TCATF 184 06
(Relates to SOP No. TCATS CTL 003)

CTL Treatment Protocol

EBV-specific CTL for Treatment of EBV-positive 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 cryopreserved in vapour-phase liquid nitrogen at <-150°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 normally be shipped together and must be transferred to suitable storage and kept cryopreserved, preferably in the vapour phase of liquid nitrogen (or equivalent <-135°C storage), 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 either 10% dimethyl sulphoxide (DMSO) and in 10% human albumin solution (HAS) or Plasma-Lyte® 148 and CryoStor® CS10 (~7% DMSO).

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 cryopreserved until ready to prepare for treatment.

Delivery of EBV-specific CTL and Transfer to Local Storage

The cryopreserved 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 cryopreserved, and quickly transfer to temperature monitored vapour phase liquid nitrogen storage.

The cryobag is fragile when frozen. Please handle with care.

Upon receipt:

- Record the time, as well as temperature / status displayed on the 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 or signs of thawing (record on page 5).

Complete page 5 and then please copy/scan the completed form back to us. If there are any concerns these must be reported as soon as possible by telephone or email to CTL staff in Edinburgh on +44 (0)131 314 5545 or nss.ctlbank@nhs.scot. Any cryobags that raise concern must be quarantined.

Patient Consent

A patient information and consent form is provided as a basis for the discussion between the patient (or their guardian) and their treating physician. The signed original should be kept in the patient notes. Two copies are also required: one for the patient and one for SNBTS, Edinburgh. Please send a copy of the completed consent form by email to nss.ctlbank@nhs.scot.

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(Relates to SOP No. TCATS CTL 003)

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Dose

For the number of bags required per treatment refer to page 5, the personalised section of this form. Approximately 1-2x10^6 CTL/kg body weight should be given at each infusion (target of 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. On occasion if excess product is available compared to the calculated dose it may be advisable to increase the dose. Increasing dose or using part of a bag should be decided in consultation with SNBTS medical staff.

Method for Infusion of EBV-specific CTL

Keep the bag(s) cryopreserved until everything is ready for the treatment. The cryoprotectant DMSO is harmful to metabolising cells so aim to **infuse the cells as soon as possible after thawing**, or keep thawed cells cool (<10°C) if there is any unexpected delay.

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

- 37°C waterbath (or equivalent, e.g. bead bath) freshly cleaned, filled with sterile water
- Insulated transport box / dry shipper to maintain treatment bag(s) < -80°C
- Insulated gloves
- Sterile wipes
- Scissors
- Blood administration set – e.g. Avon ref A100
- Sterile gloves
- Sterile normal saline for infusion (0.9%)

Method:

1. Carefully retrieve CTL bag(s) for one dose from storage (wear insulated gloves) to a dry shipper or insulated cold transport box containing dry ice. 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, retaining the other(s) frozen and waiting until the previous one has been infused before thawing the next.

4. Gently take the (first) CTL cryobag from the dry shipper / transport box. Carefully cut open the outermost bag and retrieve the over-wrapped cryobag within. Keep the large named patient label and affix to documentation.

5. Check the patient named on the label corresponds to the patient being treated and that there are no apparent signs of damage to the bag. Immerse the bag in the waterbath to thaw. The ports can be more insulating and may take longer to thaw so ensure they are fully submerged*.

   *Note: If the overwrap is inflated use sterile scissors to create a small cut in the overwrap bag at the end furthest from the bag ports, ensure the primary product container is not damaged by the cut. This will allow excess air to be released from the overwrap bag to prevent additional insulation leading to an increased thawing time. Where possible, avoid submerging the cut area.

6. Allow to thaw gently in the warmth. Leave the bag immersed without any agitation for 1 minute then gently agitate the contents until the last ice has melted. Record the thaw time and waterbath temperature. Remove the bag as soon as the ice has melted.

7. Carefully cut open the outer overwrap bag and retrieve the cryobag. Carefully inspect for the possible presence of a leak. 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 it to the blood administration set for infusion or give as bolus injection. If using a blood administration set, prime the set with sterile normal saline before starting the infusion.

9. Administer intravenously over 3 to 5 minutes (i.e. approx. 3-5mls/min). If administration was through a blood administration set, at the end of the infusion flush through with sterile normal saline to ensure that all the cells are transferred to the patient and not lost in the line.

10. Complete the relevant section (pages 6-9) and attach the cryobag labels. Where multiple bags are infused, additional sheets of paper can be used to attach labels to. Please scan and e-mail (or photocopy and post to the postal address at the bottom of page 6) the completed infusion record with labels to nss.ctlbank@nhs.scot.

