



A study endorsed by the
European Network for the
Study of Adrenal Tumours

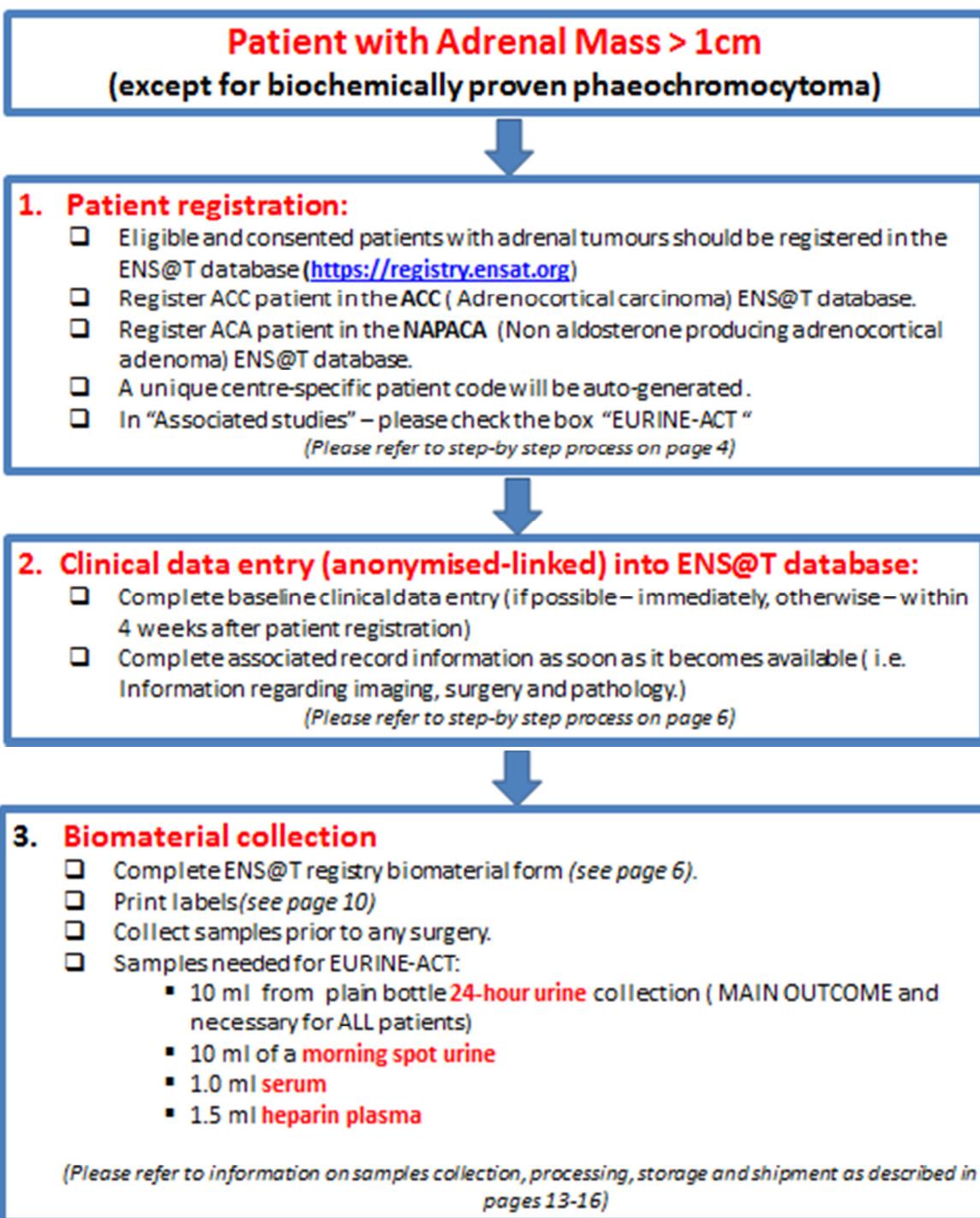


SOPs for the EURINE-ACT Study - Table of Contents and Figures

EURINE-ACT Study overview	2
Contact information.....	3
ENS@T membership	3
EURINE-ACT Patient Registration.....	4
Clinical data entry into ENS@T registry.....	6
Biomaterial form in the ENS@T registry.....	12
Biomaterial collection	13
Biomaterial Processing.....	14
Biomaterial Labeling & Storage	15
Biomaterial Shipment	16
FOLLOW-UP in EURINE-ACT patients (OPTIONAL):.....	17
Data collection in EURINE-ACT FOLLOW-UP patients.....	18
Example of the report (steroid metabolomics urine results):	20

