SOP: INPATIENT MANAGEMENT OF PATIENTS RECEIVING IMMUNE EFFECTOR CELLS (INCLUDING CAR-T CELLS)

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STANDARD OPERATING PROCEDURE

TITLE: INPATIENT MANAGEMENT OF PATIENTS RECEIVING IMMUNE EFFECTOR CELLS (INCLUDING CAR-T CELLS)

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Author	**Adrian Bloor**
Cellular Therapy Lead	**Amit Patel**
Clinical Services Manager	**Jo Tomlins**
Clinical Practice Facilitator	**Ruth Clout**
Quality Manager	**Simon Cliffe**

1.0 INDICATIONS OF PRACTICE

This document is intended to act as an outline guide for management of patients receiving immune effector cells and should be read in conjunction with detailed SOP regarding patient assessment and management of toxicities.

For patients participating in clinical trials the management of the inpatient stay may be defined within the trial protocol. It is a regulatory requirement that clinical trials are approved by the national competent authority, MHRA and a research ethics committee. In addition clinical trial protocols must undergo a local capacity and capability review to ensure the research can be conducted in accordance with the protocol (Approving apheresis and high risk immune effector cell trials SOP (QM-11) and R&D001.000 Study Set Up - Capacity and Capability Process). This SOP and trial protocol should be used in conjunction where a patient is participating in a clinical trial.

2.0 AUTHORISED PERSONNEL/TRAINING REQUIRED

Medical staff: must be familiar with the assessment of patients undergoing treatment and diagnosis and immediate management of treatment related complications. See appendix G and H for specific patient management responsibilities on the clinical areas.

Nursing staff: the nursing team should be aware of the needs of patient undergoing immune effector cell treatment and recognition and assessment of treatment related complications. Student nurses and HCA should be supervised and seek guidance when attending to patients undergoing immune effector cell treatment. See appendix G and H for specific patient management responsibilities on the clinical areas.

3.0 PRE-TREATMENT AND BASELINE INVESTIGATIONS

3.1 Acceptance criteria, pre treatment and baseline investigations

For details on all pre-treatment and baseline investigations please refer to DOC945 coordinating adoptive cell therapy: chimeric antigen receptor t-cell (car-t) therapy (including tcr, car-nk, immunotherapy)

4.0 SUPPORTIVE CARE DURING TREATMENT

4.1 Medication

Many immune effector cell protocols lead to prolonged (>1-2 weeks) of bone marrow suppression. In such cases, patients should receive anti-infective prophylaxis as per autologous stem cell transplantation (see SOP: Haematology Summary of Prophylaxis)

- Levofloxacin 500mg po od
- Aciclovir 400mg po bd
- Fluconazole 200mg od
- Co-trimoxazole (Septrin) 960mg po od mon/wed/fri, if the patient has low counts Co-trimoxazole (septrin) is stopped and pentamidine nebuliser given on discharge
- Lansoprazole 30mg od
- Consider leviracetam 500mg po bd for patients at high risk of neurological toxicity (to be discussed at MDT), to begin from the start of conditioning. Also for patients with prolonged CRS and/or ICANs greater than 0 with neurological symptoms, to begin from the start of prolonged CRS/ICANs.
- Tumour lysis prophylaxis as per standard protocols. See SOP: Tumour Lysis Syndrome: Prophylaxis and Management Guidelines (WRD-60). Patients will be tested (as per DOC945 coordinating adoptive cell therapy SOP) for G6PD deficiency if they are at high risk of TLS and have not received rasburicase previously.

4.2 Blood tests

Patients require daily blood tests with additional monitoring for treatment related complications (eg infection – CRP, coagulopathy – coag and fibrinogen, HLH – ferritin); see SOP: Palatine Ward routine samples), or as per trial protocol).

- E.g. Daily FBC, Christie profile

- Coagulation (Clauss fibrinogen), CRP, ferritin and magnesium three times weekly (Mon, Wed, Fri). If Clauss Fibrinogen is below 1.5 then supplement fibrinogen concentrate (post infusion only)
- Glucose if patient on steroids or if clinically indicated
- Additional monitoring tests for CAR-T patients are outlined in the table below:

Day	Disease monitoring	CAR-T monitoring
+7 inpatient	CRP, Ferritin, LDH	Immune monitoring HIV PCR/CMV PCR
+14 inpatient	CRP, Ferritin, LDH	Immune monitoring HIV PCR /CMV PCR
+21		Flow cytometry HIV PCR

Further specific investigations will be undertaken as clinically indicated and at the physicians discretion

- For investigations post discharge, please refer to DOC988 chimeric antigen receptor t-cell therapy discharge and follow up SOP.

