of renal cancer response will be evaluated in tissue donated before treatment to identify both tumour- and blood-based biomarkers of therapeutic response to treatment and/or development of immune-related treatment toxicity. Techniques such as multi-parameter immunofluorescence, immunohistochemistry, and DNA and RNA sequencing will be used to identify molecular markers predicting response and/or toxicity.

This translational sampling manual contains all the details and protocols needed for initial processing and shipment of translational samples for RAMPART. If samples cannot be processed as required in this manual, for whatever reason, this **must** be discussed ahead of sample collection.

1.1 CONSENT

All patients randomised into the RAMPART study have agreed to the provision of mandatory baseline TransRAMPART samples – an EDTA blood sample and archival tissue samples from nephrectomy. This requirement is detailed in the RAMPART Participant Information Sheet and written informed consent is documented on the RAMPART Consent Form. A copy of the completed Consent Form must be sent to the MRC CTU at UCL after randomisation.

2 SITE ACTIVATION

RAMPART sites will need to meet all of the activation requirements before their site can be opened and sample collection can begin. For full details on the site activation process, please refer to the **RAMPART Guide**.

2.1 TRAINING

All sites will have a site initiation training session prior to activation. This training will cover all aspects of trial conduct, and will include a specific section on sample collection. The Principal Investigator, Co-Investigators and lead contacts within the research are expected to attend all sections of the initiation training session. The lead pathologist for the study must specifically attend the section on sample collection.

The training slides will be made available on the RAMPART website (www.rampart-trial.org) for any staff who cannot attend the initiation training, as well as any new staff who start working on RAMPART.

Please note that in addition to the trial specific training that will be provided, all staff working on the study must have completed GCP training and filed a copy of the certificate along with their CV in the Investigator Site File.

2.2 DOCUMENTATION

All staff involved in the sample collection process at participating sites must be listed on the **Site Delegation Log** and **Personnel Lists**. Copies of these documents should be sent to the MRC CTU prior to activation and on at least an annual basis to ensure contact lists remain up to date.

Sites will be required to provide evidence of CPA or UKAS lab accreditation. Any unaccredited sites should contact the MRC CTU to discuss the circumstances that resulted in them losing accreditation. The MRC CTU will need assurances that unaccredited sites are undertaking the following processes:

- Regular facility audits to ensure that the laboratory and associated equipment used to conduct analysis or evaluation of clinical trial samples remain fit for purpose.
- Periodic review of the laboratory's quality systems, including control of standard operating procedures and/or laboratory policies, archiving and the maintenance of training records.
- The audit of technical procedures and methodologies used to conduct the analysis or evaluation of clinical trial samples.
- Audits performed to assess the conduct of routine and repetitive processes which are common to all trials such as; sample receipt, sample storage, temperature monitoring, pipette and balance controls, and cleaning procedures. The most robust audit schedules will ensure that all key functions, personnel and procedures are reviewed over the course of one audit cycle.
- The audit of documentation generated during the validation of computerised systems or analytical equipment.

3 EDTA BLOOD SAMPLE COLLECTION

3.1 SAMPLE REQUIREMENTS

All sites participating in the RAMPART study are required to provide a single 10ml EDTA whole blood sample for each patient randomised into the study. The sample must be taken at baseline, prior to the start of any trial treatment.