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 infusion 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 (in the appendix on page 10). 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.

- Indicate the grade of any adverse events in the adverse event form in the last 2 pages (pages 12 and 13) of the CTL treatment protocol.

- All adverse events / reactions must be reported to the CTL team as soon as possible (scan and e-mail Adverse Event form to nss.ctlbank@nhs.scot). They, in turn, will have a duty to report to the SNBTS Regulatory Compliance manager.

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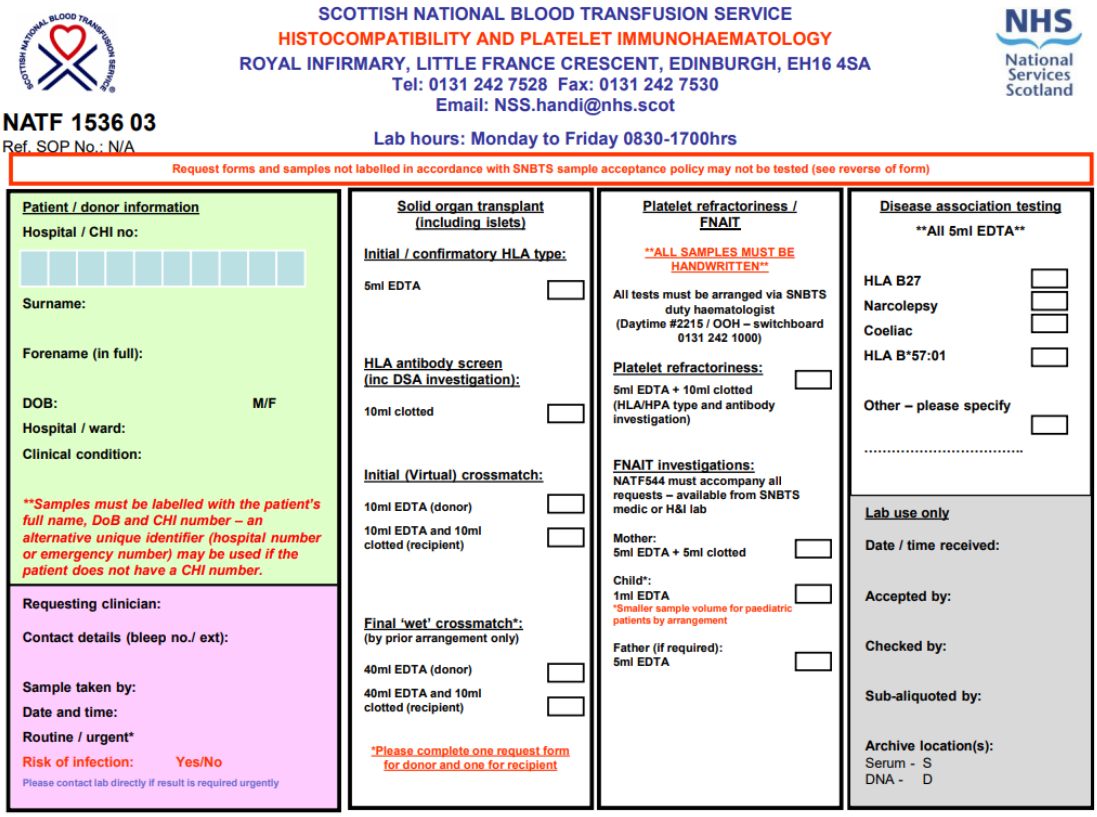
Blood Samples for HLA Antibody Testing

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

Please ensure that the tube is clearly labelled with the patient identifiers and date of sampling, placed in a double leakproof container, with sufficient absorbent material between layers to absorb all the fluids if they were to 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.scot
Lab hours: Monday to Friday 0830-1700hrs

NATF 1536 03
Ref. SOP No.: N/A

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 SNBTS duty haematologist (Daytime #2215 / OOH – switchboard 0131 242 1000)
Platelet refractoriness:
5ml EDTA + 10ml clotted (HLA/HPA type and antibody investigation)
FNAIT investigations:
NATF544 must accompany all requests – available from SNBTS medic or H&I lab
Mother: 5ml EDTA + 5ml clotted
Child*: 1ml 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:
Scottish National Blood Transfusion Service (SNBTS)
Histocompatibility and Immunogenetics (H&I)
Royal Infirmary of Edinburgh
Little France Crescent
Edinburgh
EH16 4SA

Tel: +44 (0)131 242 7528 / 7534
Email: NSS.handi@nhs.scot

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 <-135°C		**Patient details correct:**	**Yes / No***
Logger temperature display / indication when transferred		**Bags intact / free from damage: (includes breaks, tears, leaks)**	**Yes / No***

***If No or non satisfactory, contact Edinburgh SNBTS CTL team immediately and comment below**
(Tel:+44 (0)131 314 5545 or e-mail: nss.ctlbank@nhs.scot)

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

Please scan completed page and e-mail to nss.ctlbank@nhs.scot.