Figure 1: Registering a new patient in the ENS@T registry: example for the ENS@T Centre Birmingham (GBBI).....	5
Figure 2: Baseline information for ACC patient	7
Figure 3 Baseline information for NAPACA patient	8
Figure 4: Associated record information: example for NAPACA patient.....	9
Figure 5: Imaging form (NAPACA patient)	9
Figure 6: Surgery form for ACC and NAPACA patients.....	10
Figure 7: Pathology forms for ACC and NAPACA patients	11
Figure 8: Biomaterial form	12
Figure 9: Follow up form for ACC patient	18
Figure 10: Follow up form for NAPACA patient	19
Figure 11: Example of Steroid Metabolomics report.....	20

EURINE-ACT Study overview





A study endorsed by the
European Network for the
Study of Adrenal Tumours



Contact information

Name	Email address	Inquiries
Wiebke Arlt (Chief Investigator)	w.arlt@bham.ac.uk	<ul style="list-style-type: none">For any questions regarding information on EURINE-ACTFor information and question regarding EURINE-ACT ethics process and documentationSOPs in relation to EURINE-ACT
Irina Bancos (Clinical research fellow)	i.bancos@bham.ac.uk	
Donna O'Neil (specialist technician)	d.m.oneil@bham.ac.uk	<ul style="list-style-type: none">For notifications regarding shipments of samples, confirmation of sample receipt
Anthony Stell (ENS@T registry administrator)	anthony.stell@unimelb.edu.au	<ul style="list-style-type: none">For ENS@T registry LOG-IN and password and generation of ENS@T Centre Code

ENS@T membership

- In order to be able to participate in any ENS@T studies (including EURINE-ACT), you need to become a member of ENS@T.
- If you are not an ENSAT member yet, you can see information on how to become one at <https://registry.ensat.org>
- Once you become ENSAT member, you can receive a **user name and password for ENS@T registry LOG IN**. Just request it by email from Anthony Stell, ENS@T registry administrator Anthony.stell@unimelb.edu.au
- If you are the first person from your centre to become a member of ENS@T, then Anthony will also designate a four letter **ENS@T centre code**, e.g. GBBI, for Great Britain Birmingham.
- Now you can start registering your patients in the ENSAT registry:
<https://registry.ensat.org/jsp/login.jsp>
(*a message about certificate error may appear, but just click "continue" and it will work*).
- Registration will create a **unique ENS@T Patient ID** that consists of the four letter centre code and a four digit consecutive patient number, e.g. GBBI-0001 is the first patient enrolled by Birmingham. **The ENS@T registry contains anonymised-linked data**, i.e. nobody can identify personal patient information through the registry. However, locally, in your centre, you need to keep a list located on a secure server with restricted access that links the ENS@T Patient ID with the actual personal patient details.



A study endorsed by the European Network for the Study of Adrenal Tumours

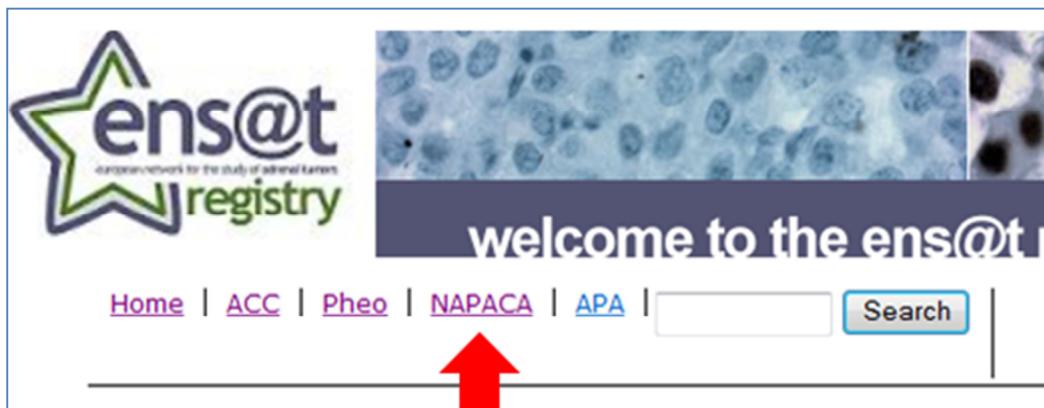


EURINE-ACT Patient Registration

- All patients with adrenal tumours should be registered in the ENS@T database (<https://registry.ensat.org>)
- Register patients with confirmed or highly suspected adrenocortical carcinoma in the **ENS@T ACC registry**.



