TCATF 184 05
(Relates to SOP No. TCATS CTL 003)

CTL Treatment Protocol

EBV-specific CTL for treatment of EBV+ lymphoma

Epstein-Barr Virus (EBV) specific cytotoxic T lymphocytes (CTL) are supplied for treatment of EBV-positive lymphoma. They are cultured from tissue typed blood donors, stored frozen in vapour-phase liquid nitrogen at <-150 ^{o}C and selected for patient treatment on the basis of best available HLA match. The anti-EBV CTL product is not licensed for marketing and is supplied on a named patient basis only.

Treatment normally involves 4 infusions of CTL at weekly intervals. Sufficient CTL for 4 infusions will be shipped together and must be transferred to suitable storage and kept frozen preferably in nitrogen vapour at <-130^{o}C until each treatment is to be given.

Note: cells are supplied only for use on a named patient basis. Any unused cells must be discarded.

EBV-specific CTL supplied

Product name: EBV-specific CTL

Description: cultured cells are supplied cryopreserved with 10% dimethyl sulphoxide (DMSO) and in 10% human albumin solution (HAS).

Packaging: the cells are supplied in double wrapped cryobags containing approximately 15ml of either 50 or 150 x10^{6} CTL, labelled for the named patient use only. They must be kept frozen until ready to prepare for treatment.

Delivery of EBV-specific CTL and transfer to local ≤-80^{o}C storage

The frozen CTL are transported in a 'dry shipper' (vapour-phase liquid nitrogen container) marked for the attention of a nominated recipient with their contact details. Ensure that the contents are kept frozen, and quickly transfer to vapour phase liquid nitrogen storage.

The cryobag ports are fragile when frozen. Please handle with care.

Upon receipt:

- Record the time, also temperature / status displayed on logger;
- Check that the number of bags corresponds to the number detailed below;
- Check that the labels visible inside the outer bag have the correct patient named;
- Check for any obvious damage (other than a small cut in the outer bag) or signs of thawing (record on page 5).

Please copy/scan or fax completed page 5 back to us and report any concerns to CTL staff in Edinburgh (Tel: 0131 314 5545) as soon as possible. Any suspect cryobags must be double bagged / quarantined.

Patient consent

A patient information and consent form is provided as a basis for discussion between the patient or guardian with the treating physician. The signed original should be kept in the patient notes. Two copies are required: one for the patient and one for SNBTS, Edinburgh.

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Method for infusion of EBV-specific CTL

For the number of bags required per treatment, refer to page 5, the personalised section of this form below. Approximately 1-2x10^6 CTL/kg body weight should be given at each infusion (50x10^6 CTL per 25kg body weight). This may involve using only a portion of the bag contents to achieve 1-2x10^6 CTL/kg body weight. Keep the bag(s) frozen until everything is ready for the treatment. The cryoprotectant DMSO is harmful to metabolising cells so aim to infuse soon after thawing, or keep thawed cells cool (<10°C) if delayed.

You will need (on each day of infusion)
Materials:

- 37°C waterbath (or equivalent, eg bead bath or sterile 37°C incubator) freshly cleaned, filled with sterile water
- Insulated transport box / dry shipper to maintain treatment bag(s) < -80°C
- Insulated gloves
- Sterile wipes
- Scissors
- Plastic bags
- Heat sealer
- Blood administration set – e.g. Avon ref A100
- Sterile gloves
- Plastic apron

Method:

1. Carefully retrieve CTL bag(s) for one dose from storage (wear insulated gloves) to an insulated cold transport box. Check the patient detailed on the label corresponds to the patient to be treated.

2. Have the materials and the cleaned water bath ready with sterile water at 37°C. Ensure staff member infusing the cells and the patient are ready before commencing thawing.

3. If more than one bag is required per treatment, prepare each one separately, waiting until the previous one has been infused before thawing the next.

4. Gently take the (first) CTL cryobag from the transport box/nitrogen shipper. Carefully cut open the outermost bag and retrieve the over-wrapped cryobag within. Keep the large label. Please note that the outer bag will have a small 1-2cm cut to prevent rapid expansion when exposed to room temperature.