4.3 Observations - general

General observations (vital signs, NEWS2 score, VIP score, weight, skin assessment, mouth assessment, bowel assessment) will be performed according to the SOP: Nursing Observations for all Haematology and Stem Cell Transplant Patients) and Trust NEWS2 policy (SOP: National Early Warning Score 2 Policy (NEWS2) or for trial patients as per protocol if the requirement is more frequent.

- Vital signs will be recorded every 4 hours for all patients
- More frequent observations will be performed according to patient's clinical condition.
- If patient experiences a temperature above 37.5 degrees, a full set of observations should repeated hourly. If the temperature remains high discuss with senior medical team. Seek advice from senior medical team prior to administering paracetamol.

4.4 Observations – Cytokine release syndrome

Patients will be monitored at least twice daily for evidence of cytokine release syndrome (CRS) or more frequently if clinical concern or as directed by medical staff or trial protocol). Routine monitoring will be undertaken by trained nursing staff or junior medical staff. CRS will be graded according to patient observations and recorded on paper form in appendix F (printed out for use with patient) or using CWP nursing assessment eform when available. See also appendix A-D with regard to assessment of organ function and differential

diagnosis of CRS, and SOP: Guidelines for management of cytokine release syndrome.

CRS typically occurs within 1-2 weeks of treatment and is more common in the following groups:

- Advanced age
- Co-morbidity
- Pre-treatment organ dysfunction
- Bulky disease
- Certain CAR-T products (available data suggest that this is more common in patients treated with CD19 CARs than for other targets although patterns will become clearer with increased use)
- Grade 3-4 CRS is more common in patients who develop evidence of CRS early (within 3 days) of initiation of treatment and earlier intervention should be considered

4.5 Observations – Immune effector cell-associated neurotoxicity syndrome (ICANS)

Patients will be monitored at least twice daily for evidence of neurotoxicity (Immune effector cell-associated neurotoxicity syndrome ICANS) or more frequently if clinical concern or as directed by medical staff or per trial protocol). Routine monitoring will be undertaken by trained nursing staff or junior medical staff. Neurotoxicity will be graded as per the ICE Score (Immune effector Cell associated Encephalopathy) system developed from the ASBMT ICANS consensus and recorded on paper form in appendix E (printed out for use with patient) or using CWP nursing assessment eform when available. See also SOP: Neurological Disease in Stem cell Transplantation and Cellular Therapy for more details. Nursing and junior medical staff must seek medical attention and senior review for patients showing signs of potential neurological toxicity (grade 1 or above) or change in grade.

Neurotoxicity most frequently occurs within 1 week of IEC (e.g.CAR-T therapy) infusion often in combination with CRS however patients should also be monitored for later neurotoxicity which may occur without evidence of CRS

5.0 TREATMENT

Complications from immune effector cell therapy may have overlapping presentation. Comparison between some of the common features of toxicities (sepsis, HLH, thrombotic microangiopathy, cytokine release syndrome) are shown in appendix C. Patients with signs of clinical deterioration must have senior medical review (Registrar and or Consultant). A treatment algorithm is shown in appendix D although treatment decisions must be taken in conjunction with senior

medical review and advice from neurology and CCU medical teams as appropriate.
For patients participating in clinical trials procedures may be defined within the trial protocol. It is a regulatory requirement that clinical trials are approved by the national competent authority, MHRA and a research ethics committee. In addition clinical trial protocols must undergo a local capacity and capability review to ensure the research can be conducted in accordance with the protocol (Approving apheresis and high risk immune effector cell trials SOP (QM-11) and R&D001.000 Study Set Up - Capacity and Capability Process). The SOPs and trial protocol are used in conjunction where a patient is participating in a clinical trial.

5.1 Sepsis

Patients with evidence of sepsis will be treated according to the sepsis and NEWS2 policies (SOP: Guidelines for the management of sepsis, SOP: National Early Warning score (NEWS2) policy) however it is very important to recognise that other complications of immune effector cell therapy (e.g. cytokine release syndrome, thrombotic microangiopathy, HLH) can also present with similar symptoms such as fever, neurological changes and organ dysfunction)

5.2 Cytokine release syndrome (CRS)

Management of CRS is as detailed in SOP: Guidelines for management of cytokine release syndrome.