- Register patients with any other adrenal mass (adrenal adenoma, incidentaloma, mass of unknown significance) in the **ENS@T NAPACA registry** (NAPACA, Non aldosterone producing adrenocortical adenoma).



EURINE-ACT does include patients with any adrenal mass except for biochemically confirmed phaeochromocytoma. Such tumours can be entered into the ENS@T Phaeo registry for other scientific collaborations, but they cannot be included in the EURINE-ACT study.



A study endorsed by the European Network for the Study of Adrenal Tumours



- A centre-specific **unique ENSA@T Patient ID Code** will be auto-generated.
- In “Associated studies” – **please check the box “EURINE-ACT”**, this will trigger an auto-generated email to the EURINE-ACT study team.

Figure 1: Registering a new patient in the ENS@T registry: example for the ENS@T Centre Birmingham (GBBI)

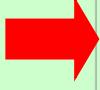
Create ACC Record

Identification

The following data points are the minimum criteria required for creating a patient record.

ENSAT ID Number:	[AutoGenerated]
Year of Birth:	1963
Sex:	M
Center ID:	GBBI
Referral doctor:	Wiebke Arlt
Email:	w.arlt@bham.ac.uk
Date of ENSAT Registration:	11-09-2013
Level of consent for clinical research (Local, National, ENSAT, International):	National
Associated studies:	<input type="checkbox"/> ACC Molecular Marker <input type="checkbox"/> ADIUVO <input type="checkbox"/> ADIUVO Observational <input checked="" type="checkbox"/> EURINE-ACT <input type="checkbox"/> HairCo

Confirm Details





A study endorsed by the
European Network for the
Study of Adrenal Tumours



Clinical data entry into ENS@T registry

- After generating an ENS@T ID, you can **complete the clinical information requested** (Figures 2 and 3). If you cannot do this at the time of registration, please complete it within 4 weeks.
- It will take you only 5 minutes to complete this, with most of the entries having convenient drop down menus with Yes/No answers or defined choices.
- **For ACC patients:**
 - Please make sure to complete information on hormonal secretion (Dexamethasone suppression test required)
 - Please make sure to complete imaging information (CT and HU)
 - **If the patient undergoes surgery**, you also need to complete a **Surgery form** and a **Pathology** form, which are both very short (see figures 6 and 7).
- **For NAPACA patients:**
 - Please make sure to complete information on hormonal secretion (Dexamethasone suppression test required)
 - We need you to complete an **Imaging form** (in Associated records, figures 4 and 5), which asks about maximum tumour diameter, type of imaging and imaging characteristics such as tumour density (HU) carried out during the baseline assessment of the patient. *Please note that if no clear characteristics of benignity is available on imaging, then either documentation of no growth on subsequent imaging study or benign pathology should be provided.*
 - **Benignity on imaging:**
 - *Unenhanced CT HU <10*
 - *Absolute contrast washout % at 10-15 minutes >60%*
 - *Relative contrast washout% at 10-15 min >40%*
 - *Drop in chemical shift on in and out of phase MRI images*
 - *No uptake on PET scan*
 - **If the patient undergoes surgery**, you also need to complete a **Surgery form** and a **Pathology** form which are both very short (see figure 6 and 7).



A study endorsed by the
European Network for the
Study of Adrenal Tumours



Date of diagnosis:	2-02-2013
Disease status:	Not free of disease ▼
Modality of diagnosis:	Hormonal + Imaging Work-Up ▼
Height:	169
Weight:	78
Symptoms related to tumor mass:	Yes ▼
Incidentally detected:	No ▼
Related to unspecific paraneoplastic symptoms:	No ▼
Symptoms related to hormonal secretion:	Yes ▼
Cushing's syndrome:	Yes ▼
Virilisation:	No ▼
Feminization:	No ▼
Mineralocorticoid excess:	Yes ▼
Hypertension:	Yes ▼
Hypokalemia:	Yes ▼
Diabetes:	Yes ▼