5. Check the patient named on the label corresponds to the patient being treated. Place the cryobag into a further plastic bag, exclude as much air as possible and seal. (If more than one bag, retain the other(s) frozen meantime). Immerse the bag in the waterbath to thaw. The ports are delicate and must be treated with care to prevent any damage to the bag. They can also be more insulating and may take longer to thaw so ensure that they are fully submerged *.

   *Note: If at any stage rapid expansion of the cryocyte bag is observed during thawing, (due to ingress of LN_2) remove from water bath, sterile wipe the bag surface and pierce the outer layers at the end furthest from the ports (without damaging the innermost bag) with a sterile needle. This will allow a controlled release of pressure. Record this action in the form below. Avoid submerging pierced area.

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6. Allow to thaw gently in the warmth and avoid any temptation to squeeze the bag contents (ice crystals may damage cells). Record thaw / waterbath temperature. Remove the bag as soon as the ice has melted (clears) paying careful attention to the ports.

7. Carefully cut open the outer bag and retrieve the cryobag. There have been rare occasions when a bag seal has failed and the bag has leaked. If this occurs, please do not use the bag. Report as an incident and we'll send a replacement, if available.

8. Working aseptically, connect in to the blood administration set for infusion or give as bolus injection.

9. Administer intravenously over 3 to 5 minutes.

10. Complete the relevant section (pages 6-9), attach the cryobag labels. Please scan and e-mail (or copy and post) the completed infusion record with labels to nss.ctlbank@nhs.scot (or fax 0131 314 5799).

MONITORING FOR ADVERSE EVENTS:

- Vital signs (temperature, BP, pulse and respiration rate) should be taken twice before (at least 15 minutes apart) and every 15 minutes after injection of the cells for 1 hour and then every hour for 2 hours. Any symptoms or signs should be recorded. If no significant changes occur during the 3-hour observation period the measurement of vital signs can stop.

- To help with consistency, please use the grading system (see appendix below). Severe (grade 3) toxicity is usually an indication to stop therapy. Life-threatening (grade 4) toxicity, if attributed to the PTLD therapy, is an absolute indication to abandon therapy. Other reactions should be assessed by the treating physician for clinical significance

- Attach grade to adverse event form in the last 2 pages of the CTL treatment protocol.

- All adverse events / reactions must be reported to CTL team as soon as possible (scan and e-mail AE form to nss.ctlbank@nhs.scot (or fax to 0131 314 5799)). They, in turn, will report to SNBTS Regulatory Compliance manager.

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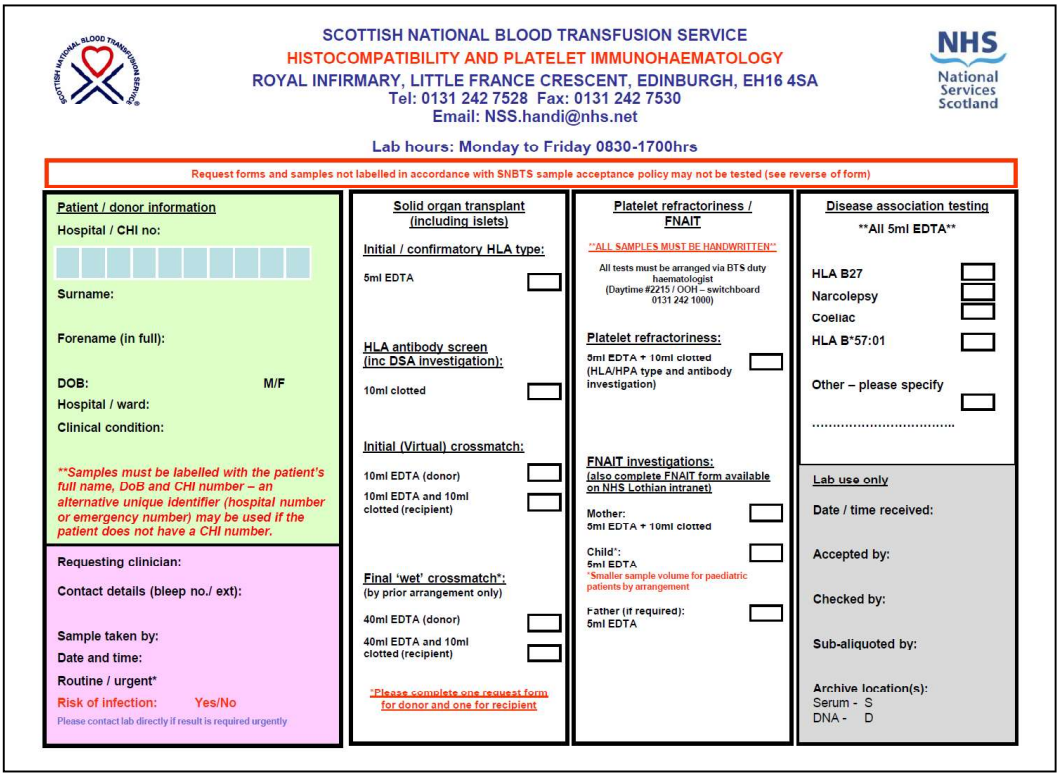
BLOOD SAMPLES for HLA antibody testing