Particular care should be taken with patients who have high tumour bulk, co-morbidities, abnormal organ function or who develop early CRS (within 3 days of initiation of treatment). In this patient group the risk of developing more significant CRS is greater and a lower threshold for initiation of anti IL6 therapy should be considered.

5.3 Neurological toxicity - **Immune effector cell-associated neurotoxicity syndrome ICANS**

Principles for management are as below, see SOP: Neurological disease in stem cell transplantation and cellular therapy for more detailed information

- Supportive care, close monitoring (including MRI, LP, EEG) for grade 1 disease
- Neurology opinion for patients with toxicity ≥ grade 2 or deteriorating patients
- Treat co-existent CRS as per protocol
- Anti-convulsants for seizures
- Steroids for grade 2 or greater disease

- CCU transfer considered for grade 2 and mandated for grade 3-4 disease. Patients with uncontrolled status epilepticus or raised intracranial pressure should be considered for transfer to neurological ITU at Salford

5.4 HLH

Patients with suspected HLH and grade ≥3 organ dysfunction should be treated with CRS protocol and consider use of etoposide and intrathecal chemotherapy for patients resistant to therapy and evidence of CNS disease respectively. See SOP: HLH and Macrophage Activation Syndrome for more information.

6.0 DISCHARGE AND FOLLOW UP

Inpatient discharge will occur approximately day +12 to Day +30:

- Day 12 onwards, as assessed by attending haematology consultant when patient is fit to be discharged to ambulatory care. To be seen by the Haematology CNS or Cellular Therapy co-ordinator to confirm follow up arrangements if possible
- Day 14 onwards all CART patients will have additional blood samples as per section 4.2
- **Patients must not be discharged on a FRIDAY or over the WEEKEND**. They will remain under the care of ambulatory care until day 30+.
- Patients will attend ambulatory care for Mon/Wed/Fri bloods, post treatment nursing review and ICANS assessment and bloods as per section 4.2 and ambulatory care nursing protocol.
- Patients will have a weekly clinic review (Tuesday PM)
- Please contact the cellular therapy co-ordinators on 0161 446 8011 if needed, who will co-ordinate day 30+ restaging and clinic appointment
- Ensure the patient has received a Christie hotline card in case of any issues post discharge.

Full follow up details can be found in DOC988 CAR-T follow up and DOC945 coordinating adoptive cell therapy: chimeric antigen receptor t-cell (car-t) therapy (including tcr, car-nk, immunotherapy) SOP.

7.0 APPENDIX A: CYTOKINE RELEASE SYNDROME (CRS)

Fever, low blood pressure and respiratory distress are the key features of CRS, however this can also present with evidence of other organ dysfunction. See appendix B for detailed organ function testing but some of the key things to watch which *can* be a sign of patient developing CRS are:

- Pulse – fast or slow even with no symptoms
- Shortness of breath

- Vomiting more than once or diarrhoea more than 4 times per day
- Abnormal liver function (eg AST > 99 iu/l, Bilirubin > 30 umol/l)
- Urine output falling or AKI alert on CWP
- Blood clotting abnormal with evidence of DIC (PT and APTT raised with low fibrinogen)
- Unexplained skin rash

Many of these abnormalities have other causes (eg infection or drug toxicity) however early identification of patients with CRS at stage 1 and 2 when on the ward is essential; if any doubt seek advice from a senior colleague or medical staff.

Grading of abnormal organ function is detailed in appendix B

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8.0 APPENDIX B: ORGAN FUNCTION ASSESSMENT (For trial patients refer to the protocol for toxicity management)

Symptom/Sign	Grade 1	Grade 2	Grade 3	Grade 4
Heart: Abnormal heart rate	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated
Heart: Heart failure	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
Respiratory: Shortness of breath	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Gastrointestinal: Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Gastrointestinal: Diarrhoea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Liver: Bilirubin elevated	20-30 umol/l	31-60 umol/l	61-200 umol/l	>200 umol/l