Hormonal hypersecretion:	
Glucocorticoids:	Yes ▼
Androgens:	No ▼
Estrogens:	No ▼
Mineralocorticoids:	Yes ▼
Precursor secretion:	No ▼
ACC during pregnancy:	No ▼
Associated malignancy:	No ▼
Site of adrenal tumor:	Right ▼
Information based on:	Imaging
Size of adrenal tumor (mm):	130
Regional lymph nodes positive:	Not Determined ▼
Extracapsular local invasion to adipose tissues:	Not Determined ▼
Extracapsular local invasion to adjacent organs:	Not Determined ▼
Tumor in vena cava or vena renalis:	Not Determined ▼
Distant metastases:	Yes ▼
Bone:	No ▼
Liver:	No ▼
Lung:	Yes ▼
Abdomen lymph nodes:	No ▼
Other metastases:	
Imaging:	CT ▼

Figure 2: Baseline information for ACC patient



A study endorsed by the
European Network for the
Study of Adrenal Tumours



Year of diagnosis of NAPACA (yyyy):	2013
Month of diagnosis of NAPACA:	Mar
Tumor found incidentally:	Yes
Symptoms related to hormonal secretion:	Yes
Cushing's syndrome:	Yes
Virilisation:	No
Feminization:	No
Mineralocorticoid excess:	No
Hypertension at presentation:	No
Diabetes type-2 at presentation:	No
Dyslipidaemia at presentation:	No
Osteoporosis at presentation:	No
Previous cardiovascular events:	No
Currently receiving anti-diabetic drugs:	No
Currently receiving lipid-lowering drugs:	No
Currently receiving osteoporosis drugs:	No
Currently receiving anti-hypertensive drugs:	No
Serum cortisol after 1mg Dex overnight:	Not Suppressed
Specific value:	5.7
Baseline plasma ACTH:	Suppressed
Specific value:	<5
Urinary free cortisol:	Elevated
Specific value:	259
Urinary free method:	[Select...]
Random plasma renin activity (ng/ml/h):	Normal
Random plasma renin concentration (ng/l):	Normal
Random serum aldosterone (ng/l):	Normal
Serum 17-Hydroxyprogesterone:	Not Done
Serum DHEAS:	Not Done
Urinary free catecholamine excretion:	Normal
Urinary metanephrine excretion:	Normal
Plasma metanephries:	Normal
Associated malignancy:	No
Tumor Size (mm):	17

Figure 3 Baseline information for NAPACA patient



A study endorsed by the European Network for the Study of Adrenal Tumours



Figure 4: Associated record information: example for NAPACA patient

Associated Record Information					
Follow-Up	Biomaterial	Surgery	Imaging	Pathology	Steroid Metabolomics
Summary of Associated Record Information					
ENSAT ID	Form ID	Date	Record Information		
GBBI-0031	1	01 Sep 2013	Imaging	Detail	Delete
NAPACA Home					

Figure 5: Imaging form (NAPACA patient)

Create NAPACA Imaging Form	
Imaging Date:	16-03-2014
Tumor sides:	Right Adrenal ▼
Right adrenal - max tumor diameter (mm):	28
CT data available:	Yes ▼
CT: pre-contrast tumor density:	< 10 ▼
Exact HU value:	7
Delayed contrast washout determined:	Yes ▼
Absolute contrast washout % value at 10-15 min (please type 0-100%) ?:	65
Relative contrast washout % value at 10-15 min (please type 0-100%) ?:	45
Imaging suggestive of extra-adrenal malignancy:	No ▼
Studies other than CT performed:	Yes ▼
MRI chemical shift analysis performed:	Yes ▼
Drop of intensity signal between in- and out-of-phase imaging by more than 30%:	Yes ▼
FDG-PET: significant uptake in adrenal tumor:	[Select...]
Comments:	
<input type="button" value="Confirm Details"/>	



A study endorsed by the European Network for the Study of Adrenal Tumours



Figure 6: Surgery form for ACC and NAPACA patients

ACC Update Surgery Record 1

Surgery date:	05-02-2013
Type:	First
Method:	Open
Overall resection status:	R0
Extended (Ctrl-click to select):	<input type="checkbox"/> Loco-Regional Relapse <input type="checkbox"/> Metastases - Liver <input type="checkbox"/> Metastases - Lymph Node <input type="checkbox"/> Metastases - Lung <input type="checkbox"/> Metastases - Others
First (Ctrl-click to select):	<input checked="" type="checkbox"/> Adrenalectomy <input type="checkbox"/> Nephrectomy <input type="checkbox"/> Other Adjacent Organs <input checked="" type="checkbox"/> Lymphadenectomy <input checked="" type="checkbox"/> Vena Cave Surgery