Approximately twelve weeks post final infusion, please take a blood sample for HLA antibody testing: 5 - 10ml blood (minimum 2ml paediatric) into a plain tube for serum.

Please ensure that the tube is clearly labelled with patient identifier and date, double leakproof wrapped, with sufficient absorbent material between layers to absorb all the fluids if they leak (UN3373 Biological Substance (Category B) and Packing Instruction 650).

Please include a completed test request form (supplied), with 'CTL treatment' as the clinical condition.



SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE
HISTOCOMPATIBILITY AND PLATELET IMMUNOHAEMATOLOGY
ROYAL INFIRMARY, LITTLE FRANCE CRESCENT, EDINBURGH, EH16 4SA
Tel: 0131 242 7528 Fax: 0131 242 7530
Email: NSS.handi@nhs.net

Lab hours: Monday to Friday 0830-1700hrs

Request forms and samples not labelled in accordance with SNBTS sample acceptance policy may not be tested (see reverse of form)

Patient / donor information
Hospital / CHI no:
Surname:
Forename (in full):
DOB: M/F
Hospital / ward:
Clinical condition:
**Samples must be labelled with the patient's full name, DoB and CHI number – an alternative unique identifier (hospital number or emergency number) may be used if the patient does not have a CHI number.

Requesting clinician:
Contact details (bleep no./ ext):
Sample taken by:
Date and time:
Routine / urgent*
Risk of infection: Yes/No
Please contact lab directly if result is required urgently

Solid organ transplant (including islets)
Initial / confirmatory HLA type:
5ml EDTA ☐
HLA antibody screen (inc DSA investigation):
10ml clotted ☐
Initial (Virtual) crossmatch:
10ml EDTA (donor) ☐
10ml EDTA and 10ml clotted (recipient) ☐
Final 'wet' crossmatch*:
(by prior arrangement only)
40ml EDTA (donor) ☐
40ml EDTA and 10ml clotted (recipient) ☐
*Please complete one request form for donor and one for recipient

Platelet refractoriness / FNAIT
ALL SAMPLES MUST BE HANDWRITTEN
All tests must be arranged via BTS duty haematologist (Daytime #2215 / OOH – switchboard 0131 242 1000)
Platelet refractoriness:
5ml EDTA + 10ml clotted (HLA/HPA type and antibody investigation) ☐
FNAIT investigations:
(also complete FNAIT form available on NHS Lothian intranet)
Mother: 5ml EDTA + 10ml clotted ☐
Child*: 5ml EDTA ☐
*Smaller sample volume for paediatric patients by arrangement
Father (if required): 5ml EDTA ☐

Disease association testing
All 5ml EDTA
HLA B27 ☐
Narcolepsy ☐
Coeliac ☐
HLA B*57:01 ☐
Other – please specify ☐
.....