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Liver: AST elevated	34-99 iu/l	100-165 iu/l	166-660 umol/l	>660 umol/l
Kidney: AKI	≥1.5–1.9x baseline serum creatinine level or ≥26 umol/l above baseline. Urine output: <0.5 ml/kg/hr for >6 hr.	>2.0–2.9x baseline serum creatinine level. Urine output: <0.5 ml/kg/hr for >12 hr.	≥3.0x baseline serum creatinine level or serum creatinine level ≥353 umol/l with a rapid increase of 44 umol/l within 48 hr, or need for renal replacement therapy. Urine output: <0.3 ml/kg/hr ≥24 hr or anuria for >12 hr	
Bleeding: Disseminated intravascular coagulation		Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated
Skin: Rash	Covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences

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9.0 APPENDIX C: COMPARISON OF SERIOUS TOXICITIES FOLLOWING IMMUNE EFFECTOR CELL THERAPY (For trial patients refer to the protocol for toxicity management)

The table below compares some of the clinical and laboratory parameters encountered in patients following immune effector cell therapy. This is not exhaustive and should not be relied on in isolation to make a diagnosis. Some patients may present with more than one syndrome at the same time and there is significant overlap between these (notably HLH and cytokine release syndrome which may be best regarded as being on the same spectrum of disorders).

Parameter	Sepsis	HLH	Thrombotic microangiopathy	Cytokine release syndrome[1]
Fever	Yes	Yes	Yes	Yes
Tachycardia	Yes	Yes	No	Yes
Hypotension	Yes	Yes	No	Yes
Neurology	Non-specific findings (eg drowsiness) maybe observed but significant neurology uncommon (unless CNS infection)	Non-specific including ataxia, confusion and seizures	Wide range of symptoms including headache, confusion, change in personality (including irritability) and seizures.	May lead to associated encephalopathy syndrome
Renal	May complicate sepsis due to hypoperfusion	Renal dysfunction common. Low Na due to SIADH frequent	Renal disease common especially in HUS like presentation	Common related to hypoperfusion. Electrolyte disturbance (low Na, K, PO4 common)
Liver	Not characteristically affected	Hepatic dysfunction very common	Not characteristically elevated	Hepatic dysfunction common
Rash	Not characteristically present	Yes – rash and bleeding	Not typical	Yes – less common than with HLH
CRP	Elevated	Elevated	Not typically elevated	Typically elevated (although not seen in all cases) and high values(>150 mg/l) typical for grade 3-4 disease.
LDH	Not characteristically effected	Typically elevated	Characteristic abrupt rise in LDH	Typically elevated and high values (>1500 iu/l) in grade 3-4 disease
Ferritin	Elevated	Markedly elevated (maybe >10000	Not typically elevated	Typically elevated (although not seen in

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		ng/ml)		all cases) especially with grade 3-4 disease (maybe >10000 ng/ml)
Blood count	Raised white count although may not be observed in patients following chemotherapy	Pancytopenia is characteristic	Thrombocytopenia, and microangiopathic haemolysis leading to red cell fragmentation (schistocytes on blood film)	No specific abnormalities – counts may be low due to conditioning chemotherapy
Clotting	DIC may be seen in severe cases	Low fibrinogen and coagulopathy. DIC is common	Normal	May develop DIC picture but less common than with HLH
Other	Wide range of clinical presentation depending on the site and severity of infection	May cause significant respiratory distress. Bone marrow shows evidence of haemophagocytosis	Decreased haptoglobin,Direct Antiglobin Test (DAT or Coomb's test)negative	Severe respiratory distress in up to 15% of patients.