3.2 SUPPLIES

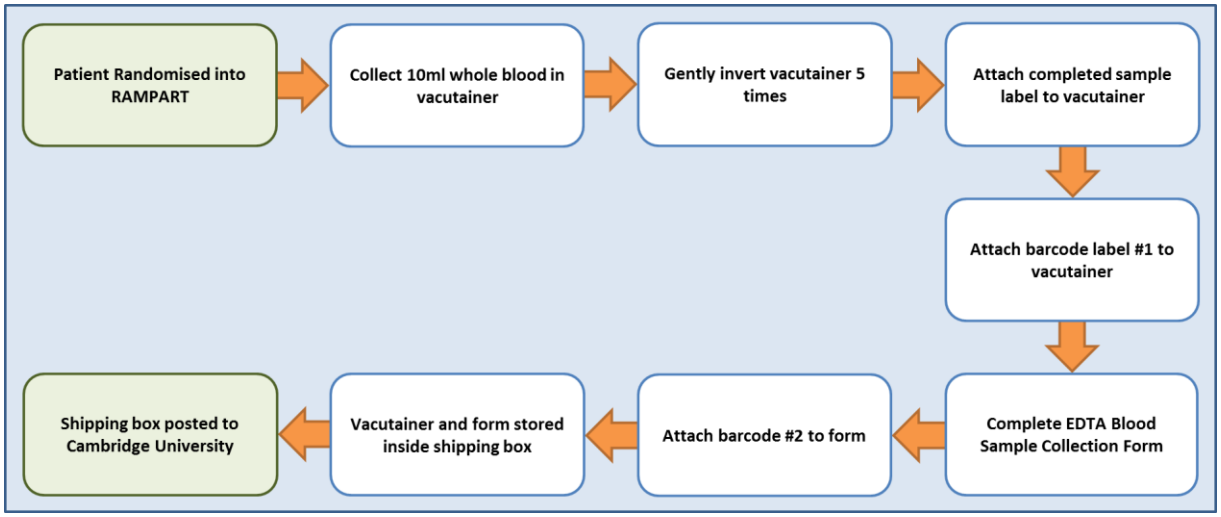
Sites will be provided with an EDTA blood sample collection kit, including the following items:

- 1 x 10ml EDTA vacutainer
- 1 x vacutainer needle and holder
- 1 x pre-paid shipping box for transporting EDTA blood sample
- 1 x sample label
- 2 x barcode labels
- 1 x EDTA Blood Sample Collection Form (see **Appendix A**)

All other equipment and reagents are expected to be provided by local sites.

In your initial shipment, once all site activation requirements are met, you will receive supplies for your first 5 patients. Participating sites need to actively monitor inventory of kits and shipping materials. Collection kits are not automatically re-supplied and must be ordered by contacting the RAMPART team. Please refer to **Section 6** for full contact details.

3.3 SAMPLE COLLECTION PROCESS



The following steps should be followed for the collection of EDTA samples for the RAMPART study:

- Collect 10ml whole blood into the vacutainer provided.
- Invert the tube gently 5 times to mix the sample.

- Label the vacutainer with the sample label, recording the patient's individual trial number, initials, date of birth and the date and time that the sample was taken.
- Label the vacutainer with the first barcode label
- Place the vacutainer inside the specimen bag.
- Complete the EDTA Blood Sample Collection Form making sure to affix the second barcode label.

3.4 SHIPPING

The labelled sample should be shipped together with the completed EDTA Blood Sample Form at ambient temperature in the shipping box provided to Cambridge University at the address below.

Jo Burge (Urology Trials)
Oncology Outpatient Reception
Oncology Centre
Robinson Way
Cambridge Biomedical Campus
Addenbrooke's Hospital
Cambridge
CB2 0QQ
Tel: 07791694220

Please note that the Cambridge University labs are not staffed on weekends or bank holidays. Samples must therefore only be sent from **Monday to Wednesday** to ensure there is somebody able to receive and store the samples appropriately.

Any samples collected from Thursday onwards should be temporarily stored in a local fridge, before being sent to Cambridge at the start of the next week.

4 FFPE TISSUE BLOCK COLLECTION

4.1 SAMPLE REQUIREMENTS

All sites are required to provide archival tissue samples for each patient randomised into the study. As a minimum, one formalin-fixed, paraffin-embedded (FFPE) archival tumour block (or 10-15 unstained slides) taken from tissue collected at the time of surgery is required for testing coordinated by the University of Cambridge. Wherever possible the TransRAMPART Investigators ask that you provide additional FFPE tumour blocks, as well as a normal tissue block.

	FFPE Tumour Blocks	FFPE Normal Tissue Blocks	Unstained Tumour Slides
Expected Standard	2+	1	0
Minimum Accepted Standard*	1	0	10-15