Lab use only
Date / time received:
Accepted by:
Checked by:
Sub-aliquoted by:
Archive location(s):
Serum - S
DNA - D

Please send to:
Dr David Turner,
H&I, Edinburgh SE Scotland Blood Transfusion Service,
Royal Infirmary of Edinburgh,
Old Dalkeith Road,
Edinburgh,
EH16 4SA

T: 0131 242 7534 / 7528

As part of a follow up / review programme and as part of required pharmacovigilance, further patient information may be requested. This will remain confidential.

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EBV-specific CTL supplied for named patient

EBV-specific CTL supplied			
CTL batch code number:		Patient first name surname	
Total number of bags:		D.o.B.	
Number of CTL per bag:		Other identifier	
Number of bags per treatment:		Patient weight (kg)	

Prepared by					
Name:		Signature:		Date:	

Receipt of EBV-specific CTL

Receipt of CTL			
Date/Time of receipt:		Security Tag Number:	Tag intact: Yes / No*
Number of bags:		Time of transfer to storage:	
Storage location: LN_2 or -80°C		Patient details correct:	Yes / No*
Temperature display / indication when transferred		Bags Intact and no damage: (includes breaks, tears, leaks[1])	Yes / No*

[1] Outer bag will have a small cut to prevent rapid expansion.
*If No or non satisfactory, contact Edinburgh SNBTS CTLbank team and comment below
(Tel: 0131 314 5545 or e-mail: nss.ctlbank@nhs.scot)

Comment					
Name:		Signature:		Date:	

Please scan completed page and e-mail to nss.ctlbank@nhs.scot (or fax to 0131 314 5799).

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CTL Treatment Protocol

Preparation for Infusion 1 : documentation

Surname:		**Forename**	
Date of Birth:		**ID number.**	

Prior to infusion					
Patient information and consent (form TCATF 189) signed: Yes/No*					
Please indicate patient health status prior to infusion: (4 point Modified International Prognostic Index)					
Stage		**ECOG (0-4) performance status**		**LDH Elevated / normal**	

Infusion 1 : EBV-specific CTL			
Date of infusion:		**Patient details correct?**	**Yes / No***
Time of thawing:		**Contents frozen before thawing?**	**Yes / No***
Preparation satisfactory?	**Yes / No***	**Time of infusion:**	
Bags Intact and no damage[1]?	**Yes / No***	**Thaw/waterbath temperature (°C)**	
Infusion well received?	**Yes / No***	**Number of bags:**	

[1] **Outer bag will have a small cut to prevent rapid expansion.**
***If No or non satisfactory, contact Edinburgh SNBTS CTLbank team and comment below**
(Tel: 0131 314 5545 or e-mail: nss.ctlbank@nhs.scot)

Attach labels in this space	**Comment**

Name:		**Signature:**		**Date:**	

Please scan completed page + label(s) and e-mail to nss.ctlbank@nhs.scot (or fax 0131 314 5799).

CTL bank, TCAT, SNBTS, The Jack Copland Centre 52 Research Avenue North, Edinburgh, EH14 4BE	Tel: 0131 314 5545 e-mail: nss.ctlbank@nhs.scot Fax: 0131 314 5799

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CTL Treatment Protocol

Preparation for 2 : EBV-specific CTL

Surname:		**Forename**	
Date of Birth:		**ID number.**	

Infusion 2 : EBV-specific CTL			
Date of infusion:		**Patient details correct?**	**Yes / No***
Time of thawing:		**Contents frozen before thawing?**	**Yes / No***
Preparation satisfactory?	**Yes / No***	**Time of infusion:**	
Bags Intact and no damage[1]?	**Yes / No***	**Thaw/waterbath temperature (°C)**	
Infusion well received?	**Yes / No***	**Number of bags:**	

[1] **Outer bag will have a small cut to prevent rapid expansion.**
***If No or non satisfactory, contact Edinburgh SNBTS CTLbank team and comment below**
(Tel: 0131 314 5545 or e-mail: nss.ctlbank@nhs.scot)

Attach labels in this space	Comment

Name:		**Signature:**		**Date:**	

Please scan completed page + label(s) and e-mail to nss.ctlbank@nhs.scot (or fax 0131 314 5799).