[1]Teachey DT *el al.* Cancer Discov 2016;6:664

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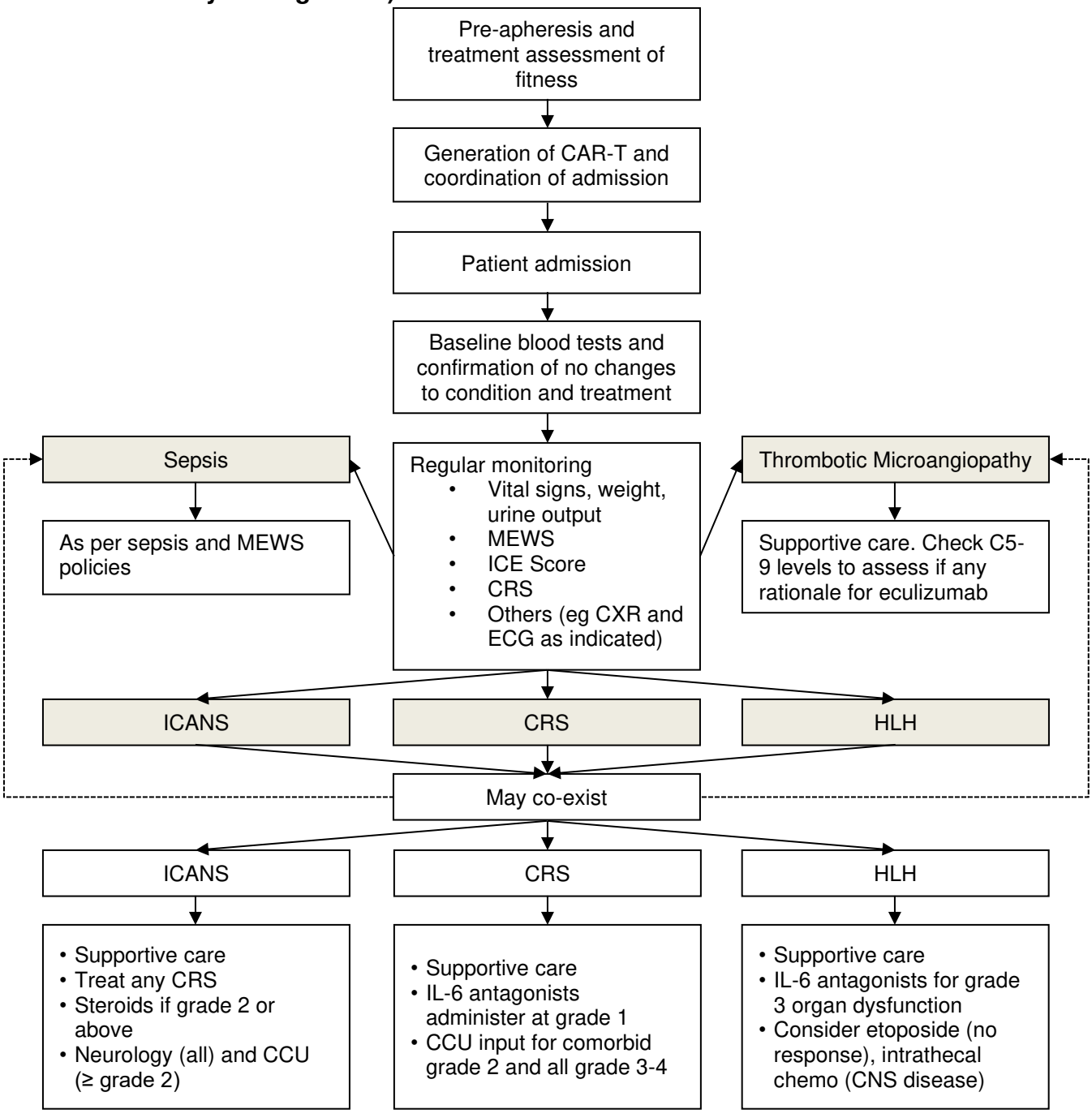
10.0 APPENDIX D: FLOW CHART FOR MANAGEMENT OF TOXICITIES FROM IEC THERAPIES (For trial patients refer to the protocol for toxicity management)



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10.0 APPENDIX E: ASSESSMENT OF NEUROLOGICAL STATUS FOR PATIENTS RECEIVING IMMUNE EFFECTOR CELLS (CAR-T, TCR) ICANS IMMUNE EFFECTOR CELL-ASSOCIATED ENCEPHALOPATHY (For trial patients refer to the protocol for neurological status assessments)

Name										**Hospital Number**				
	Year	Month	City	Where are we	Follows command	Name object 1	Name object 2	Name object 3	Serial 10s	ICE Score	ICE Grade	Seizure Grade	Conscious Level Grade	Overall Grade
Date and time														
Name	**Sentence**													
Date and time														
Name	**Sentence**													

ICE Score	**ICE grade**	**Seizure grade**	**Conscious level grade**	**Overall grade**
Score 1 point for correct answer to each of 9 questions and correctly writing any sentence. The total (maximum 10) is the ICE score used to calculate the ICE grade	Grade 0 – ICE score 10 Grade 1 – ICE score 7-9 Grade 2 – ICE score 3-6 Grade 3 – ICE score 0-2 Grade 4 – unresponsive	Grade 0 – no seizures Grade 3 – seizures that resolve rapidly Grade 4 – seizures that take >5 mins to resolve	Grade 0 – AVPU Awake Grade 2 – AVPU Verbal Grade 3 – AVPU Pain Grade 4 – AVPU Unresponsive	Highest grade (ICE, seizure, conscious level)