***** Either 1 block **or** unstained slides

4.2 SUPPLIES

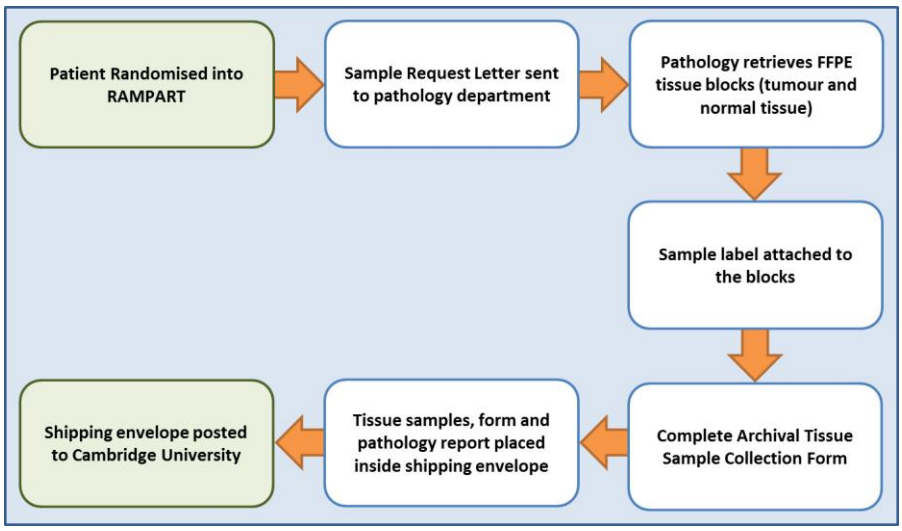
Sites will be provided with the following items to assist with the collection and shipping of archival tumour samples:

- 1 x pre-paid shipping envelope for transporting tumour block and anonymised pathology report
- 1 x archival Tissue Sample Collection Form (see **Appendix B**)
- 1 x sample label

All other equipment and reagents are expected to be provided by local sites.

In your initial shipment, you will receive supplies for your first 5 patients. Participating sites need to actively monitor inventory of shipping materials. Shipping supplies are not automatically resupplied and must be ordered by contacting the RAMPART team. Please refer to **Section 6** for full contact details.

4.3 SAMPLE COLLECTION PROCESS



No kit is provided by RAMPART to prepare archival tissue blocks. The samples are expected to be prepared by appropriately trained personnel, according to local hospital protocols.

Normal and tumour (FFPE) tissue blocks should be provided wherever possible. Most tumours are large and multiple blocks are therefore required to characterise them accurately. However, microscopy usually reveals a degree of overlap between blocks. In most cases therefore, it should be possible to provide additional surplus blocks. The tumour blocks should be representative of the overall grade assigned. Ideally, the block of normal tissue should be taken at a distance from the tumour.

In cases where it is not possible to provide tissue blocks, it is acceptable to provide slides instead. Sites should prepare 10-15 unstained slides with all sections cut at a thickness of 4 micrometres.

The blocks or slides should all be labelled with the patient's individual trial number, initials, DOB the date the sample was taken, and the local sample reference number. An Archival Tissue Sample Collection Form should be completed with details of all samples being provided.

4.4 SHIPPING

The labelled blocks or slides should be shipped at ambient temperature in the pre-paid envelope provided, to Cambridge University at the address below. A copy of the pathology report (labelled with the patient's individual trial number and the site number), and a fully completed Archival Tissue Collection Form should be enclosed with the samples.

Tissue Bank Manager (RAMPART Clinical Trial)
Cambridge University Hospitals NHS Trust Biorepository
Addenbrookes Hospital
Cambridge
CB2 0QQ
United Kingdom

4.5 SAMPLE REQUEST LETTER

The Sample Request Letter should be sent to the relevant local pathology laboratory in order to request the release of archival tissue blocks and a copy of the pathology report. Please see **Appendix C** for a copy of the letter.

5 SAMPLE TRACKING

The receipt of TransRAMPART samples will be recorded on the main RAMPART database. Sites will be provided with regular Sample Chase Reports showing which samples have been received, and highlighting those that are outstanding.

If sites experience problems obtaining the required samples, this should be discussed with the MRC CTU team in the first instance. Any mandatory samples that cannot be obtained will be recorded and followed up as protocol deviations.

6 CONTACT INFORMATION

All queries regarding sample collection, storage and dispatch (including requests for new sample collection packs) should in the first instance be directed to a member of the RAMPART Trial Management Team based at the MRC CTU at UCL.