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CTL Treatment Protocol

Preparation for 3 : EBV-specific CTL

Surname:		**Forename**	
Date of Birth:		**ID number.**	

Infusion 3 : EBV-specific CTL			
Date of infusion:		**Patient details correct?**	**Yes / No***
Time of thawing:		**Contents frozen before thawing?**	**Yes / No***
Preparation satisfactory?	**Yes / No***	**Time of infusion:**	
Bags Intact and no damage[1]?	**Yes / No***	**Thaw/waterbath temperature (°C)**	
Infusion well received?	**Yes / No***	**Number of bags:**	

[1] **Outer bag will have a small cut to prevent rapid expansion.**
***If No or non satisfactory, contact Edinburgh SNBTS CTLbank team and comment below**
(Tel: 0131 314 5545 or e-mail: nss.ctlbank@nhs.scot)

Attach labels in this space	Comment

Name:		**Signature:**		**Date:**	

Please scan completed page + label(s) and e-mail to nss.ctlbank@nhs.scot (or fax 0131 314 5799).

CTL bank, TCAT, SNBTS, The Jack Copland Centre 52 Research Avenue North, Edinburgh, EH14 4BE	Tel: 0131 314 5545 e-mail: nss.ctlbank@nhs.scot Fax: 0131 314 5799

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CTL Treatment Protocol

Preparation for 4 : EBV-specific CTL

Surname:		**Forename**	
Date of Birth:		**ID number.**	

Infusion 4 : EBV-specific CTL			
Date of infusion:		**Patient details correct?**	**Yes / No***
Time of thawing:		**Contents frozen before thawing?**	**Yes / No***
Preparation satisfactory?	**Yes / No***	**Time of infusion:**	
Bags Intact and no damage[1]?	**Yes / No***	**Thaw/waterbath temperature (°C)**	
Infusion well received?	**Yes / No***	**Number of bags:**	

[1] **Outer bag will have a small cut to prevent rapid expansion.**
***If No or non satisfactory, contact Edinburgh SNBTS CTLbank team and comment below**
(Tel: 0131 314 5545 or e-mail: nss.ctlbank@nhs.scot)

Attach labels in this space	**Comment**

Name:		**Signature:**		**Date:**	

Please scan completed page + label(s) and e-mail to nss.ctlbank@nhs.scot (or fax 0131 314 5799).

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Appendix Grading of acute and subacute toxic effects

Toxicity	Mild 1	Moderate 2	Severe 3	Life-threatening 4
Systemic				
Fever (°C)	<38.5	38.5 - 40	>40	>40 + hypotension
Chills	Mild - mod	Severe	Rigors <2 hr	Rigors >2 hr
Skin	M-p rash <25% of body	Rash 25-50% of body	Gen. erythroderma	Exfoliative dermatitis, bullae
Allergy	Transient rash	Urticaria, drug fever >38°C	Bronchospasm or serum sickness	Anaphylaxis
Haematological*				
Hb - g/dl	9.5 - 10.9	8.0 - 9.4	6.5 - 7.9	<6.5
PMN x 10^9/L	1.3 - 2.0	0.75 - 1.29	0.5 - 0.74	<0.5
Platelet x10^{11}/L	75 - 100	50 - 74	25 - 49	<25
Haemorrhage	Petechiae	Mild loss	BT <4 units	BT ≥4 units
GI/Hepatic				
Nausea & vomiting	Nausea	Vomiting	Vomiting + iv Rx	Intractable
Diarrhoea (ml/day)	Stool >500	Stool >1000	Stool >1500	Haemorrhagic or stool >2000
Bilirubin x N	1.25 - 2.0	2.1 - 3	3.1 - 5	>5
AST x N	1.25 - 2.5	2.6 - 5	5.1 - 20	>20
Amylase x N	1.25 - 2.0	2.1 - 3	3.1 - 5	>5
ALP x N	1.25 - 2.5	2.6 - 5	5.1 - 20	>20
Renal				
Creatinine x N	1.25 - 2	2.1 - 3	>3	Needs dialysis
Proteinuria g/d	0.25 - 2	2.1 - 5	>5	Nephrotic syndrome
Haematuria	Microscopic	Gross	Gross + clots	Needs transfusion
Neurological*				
Central	Poor memory	Confusion or lethargy	Disorientation or stupor	Coma and/or seizures
Peripheral	Paraesthesia ↓ DTR	Absent DTR + weakness	+++ weakness	Paralysis
Headache	Mild, untreated	With analgesia	With narcotic	Intractable
Constipation	Mild	Moderate treated	Abdominal distension	Distension and vomiting
Pulmonary*	Mild	SOBOE	Dyspnoea at rest	Bedridden
Cardiac				
Rhythm	ST >110 at rest	Unifocal PVC atrial arrhythmia	Multifocal PVC	Ventricular tachycardia
Function	Abnormal signs	Untreated dysfunction	Treated dysfunction	Unresponsive to therapy