Seek senior medical review if clinical concerns, changes to grade/symptoms or overall grade ≥1

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11.0 APPENDIX F: ASSESSMENT OF CYTOKINE RELEASE SYNDROME (For trial patients refer to the protocol for neurological status assessments)

Assessment for cytokine release syndrome (CRS)								
Patient name and number or addressograph	Date and time	Date and time	Date and time	Date and time	Date and time	Date and time	Date and time	Date and time
	Name	Name	Name	Name	Name	Name	Name	Name
	Grade	**Grade**	**Grade**	**Grade**	**Grade**	**Grade**	**Grade**	**Grade**
Temperature 0- None 1- ≥38C or has received antipyretics or tocilizumab for CRS								
WITH								
Blood Pressure support 0- None 2- Low blood pressure requiring iv fluids not requiring vasopressors 3- Requiring a vasopressor with or without vasopressin								
AND/OR								
Breathing 0- None 2- Requiring low-flow oxygen < 6l / minute 3- Requiring high-flow oxygen >6l / minute, non-rebreather mask or venturi mask 4- Requiring positive pressure (eg.CPAP, BiPAP intubation or mechanical ventilation)								
Overall Grade The **MAXIMUM** grade recorded								

Patients require medical review if they develop any signs of CRS.

Urgent senior review is required if deteriorating, changes to CRS grade or CRS > grade 1

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12.0 APPENDIX G: IEC Clinical Trial Patient Management on Palatine Ward

- This document outlines arrangements and responsibilities for the inpatient management of CART trial patients on Palatine Ward.
- Clinical trials of investigational medicinal products are regulated by the MHRA and the clinical trial protocol is a legal document. The trial protocol must be followed at all times.
- The trial PI will oversee all aspects of trial conduct at The Christie; all protocol related decisions must be made in consultation with the PI or delegated sub-I on their team.

Pre-treatment

Trial team	**Haematology Transplant Team**
Review trial protocols during the set-up phase as per the SOP QM-11 and in line with the CTRG process.	
Mandatory attendance at the ATMP R&I, trial SIV and related trial training sessions, as well as the weekly transplant MDT/scheduling meetings pre-admission.	
GCP and trial-specific training with designated roles and responsibilities listed on the signed trial delegation log (It is the responsibility of the PI/trials team to ensure the delegation log is maintained).	
All protocol mandated activities including but not limited to: • Patient identification and distribution of patient information sheet • Signed informed trial consent • Trial Screening • Confirmation of trial eligibility	
Written communication with apheresis and transplant teams, and support service leads (e.g. CCU, neurology etc)	Apheresis and admission scheduling at Transplant MDT as per co-ordination of CART SOP. Apheresis assessment, consent & procedure (as per trial protocol)
Clinical documentation review of trial patients at scheduled and unscheduled outpatient visits	
Co-ordination of the patient timeline including apheresis, LD chemotherapy and admission for C1D1 must be discussed on a case-by-case basis initiated by the trial team and the Sponsor, and discussed with apheresis and transplant teams (via the Transplant MDT) and support service leads (via written correspondence)	

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Treatment (conditioning treatment, CART infusion and management of toxicities)

Trial team	Haematology Transplant Team
Patients will be admitted to PTW under the Attending Physician who will be responsible for the management of the patient according to the trial protocol and Trust polices where this is not specified in the protocol. All protocol-specified decisions must be discussed with the trial PI/delegated sub-I. The length of admission will be determined by the trial protocol and the medical condition of the patient. The treatment period also covers readmission for management of TEAEs e.g. late CRS/neurological toxicity and repatriation to PTW following escalation of care (e.g. to CCU)	
The PI/disease group Sub-I and Attending Physician will attend the weekly grand ward round to discuss patient management.	
Administration of conditioning treatment and ATIMP by trial research nurses	PTW ward nurses/CPF to support cellular therapy research nurses
Trial PI to maintain oversight of patient management	Patient management in accordance with the trial protocol and in discussion with the trial team including management of TEAEs
All protocol mandated activities including but not limited to: • Safety assessments and reporting of AE/SAE/SUSARs • Review of concomitant medications • Investigations (trial bloods, scans etc) • Response assessments • Study questionnaires	Non protocol mandated activities including but not limited to: • Management of unrelated medical complications or conditions • Physical examinations, ECOG score, neurological examinations, vital signs • Investigations as required
Escalation of care and referrals for supportive care (e.g. CCU/neurology) must be done in accordance with the trial protocol and discussed and agreed by the Attending Physician. Patients will be repatriated to PTW after admission for escalated care e.g. CCU.	