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CTL Treatment Protocol

Preparation for Infusion 1: EBV-specific CTL

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***
Contents frozen before thawing?	**Yes / No***	**Waterbath temperature (°C)**	
Time of thawing:		**Preparation satisfactory?**	**Yes / No***
Bags intact/free from damage?	**Yes / No***	**Time of infusion:**	
Number of bags:		**Infusion well received?**	**Yes / No***

***If No or non satisfactory, contact Edinburgh SNBTS CTL team immediately and comment below**
(Tel: +44 (0)131 314 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.

CTL, TCAT, SNBTS, The Jack Copland Centre
52 Research Avenue North, Edinburgh, EH14 4BE
Tel: +44 (0)131 314 5545
e-mail: nss.ctlbank@nhs.scot

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CTL Treatment Protocol

Preparation for Infusion 2: EBV-specific CTL

Surname:		**Forename:**	
Date of Birth:		**ID Number:**	

Infusion 2: EBV-specific CTL			
Date of infusion:		**Patient details correct?**	**Yes / No***
Contents frozen before thawing?	**Yes / No***	**Waterbath temperature (°C)**	
Time of thawing:		**Preparation satisfactory?**	**Yes / No***
Bags intact/free from damage?	**Yes / No***	**Time of infusion:**	
Number of bags:		**Infusion well received?**	**Yes / No***

***If No or non satisfactory, contact Edinburgh SNBTS CTL team immediately and comment below**
(Tel: +44 (0)131 314 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.

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CTL Treatment Protocol

Preparation for Infusion 3: EBV-specific CTL

Surname:		**Forename:**	
Date of Birth:		**ID Number:**	

Infusion 3: EBV-specific CTL			
Date of infusion:		**Patient details correct?**	**Yes / No***
Contents frozen before thawing?	**Yes / No***	**Waterbath temperature (°C)**	
Time of thawing:		**Preparation satisfactory?**	**Yes / No***
Bags intact/free from damage?	**Yes / No***	**Time of infusion:**	
Number of bags:		**Infusion well received?**	**Yes / No***

***If No or non satisfactory, contact Edinburgh SNBTS CTL team immediately and comment below**
(Tel: +44 (0)131 314 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.

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52 Research Avenue North, Edinburgh, EH14 4BE
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e-mail: nss.ctlbank@nhs.scot

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CTL Treatment Protocol

Preparation for Infusion 4: EBV-specific CTL

Surname:		**Forename:**	
Date of Birth:		**ID Number:**	

Infusion 4: EBV-specific CTL			
Date of infusion:		**Patient details correct?**	**Yes / No***
Contents frozen before thawing?	**Yes / No***	**Waterbath temperature (°C)**	
Time of thawing:		**Preparation satisfactory?**	**Yes / No***
Bags intact/free from damage?	**Yes / No***	**Time of infusion:**	
Number of bags:		**Infusion well received?**	**Yes / No***

***If No or non satisfactory, contact Edinburgh SNBTS CTL team immediately and comment below**
(Tel: +44 (0)131 314 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.

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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 difficult to assess in children
N = upper end of normal range

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CTL Treatment Protocol

Reporting of Adverse Events or Reactions

Any adverse event / reaction must be reported immediately to the CTL team by email and/or telephone.

- E-mail NSS.ctlbank@nhs.scot
- Tel +44 (0)1224 812 401 or +44 (0)131 314 5545
- Mob +44 (0)7734 805 003.

Serious adverse event arising from the use of Human Cells as the starting material (As per Statutory Instrument 2007 No. 1523: The Human Tissue (Quality and Safety for Human Application) Regulations, as amended)	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 anti-EBV 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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CTL Treatment Protocol

PLEASE COMPLETE ONE FORM FOR EACH ADVERSE EVENT / REACTION

REPORTING INFORMATION

Hospital Name _____

Name of Person completing this form _____

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 ☐☐☐☐☐☐ Day Month Year Time of treatment ☐☐☐☐ 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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CTL Treatment Protocol

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.