Update Details

[Back to Surgery summary](#)

Create NAPACA Surgery Form

Surgery Date:	03-10-2013
Surgical Approach:	Minimal Invasive

Confirm Details



A study endorsed by the European Network for the Study of Adrenal Tumours



Figure 7: Pathology forms for ACC and NAPACA patients

ACC Update Pathology Record 1

Pathology derived from:	Surgery 1
Local pathologist:	John Smith
Central pathology review:	Yes
Central review pathologist:	Joann Smith
Number of mitoses (Exact count per 50 HPF):	10
Ki67 (in %/50 HPF):	50
17p13 loss of heterozygosity:	Not Available
IGF overexpression:	Yes
Weiss score:	8
Nuclear atypia:	Yes
Atypical mitosis:	Yes
Spongiocytic tumor cells:	Yes
Diffuse architecture:	Yes
Venous invasion:	Yes
Sinus invasion:	Yes
Capsular invasion:	Yes
Necrosis:	No
Number of mitoses (> 5/50 HPF):	Yes

[Back to Pathology summary](#)

NAPACA Update Pathology Record 1

Pathologist Name:	John Smith
Pathologist Location:	Birmingham
Pathology Diagnosis:	Adrenocortical Adenoma
Number of mitoses (exact count per 50 HPF):	3
Ki67 (in %/50 HPF):	6
Weiss Score:	
Nuclear Atypia:	No
Atypical Mitosis:	No
Spongiocytic Tumor Cells:	No
Diffuse Architecture:	No
Venous Invasion:	No
Sinus Invasion:	No
Capsular Invasion:	No
Necrosis:	Yes
Number of Mitoses (> 5/50 HPF):	No

Biomaterial form in the ENS@T registry

- Choose “**Biomaterial**” in the “Associated Record Information”.
- Click on “**Create New Biomaterial Record**”
- Choose “24h Urine Volume” and enter **24-h Urine Volume** in ml, which is mandatory!
Only patients with available 24-hour urine samples and recorded 24-h urine volumes can be processed and included in EURINE-ACT.
- Choose the other samples you are sending in addition to 24h urine sample, this should include: a spontaneously produced **morning spot urine, serum and heparin plasma** samples.
- Click on “**Confirm details**”

Figure 8: Biomaterial form

Biomaterial Date:	11-09-2013	
Associated Study:	EURINE-ACT	
Associated Study (Phase/Visit):		
Tumor Tissue (Frozen):	[Select..]	
Tumor Tissue (Paraffin):	No	
Tumor Tissue (DNA):	No	
Leukocyte DNA:	No	
EDTA Plasma:	No	
Heparin Plasma:	Yes	1
Serum:	Yes	1
24h Urine:	Yes	1
24h Urine Volume (ml):	2800	1
Spot Urine:	Yes	1
Normal Tissue (Frozen):	No	
Normal Tissue (Paraffin):	No	
Normal Tissue (DNA):	No	
Freezer information:		
Whole blood:	No	
Blood clot:	No	
Confirm Details		

Biomaterial collection

24-hour urine	<ul style="list-style-type: none"> Collections should be performed using plain collection bottles without addition of preservatives. In women, avoid collections during menstrual bleeding The collection should be returned to hospital on the day of completion, if this is not possible, it is acceptable to store the bottle for up to 3 days at 4°C (in the fridge).
Spot urine	<ul style="list-style-type: none"> A single urine sample spontaneously produced during the morning before 12 noon.
Serum	<ul style="list-style-type: none"> Collect blood samples from a peripheral vein into a suitable tube for serum collection, e.g. a plastic no-additive serum collection tube with clotting activator. Examples: 6 ml Vacutette, red top, with clot activator Greiner Bio-One; 8.5 BD vacutainer; S-Monovette 2.7 ml Z, code white, for serum separation, with additive carrier/clot activator, SARSTEDT AG) After collection, please invert the tube gently several times.
Heparin plasma	<ul style="list-style-type: none"> Collect blood samples from a peripheral vein directly into plasma collection tubes. Examples: 6 ml Vacutette, green top, with Heparin Lithium, Greiner Bio-One; 8.5 BD heparin vacutainer; Plasma tube, 60 USP Units of Sodium Heparin (spray-coated), 4 ml, BD vacutainer; Probenrohrchen zur Plasmagewinnung 1 ml, KABE Labortechnik GmbH Numbrecht-Elsenroth. After collection, please invert the tube gently several times.