Post Treatment (discharge from PTW)

Trial team	Haematology Transplant Team
Follow-up per the trial protocol	Patient to be referred back to PI/DG consultant upon recovery. Post treatment day unit/ clinic visit if required[2]
	Collection of survival data for JACIE/EBMT

Notes:
1. Transplant MDT discussion, attendance required for initial discussion of suitability for therapy and subsequent scheduling of patients.
2. Acute Lymphoblastic Leukaemia patients – Dr Castleton Monday Pm clinic, lymphoma patients- Dr Bloor Friday am clinic

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13.0 APPENDIX H: IEC Clinical Trial Patient Management on the CRF

- This document outlines arrangements and responsibilities for the inpatient management of IEC trial patients on CRF.
- Clinical trials of investigational medicinal products are regulated by the MHRA and the clinical trial protocol is a legal document. The trial protocol must be followed at all times.
- The trial PI will oversee all aspects of trial conduct at The Christie; all protocol related decisions must be made in consultation with the PI or delegated sub-I on their team.

Pre-treatment

Disease Specific Trial team	CRF Team	Haematology Transplant Team
Review trial protocols during the set-up phase as per the SOP QM-11 and in line with the capacity and capability process.		
Mandatory attendance at the ATMP R&I, trial SIV (CRF only if required) and related trial training sessions, as well as the weekly transplant MDT/scheduling meetings pre-admission.		
GCP and trial-specific training with designated roles and responsibilities listed on the signed trial delegation log (It is the responsibility of the PI/trials team to ensure the delegation log is maintained).		
All protocol mandated activities including but not limited to: • Patient identification and distribution of patient information sheet • Signed informed trial consent • Trial Screening • Confirmation of trial eligibility		
Written communication with apheresis, procurement and transplant teams, and support service leads (e.g. CCU, neurology etc)		Apheresis (if applicable) and admission scheduling at Transplant MDT. Apheresis assessment, consent & procedure (as per trial protocol)
Clinical documentation review of trial patients at scheduled and		

unscheduled outpatient visits		
Co-ordination of the patient timeline including procurement, apheresis, LD chemotherapy and admission for C1D1 must be discussed on a case-by-case basis initiated by the trial team and the Sponsor, and discussed with apheresis and transplant teams (via the Transplant MDT) and support service leads (via written correspondence)		

Treatment (conditioning treatment, IEC infusion and management of toxicities)

Trial team	**CRF Team**	**Haematology Transplant Team**
Patients will be admitted to the CRF under the PI. The attending physician or PI will be responsible for the management of the patient according to the trial protocol and Trust polices where this is not specified in the protocol. All protocol-specified decisions must be discussed with the trial PI/delegated sub-I. The length of admission will be determined by the trial protocol and the medical condition of the patient. The treatment period also covers readmission for management of TEAEs e.g. late CRS/neurological toxicity and repatriation to CRF following escalation of care (e.g. to CCU)		
The PI/disease group Sub-I and Attending Physician will attend the weekly transplant meeting to discuss patient management.		
Administration of ATIMP by trial research nurses	Administration of conditioning treatment and supporting medication	
Trial PI to maintain oversight of patient management	Patient management in accordance with the trial protocol and in discussion with the trial team including management of TEAEs	
All protocol mandated activities and/or delegation of relevant activities to CRF staff, including but not limited to: • Safety assessments and reporting of AE/SAE/SUSARs • Review of concomitant medications • Investigations (arranging trial bloods, scans etc)	Non protocol mandated activities and delegated protocol mandated activities, including but not limited to: • Management of medical complications or conditions • Physical examinations, ECOG score, neurological examinations, vital	

• Response assessments • Study questionnaires	signs • Investigations as required, including collection of trial bloods	
Escalation of care and referrals for supportive care (e.g. CCU/neurology) must be done in accordance with the trial protocol and discussed and agreed by the Attending Physician. Patients will be repatriated to CRF after admission for escalated care e.g. CCU.		

Post Treatment (discharge from CRF)

Trial team	**CRF Team**	**Haematology Transplant Team**
Follow-up per the trial protocol	Patient to be referred back to PI/DG consultant upon recovery. Post treatment day unit/ clinic visit if required	