*These values may be age dependent and/or are difficult to assess in children
N = upper end of normal range

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Reporting of adverse events or reactions

Any adverse event / reaction must be reported immediately to CTL team by e-mail NSS.ctlbank@nhs.scot (or fax to 0131 314 5799). Tel 01224 812 401 or 0131 314 5545.

Serious adverse event arising from the use of Human Cells as the starting material (As per EUTCD 2004/23/EC)	Any untoward occurrence which may be associated with the procurement, testing, processing, storage or distribution of tissue or cells intended for human application and which, in relation to a donor of tissue or cells intended for human application or a recipient of tissue or cells: – (a) **might** lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions, or (b) **might** result in, or prolong, hospitalisation or morbidity
Serious adverse reaction from the use of the unlicensed medicinal product	Any reaction associated with the use of the antiEBV CTL product which **might** lead to death or life-threatening, disabling or incapacitating conditions, result in, or prolong, hospitalisation or morbidity or any other medically significant adverse reaction including (but not restricted to the transmission of a communicable disease

PLEASE COMPLETE ONE FORM FOR EACH ADVERSE EVENT / ADVERSE REACTION

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PLEASE COMPLETE ONE FORM FOR EACH ADVERSE EVENT / REACTION

REPORTING INFORMATION

Hospital Name _____

Person completing this form (Name)_____

Designation _____

Date form completed _____ (DD/MM/YYYY)

PATIENT IDENTIFICATION

SNBTS issue code **Named Patient Basis use** Patient hospital/id number _____

Patient's Initials _____ Patient Sex M ☐ F ☐

Date of birth _____ (DD/MM/YYYY)

TREATMENT INFORMATION

Date of CTL treatment ☐☐☐☐☐☐ Time of treatment ☐☐☐☐
Day Month Year 24 hour

Batch No _____

DETAILS OF EVENT / REACTION

Please record the diagnosis or describe the event in as few words as possible:

_____

Date event/reaction started ☐☐☐☐☐☐ Day Month Year Time event/reaction started ☐☐☐☐ 24 hour

Date event/reaction resolved ☐☐☐☐☐☐ Day Month Year Time event/reaction resolved ☐☐☐☐ 24 hour

Outcome
Recovered ☐ Recovering ☐ Continuing ☐ Patient Died ☐ Outcome Unknown ☐

Are there any clinical sequelae? Yes ☐ No ☐
If yes, please describe:

_____

Is the event related to the CTL treatment ? Probably ☐ Possibly ☐ Unrelated ☐

TREATMENT REQUIRED (please give details on next page)

None ☐

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Specific drug therapy Yes ☐ No ☐

if yes, list all drugs used:

Drug (Brand, if known)	Daily dose/route of admin	Date started	Time started
_____	_____	Day Month Year	24hour
_____	_____	Day Month Year	24hour
_____	_____	Day Month Year	24hour

Other treatment Yes No
If yes, please describe

_____

CONCOMITANT MEDICATION

List other generic drugs being given:-

Generic Name	Dosage regimen	Route	Date Started	Time Started
_____			Day Month Year	24 hour
_____			Day Month Year	24 hour
_____			Day Month Year	24 hour
_____			Day Month Year	24 hour
_____			Day Month Year	24 hour

ADDITIONAL RELEVANT INFORMATION **(e.g. test results etc)**

Clinician review and approval of content

signed_____

Name _____ Date _____

Please scan completed pages and e-mail to nss.ctlbank@nhs.scot (or fax to 0131 314 5799).