Biomaterial Processing

24-hour urine	<ul style="list-style-type: none"> Gently invert the collection bottle several times. If a subject provides a sample of more than 3000mL, i.e. more than one bottle, it is important to mix the two volumes well before taking an aliquot. Transfer two 10ml aliquots into 15 ml falcon tubes. Centrifuge at 1500 rpm for 5 minutes. One sample should be sent to Birmingham and one stored locally.
Spot urine	<ul style="list-style-type: none"> Transfer two 10ml aliquots into 15 ml falcon tubes. Centrifuge at 1500 rpm for 5 minutes. One sample should be sent to Birmingham and one stored locally.
Serum	<ul style="list-style-type: none"> Store the vial at room temperature (20-28 C°) in an upright position to allow coagulation. Clot formation should be completed after 20-30 minutes. If centrifugation is not performed at the place of sample collection, use this time for transportation. Time at room temperature until centrifugation should not exceed 40 minutes Centrifuge to separate the serum from the blood clot at 15C°, 10 min, 2750 rpm. Transfer the serum into a pre-cooled collection vial (e.g. Falcon) without aspirating blood cells. Use disposable pipette tips. Perform pipetting steps on ice. Aliquot the serum in suitable portions into the pre-cooled, labelled storage vials/cryotubes to avoid later freeze/thaw cycles. 1mL of serum will need to be sent to Birmingham. You could divide into 2x 500µl aliquots, if you like. The filling of the tubes should not exceed 75% of tubes capacity, thus choose the appropriate storage vials / cryotubes accordingly. <p>Examples: Safe-Lock-Vials, 1.5 ml or 2 ml, Eppendorf; Biozym vials, 1.5 ml with screw cap; Thermo Scientific Nunc and Nalgene storage vials.</p>
Heparin plasma	<ul style="list-style-type: none"> Do not cool blood before plasma separation is finished. Separate cells and plasma using centrifugation as soon as possible Time from blood collection to centrifugation must not exceed 40 minutes. Spinning conditions are as follows: 20-24 C°, 10 minutes at 2750rpm Transfer the plasma into a pre-cooled collection tube (e.g. Falcon) without aspirating blood cells. Use disposable pipette tips. Place plasma on ice. Aliquot the plasma in suitable portions into the labelled sample storage vials to avoid later freeze/thaw cycles. 1.5mL of heparin plasma will need to be sent to Birmingham. You can decide to split this into 2-3 smaller aliquots. The filling of the vials should not exceed 75% of their capacity, thus choose the appropriate storage vials / cryotubes accordingly. <p>Examples: Safe-Lock-Vials, 2 ml, Eppendorf; Biozym vials, 1.5 ml with screw cap; Thermo Scientific Nunc and Nalgene storage vials.</p>



A study endorsed by the European Network for the Study of Adrenal Tumours



Biomaterial Labeling & Storage

- Each sample should be labeled with the unique ENSAT patient identifier, the date the sample was taken and volume. Without this information samples will NOT be processed.
- Ensure that all labeling is waterproof and resistant to cold storage conditions.
- If you like, you can print automatically-generated labels using the ENS@T registry:

ACC Print Biomaterial Record 1

Date: 2013-06-13	
Sample	Number of labels required
Heparin Plasma	1 ▾
Serum	1 ▾
24h Urine	1 ▾
Spot Urine	1 ▾

Print Labels (A4) **Print Labels**

- Examples of labels (needs to show ENS@T Patient ID, date of sampling and type of sample :

GBBI-0028 bio-ID 1 Study: EURINE-ACT Date: 2013-06-13 Spot Urine Aliquot: 1	GBBI-0028 bio-ID 1 Study: EURINE-ACT Date: 2013-06-13 Heparin Plasma Aliquot: 1
GBBI-0028 bio-ID 1 Study: EURINE-ACT Date: 2013-06-13 24h Urine (2800 ml) Aliquot: 1	GBBI-0028 bio-ID 1 Study: EURINE-ACT Date: 2013-06-13 Serum Aliquot: 1

- Urine samples need to be frozen immediately at -20C° and stored ideally at -80C° (-20C° is also acceptable for up to 12 months).
- Once frozen, avoid thawing of samples.
- Handle and transport on dry ice (see below).