MRC CTU AT UCL

Address: RAMPART Trial Management Team
MRC Clinical Trials Unit at UCL
90 High Holborn
London WC1V 6LJ
UK

Switchboard: 0207 670 4700
Fax: 0207 670 4653
Email: mrcctu.rampart@ucl.ac.uk

Contacts			
Trial Manager:	Mr Ben Smith	0207 670 4743	ben.m.smith@ucl.ac.uk
Trial Manager:	Dr Francesca Schiavone	0207 670 4683	f.schiavone@ucl.ac.uk
Data Manager:	Mr Kalam Hussain	0207 670 4640	jiaull.hussain.15@ucl.ac.uk
Data Manager:	Mr Nat Thorogood	0207 670 4720	n.thorogood@ucl.ac.uk

CAMBRIDGE UNIVERSITY

Address: Academic Urology Group
Norman Bleehan Oncology Offices
The Former Clinical Workshops
Robinson Way
Cambridge Biomedical Campus
Addenbrookes Hospital
Cambridge CB2 0QQ
UK

Contacts			
Research Assistant:	Ms Jo Burge	01223 348441	johanna.burge@addenbrookes.nhs.uk
Lead Investigator:	Mr Grant Stewart	01223 256211	gds35@cam.ac.uk

APPENDIX A – EDTA BLOOD SAMPLE COLLECTION FORM

TransRAMPART: EDTA Blood Sample Collection Form

Patient Trial Identified Number:	
Date of Birth:	
Collection Date:	

1 x 10ml EDTA blood to be collected for RCC research study

Please return blood samples with sample form in addressed box provided to:

Jo Burge (Urology Trials)
Oncology Outpatient Reception
Oncology Centre
Robinson Way
Cambridge Biomedical Campus
Addenbrooke's Hospital
Cambridge
CB2 0QQ

APPENDIX B – ARCHIVAL TISSUE COLLECTION FORM

TransRAMPART: Archival Tissue Collection Form

Patient Trial Identified Number:	
Date of Birth:	
Nephrectomy Date:	
Samples Enclosed:	☐ FFPE Tumour Block(s) *Sample IDs:*
	☐ FFPE Normal Tissue Block *Sample ID:*
	☐ Tumour Slides *Number of Slides:*

FFPE tissue blocks or slides and pathology report to be collected for RCC research study

Please ensure that all patient identifiable data are removed from the report or completely obscured. Please then return tissue samples with sample form to:

Tissue Bank Manager (RAMPART Clinical Trial)
Cambridge University Hospitals NHS Trust Biorepository
Addenbrookes Hospital
Cambridge
CB2 0QQ
United Kingdom

APPENDIX C – SAMPLE REQUEST FORM

Date: ……/……/……

Dear Sir or Madam,

Re: Formalin-fixed paraffin-embedded (FFPE) Pathology Sample Retrieval for the RAMPART Study

Patient Name:…… D.O.B……

Nephrectomy Date:……

RAMPART is an international phase III clinical trial of adjuvant therapy in patients with resected primary renal cell carcinoma (RCC) at high or intermediate risk of relapse.

A translational sub-study called TransRAMPART is being run alongside the main RAMPART trial. The aim of TransRAMPART is to collect tissue, blood and urine samples from patients randomised to the RAMPART clinical trial for the development of novel molecular markers of prognosis, response prediction and toxicity.

The purpose of this letter is to request your help in collecting pathological material for TransRAMPART. The above named patient has given consent for archival tissue samples from their nephrectomy to be collected and used in the TransRAMPART study (a copy of their consent form is attached for your information). We would therefore appreciate it if you could return the following in the supplied envelope:

- 2+ blocks of FFPE tumour tissue
- 1 block of FFPE normal tissue
- a copy of the associated pathology report
- completed Archival Tissue Collection Form

If it is not possible to provide all of the tissue outlined above, we would ask that you provide at least the minimum requirements – either 1 FFPE tumour block, or 10-15 unstained slides (cut at 4 micrometre sections). Blocks should normally be surplus to diagnostic requirements, and will only be returned on request.

Research on the FFPE blocks or slides you provide will be undertaken by the Academic Urology Department at Cambridge University under the direction of Mr Grant Stewart.

Yours faithfully,

RAMPART Trial Research Nurse

On behalf of <insert PI name here>. RAMPART Principal Investigator

Further information about any aspect of TransRAMPART or the RAMPART trial is available from RAMPART Trial Team at the MRC CTU at UCL

(Tel: 020 7670 4743/4683, fax: 020 7670 4653 or e-mail mrcctu.rampart@ucl.ac.uk)