A study endorsed by the
European Network for the
Study of Adrenal Tumours



Biomaterial Shipment

- Once you have accumulated the samples of 10-20 EURINE-ACT patients, i.e. generating 40-80 aliquots to send, you can prepare the shipment by dry ice parcel.
- Samples must not thaw during transportation – please use dry ice in insulated boxes.
- Please contact us to ensure there is somebody in the lab that week to receive the parcel: (Wiebke Arlt (w.arlt@bham.ac.uk), Donna O'Neil (d.m.oneil@bham.ac.uk) and Irina Bancos (i.bancos@bham.ac.uk)).
- Ship the samples early in the week, if possible, to avoid long periods without replacement of dry ice.
- Please provide us with the tracking number and courier information.
- We will confirm safe arrival upon receipt of the parcel.
- Samples should be shipped to:

Centre for Endocrinology, Diabetes and Metabolism (CEDAM)

(To the attention of Dr. Donna O'Neil (EURINE-ACT))

Institute of Biomedical Research, Room 238

University of Birmingham

Edgbaston, Birmingham, B15 2TT

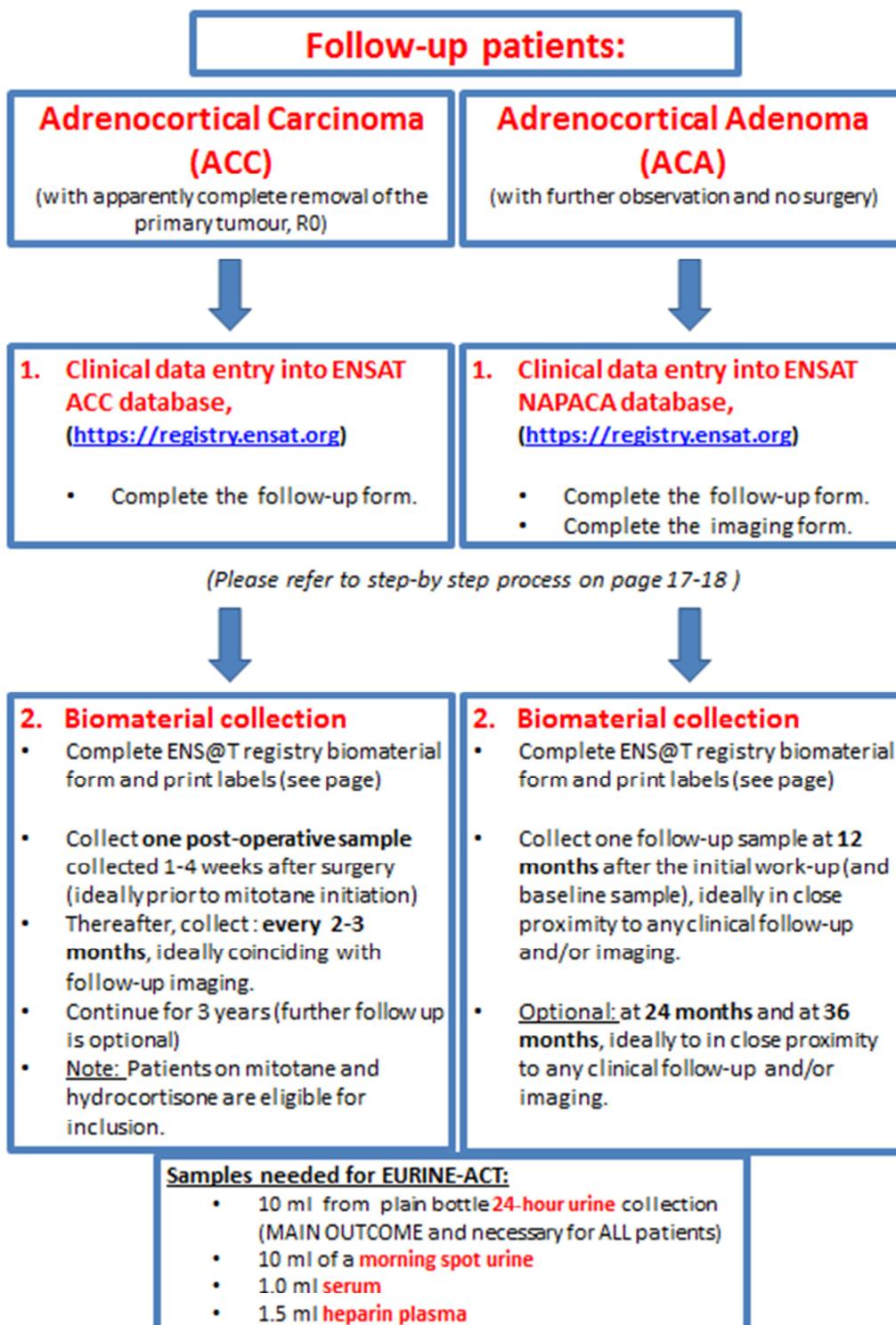
United Kingdom

If the courier requires a fax and a phone number to be given:

Fax +44-121-415-8712

Phone +44-121-414 3768

FOLLOW-UP in EURINE-ACT patients (OPTIONAL):



Data collection in EURINE-ACT FOLLOW-UP patients

- For all **EURINE-ACT ACC patients** who are apparently tumour-free after surgical removal of their primary tumour (R0 resection) further follow-up can be undertaken, as per above, with 24-h urine samples to be sent **every 3 months for up to 3 years after the surgery**.
- On each occasion you need to complete a **Biomaterial Form**, and for the clinical information a **Follow-up form**; these forms can be found under “Associated Record Information”.

Figure 9: Follow up form for ACC patient

Create ACC Follow Up Form	
Follow-up date:	12-09-2013
Patient status:	Alive without evidence disease
Comment:	
Alive with disease (Ctrl-click to select):	<input type="checkbox"/> Local Recurrence <input type="checkbox"/> Thoracal Lymph Nodes <input type="checkbox"/> Remaining Adrenal Tumor <input type="checkbox"/> Lung <input type="checkbox"/> Liver
Lost to follow-up:	No
Most recent imaging date:	09-09-2013
Imaging method:	CT
Currently on mitotane:	Yes
Mitotane ongoing:	Yes
Recent level (mg/L):	18
Recent dose (mg/daily):	3
Current glucocorticoid replacement:	Hydrocortisone
Current steroid dose (mg/daily):	50
Current fludrocortisone replacement:	Yes
Replacement choice:	Testo gel
Testosterone replacement:	Yes
<input type="button" value="Confirm Details"/>	

- For all EURINE-ACT NAPACA patients who have not undergone surgery, you could send us annual follow-up samples for up to 3 years after the baseline assessment.
- If you send us annual follow-up biomaterial, you need to complete a **Biomaterial Form**, and for the clinical information a **Follow-up form** and, if there is also imaging follow-up, an **Imaging Form**; these forms can be found under “Associated Record Information”.

Figure 10: Follow up form for NAPACA patient

NAPACA Update Follow-Up Record 1	
Follow-Up Date:	21-02-2014
Alive:	Yes ▼
Imaging:	No ▼
Changes in hormone secretion:	No ▼
Serum cortisol after 1mg Dex overnight:	Suppressed ▼
Cortisol value:	45
Cortisol units:	nmol/l ▼
Baseline plasma ACTH:	Normal ▼
Urinary free cortisol:	Normal ▼
Random plasma renin activity:	Not Done ▼
Random plasma renin concentration:	Normal ▼
Random serum aldosterone:	Normal ▼
Serum 17-Hydroxyprogesterone:	Normal ▼
Serum DHEAS:	Normal ▼
Urinary free catecholamine excretion:	Not Done ▼
Urinary metanephrine excretion:	Not Done ▼
Plasma metanephries:	Normal ▼
Further plans for follow-up:	Further Monitoring ▼
Update Details	

Example of the report (steroid metabolomics urine results):

Figure 11: Example of Steroid Metabolomics report

Adrenal Tumor Prediction

Computer-determined likelihood of adrenocortical adenoma (ACA) and adrenocortical carcinoma (ACC):

ENSAT-ID XXXXX	ACA	ACC
	8%	92%

The figure shows the analysed sample(s) in comparison to the study population of adrenal tumor patients presented in [1]. The figure was generated by projecting the data and the sample(s) onto the first two eigenvectors of the matrix of metric parameters (see [1] for details)

Discriminative visualization:

