Bone Marrow Transplant Programme Standard Operating Procedure

Title: **Clinical Adverse Events to Chimeric Antigen Receptor T-cell therapy (CAR-T-cells)**

Index Code: SOP PRB76

Version: 4.0

Area of Application: Clinical Unit / Collection Facility / CAR-T cell Programme

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Amendments to Version:

Version	Amendment	Released	Implemented	Archived
2.0	Added the use of nervecentre to the equipment list and in the recording of CRS	05-June-2023	5-June-2023	02/11/2023
3.0	Updated use of Anakinra in CRS/ICANs, prophylactic anti-epiletics and antibiotic use.	02/11/2023	02/11/2023	03/10/2025
4.0	Full review Section 6.1: NPD0493 Liso-cell Protocol added. Section 6.5: Section added around informing external parties such as CAR-T manufacturer in the event of an incident, adverse event or reaction. Section 7.2: Names removed.	03/10/2025	03/10/2025	

Contents

1. Principles and Purpose / Objective:

Chimeric antigen receptor (CAR) T-cell therapy is a therapeutic option for patients diagnosed with relapsed cartain lymphoma subtypes and Acute Lymphpblastic Leukaemia (ALL). The unique mechanism of actions of these immune-effector cells, translates into a subset of toxicities that are rare for other cancer therapies.

These toxicities may be severe and require specialised monitoring and prompt treatment. The two more relevant specific toxicities to CAR-T-Cell therapy are: cytokine-release syndrome (CRS) and Immune effector cell-associated neurotoxicity syndrome (ICANS). In both situations, prompt recognition and specific management are paramount to limit the severity and maximise the outcomes of patients after treatment.

CRS, the most common adverse event observed after CAR T-cell therapy, is an escalated, disproportionate and dysregulated immune response that can result in a distributive-type shock akin to septic shock and, on rare occasions can evolve into fulminant haemophagocytic lymphohistiocytosis (HLH) [also known as macrophage activation syndrome (MAS)]. CRS is characterised by high fever, hypotension, hypoxia, and potential multiorgan toxicity/failure and it typically occurs within the first 10 days after re-infusion of CAR-T cells.

ICANS is the second most common adverse event and can occur concurrently with CRS. ICANS is typically characterized by a toxic encephalopathic state with symptoms of confusion and delirium, and occasionally seizures and cerebral oedema. ICANS may be fatal due to the effects of severe cerebral oedema.

2. Related Documentation:

- PRB49 Reporting of Adverse Events Reactions
- PRA03 Audit Process
- PRB80 Nursing Guideline – Care of patients undergoing CAR-T therapy
- NPD0228 Adverse reaction form

3. Terminology, Abbreviations and Definitions:

See Glossary in current Bone Marrow Transplant Programme Operational Policy and Quality Manual.

- CRS: Cytokine Release Syndrome
- ICANS: Immune effector cell-associated neurotoxicity syndrome
- HLH: Haemophagocytic lymphohistiocytosis
- CAR-T: Chimeric Antigen Receptor T-cells
- MAS: Macrophage ctivation syndrome
- ASTCT: American Society for Transplantation and Cellular Therapy
- NK: Natural killer
- CNS: Central nervous system

4. Personnel and Training Requirement:

This procedure applies to all staff in clinical areas including Fletcher Ward, Toghill ward, Apheresis and Haematology Daycase unit.

5. Equipment:

- NPD0228 Adverse reaction form (provided by Stem Cell Lab team)
- NUH Trust Datix for reporting Incidents
- Patient medical notes
- Nervecentre for recording CRS and ICANS

6. Procedure / Method:

6.1. General supportive care and monitoring guidelines for early diagnosis of CAR-T cell therapy associated complications

- Assessment of vital signs at least every 4-6 hours and every 2 hours in patient with fevers and tachycardia.
- Daily review of organ systems and physical exam
- Daily bloods will include:
    - FBC/differential
    - U&E, LFT, bone profile
- CRP, ferritin, coagulation profiles and fibrinogen will be checked twice weekly.
- If patient considered at high risk, tumour lysis bloods should be repeated every 6 hours for 24h (U+E, LFT, uric Acid, LDH) post CAR-T infusion.
- Daily fluid balance and bodyweights, continuous IV hydration during days 2-3, aim for total 1-1.5 L/m2.
- Levetiracetam 500mg BD will be given as seizure prophylaxis to all patients, from day 1, according to the conditioning protocols (NPD 0440/0441/0442/0493)

- The CRS grade should be determined at least twice a day and whenever a change in the patient's status is observed. The CRS assessment will be done using the Nervecentre CRS assessment tool.

  Twice daily assessment and grading of ICANS using the American Society for Transplantation and Cellular Therapy (ASTCT) grading. The ICANS assessment will be done using the Nervecentre CRS assessment tool.

- Standard septic screen should be performed for patients developing fever after CAR-T infusion and repeated every 48h if clinically indicated. Additional tests such as CMV PCR, respiratory viral screening, fungal markers (BDG/galactomannan) and HRCT should be performed as clinically indicated.

- Other general supportive measures are outlined in table 1

NOTE: Escalation of any deteriorating patient after CAR-T cell infusion must be made via Clinical Haematology Registrar and Consultant. If neither registrar or Consultant are not available, then escalate to Hosptial 24 and informing spr or consultant if not available.

Table 1. Summary of general supportive measures for patients undergoing CAR-T cell therapy

TOXICITY	INTERVENTION
Constitutional	• Paracetamol for symptomatic management of fevers in patients with normal hepatic function. • Provide cooling blankets for fevers >40°C. • Avoid corticosteroids and non-steroidal anti-inflammatory drugs unless treating CRS/ICANS.
Cardiovascular	• Stop/reduce antihypertensive medications prior to cell infusion. • Initiate replacement IV fluids for patients with poor oral intake or high insensible losses to maintain net even fluid balance. • Patients with a systolic blood pressure <80% of their pre-infusion baseline or <100 mm Hg receive a 1 litre normal saline bolus. • Patients with persistent hypotension should have serum troponin, ECG and ECHO performed to evaluate for cardiac toxicity.
Infectious disease	• All patients with fevers and neutropenia have blood cultures drawn and assessment for broad-spectrum antibiotics as per trust guideline and/or neutropenic fever guidelines. • All patients should be started on prophylactic antimicrobials prior to conditioning chemotherapy: Co-trimoxazole (or equivalent) for *Pneumocystis* prophylaxis and acyclovir for herpes virus prophylaxis. • Anti-fungal prophylaxis may include fluconazole or posaconazole depending on prior therapies and patient risk. There is a low threshold for fungal marker assessment, HRCT and empirical therapeutic antifungal therapy in patients with non-resolving fevers.
Haematological	• Initiate allopurinol for TLS prophylaxis in patients without a contraindication prior to conditioning chemotherapy. • Target Hb during admission ≥ 80 g/dL. • Target platelets during admission ≥20x10^9/L. • GCSF injections are to be avoided between days 0-21 due to theoretical risk of increased severity of CRS but can be considered in some circumstances from day +5.

	• Consider use of cryoprecipitate/fresh frozen plasma if active bleeding and deranged coagulation or fibrinogen ≥1g/L.

6.2. Cytokine Release Syndrome (CRS)

CRS is triggered by the activation of T-cells on engagement of their CARs with cognate antigens expressed by tumour cells. The activated T cells release cytokines and chemokines, as do bystander immune cells, such as monocytes and/or macrophages, dendritic cells, and others. CRS typically manifests with constitutional symptoms, such as fever, malaise, anorexia, and myalgias, but can affect any organ system in the body, including cardiovascular, respiratory, integumentary, gastrointestinal, hepatic, renal, haematological and nervous systems.

Risk factors for severe CRS include bulky disease, comorbidities, and early-onset CRS (within 3 days of T-cell re-infusion); however, the correlation between the development of severe CRS and clinical parameters is imperfect. The onset of CRS toxicity usually occurs within the first week after CAR-T cells therapy and typically peaks within 1-2 weeks of cell administration.

CRS is graded according to the criteria of the American Society for Transplantation and Cellular Therapy (ASTCT). The grading is summarised in Table 1. Significant alterations in many laboratory parameters occur with CRS eg CRP, ALT, ferritin and cytokine profiles; however the definition and grading of CRS is based on clinical observation rather than laboratory parameters. Serum CRP and Ferritin levels should however be monitored daily.

The CRS grade should be determined at least twice a day and recorded on nervecentre and whenever a change in the patient's status is observed, CRS assessment charts should be used. It is of utmost importance that local critical care team is be aware of all CAR T cell treated patients in the hospital, in order to facilitate prompt transfers to the ICU, when needed, in the event of severe or non-responding CRS.

Table 2. Grading of CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature ≥38ºC	Temperature ≥38ºC	Temperature ≥38ºC	Temperature ≥38ºC
		With		
Hypotension	None	Not requiring Vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or[†]		
Hypoxia	None	Requiring <40% oxygen	Requiring high-flow nasal cannula[‡]	Requiring positive pressure (eg. CPAP, BiPAP, intubation and

			facemask, nonerebreather mask, or Venturi mask	mechanical ventilation)

Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity and CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6L/minute.

Table 3. Management of Cytokine Release Syndrome

CRS GRADE	TREATMENT
Grade 1	○ Supportive care including oral paracetamol and anti-histamines (e.g. chlorphenamine) up to every 4 hours and IV saline with careful fluid balance. ○ Assess and treat for neutropenic infections with the allograft patient antibiotic regime (Ceftazidime-based) as per intranet guideline**(1866 - Guideline for the Management of Neutropenic Sepsis in Haematology).** ○ Consider **tocilizumab** 8 mg/kg IV over 1 hour (not to exceed 800 mg) for persistent fevers (lasting >3 days).
Grade 2	○ Grade 1 supportive treatment as above in addition to >40% oxygen as required. ○ Urgent referral for Critical Care Outreach review. ○ Use **tocilizumab** 8 mg/kg IV over 1 hour (not to exceed 800 mg). ○ Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen; maximum of three doses in a 24-hour period. Maximum total of four doses if no clinical improvement in the signs and symptoms of CRS. ○ If not response to tocilizumab within 24 hours, add **dexamethasone** 10 mg IV every 6 hours. ○ Consider **Anakinra** after further 24h if no response to steroids, starting at a dose of 2mg/kg as per HLH guidelines **(3111- Guideline for the**

	management of adult patients with a suspected diagnosis of Haemophagocytic Lymphohistiocytosis). ○ If the patient is improving, discontinue tocilizumab followed by Anakinra.
Grade 3	○ Discuss with intensive care team and transfer to ITU. ○ Grade 1 supportive treatment in addition to high flow oxygen as needed. ○ Administer **tocilizumab** as per grade 2 CRS. ○ If not response to tocilizumab within 24 hours, add **dexamethasone** 10 mg IV every 6 hours. ○ If no improvement within 24 hours after starting dexamethasone, consider **Anakinra** 2mg/kg as per HLH guidelines **(3111- Guideline for the management of adult patients with a suspected diagnosis of Haemophagocytic Lymphohistiocytosis).** Consider troponin, ECG and ECHO to exclude CRS-related left ventricular dysfunction if persistent hypotension. ○ If the patient is improving, discontinue tocilizumab and taper corticosteroids if administered*.
Grade 4	○ Discuss with intensive care team and transfer to ITU, supportive treatment and investigations as per CRS grade 3. ○ Administer **tocilizumab** as per grade 2 and 3 CRS. ○ **Methylprednisolone** 1 g/day IV for three days. ○ If no improvement within 24 hours consider **Anakinra** 2mg/kg as per HLH guidelines. If anakinra started previously,maximise dose up to 8 mg/kg. ○ Use of specific agents to activate safety-switch may be possible in specific CAR-T cell therapies – refer to trial protocol or CAR-T SPC. ○ If the patient is improving, discontinue tocilizumab and taper corticosteroids*.

*Corticosteroids tapering should be individualised depending on the patient's response and any adverse effects but is recommended to be as rapid as possible.

Tocilizumab may also be indicated if other severe organ damage is thought to be related to CRS, such as:

- An acute drop in LV ejection fraction by ECHO.
- Creatinine increase to >2.5-fold baseline.
- Activated PTT >x2 upper limit of normal with clinically significant bleeding.
- Creatinine kinase >x5 upper limit of normal for longer than 2 days.

Other significant acute organ dysfunction considered related to CRS.

CRP levels will persistently low following the use of tocilizumab and must not be used as a marker of sepsis for several weeks afterwards. Additionally, care must be taken in the interpretation of CRP after Tocilizumab, as negative CRP may not correlate perfectly with improvement in CRS. The return of CRP levels to baseline indicates that the CRS phase of CAR-T-cell therapy has ended, and the patient can be considered for discharge from the hospital, assuming other toxicities that require monitoring and/or intervention have resolved. The correlation between serum ferritin levels and CRS is even less consistent. Ferritin is useful for the diagnosis of CAR-T-cell-related HLH/MAS.

6.3. Immune Effector cell-associated neurotoxicity syndrome (ICANS)

ICANS of any severity occurs in 20-70% of patients treated with CAR-T cell therapy, and severe ICANS has been observed in all of the pivotal studies of licensed studies to date. Risk factors for developing ICANS include: younger patient age, pre-existing neurologic and medical comorbidities, high disease burden, increased intensity of lympho-depleting therapy and early and severe CRS. The underlying pathophysiological mechanism of ICANS remains unclear. Passive diffusion of cytokines into the brain and trafficking of T cells into the CNS have both been postulated. These are supported by high serum levels of IL 6 and IL 15 are associated with severe neurotoxicity in patients treated with CAR T cell therapy and also by detection of CAR T cells in cerebrospinal fluid (CSF) from patients with neurotoxicity. Protein levels in the CSF are usually elevated in patients with ICANS, compared with baseline measurements, suggesting disruption of the blood-brain barrier. Other organ dysfunction (hepatic and renal), as well as hypoxaemia, and infection, may contribute to the encephalopathy.

The clinical course of ICANS can be biphasic; the first phase occurs in the context of CRS symptoms, with neurologic symptoms beginning within two to four days of the onset of CRS, The second phase may occur after fever and other CRS symptoms subside, beyond 5 days after cell infusion. Delayed neurotoxicity with seizures or episodes of confusion can occur during the third or fourth week after CAR T cell therapy in up to 10% of patients.

ICANS typically manifests as a toxic encephalopathy, with the earliest signs being diminished attention, language disturbance and impaired handwriting; other symptoms and signs include confusion, disorientation, agitation, aphasia, somnolence, and tremors. More severe cases of ICANS (grade >2), can result in seizures, motor weakness, incontinence, mental obtundation, increased intracranial pressure, papilloedema, and cerebral oedema.

The ASTCT grading scale includes a 10-point encephalopathy assessment, termed the “Immune effector cell-associated encephalopathy (ICE) score, which has five components: orientation, naming, following commands, writing, and attention (table 3). Patients are graded according to the most severe symptom attributable to ICANS in five domains: the ICE score level of consciousness, seizure, motor findings, and elevated intracranial pressure (ICP)/cerebral oedema.

- Grade 1 (mild) – A patient with grade 1 ICANS may demonstrate inattentiveness, mild disorientation, and mild expressive and/or receptive language dysfunction but will be able to communicate.
- Grade 2 (moderate) – A patient with grade 2 ICANS may have a moderately impaired level of consciousness but is responsive to voice, usually slow to respond, and disoriented to time and location

- Grade 3/4 (severe) – Grade 3/4 ICANS includes patients with more severe and significant language dysfunction or mutism, those who are difficult to arouse (ie, only responsive to tactile or noxious stimulation), and potentially those with seizures.

Table 4. Grading of ICANS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score*	7 to 9	3 to 6	0 to 2	0 (patient is unarousable and unable to prform ICE)
Depressed Level of consciousness	Awakens spontaneously	Awakens to voice	Awakens on to tacitle stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical seizure, focal or generalised, that resolves rapidly, or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 minutes), or repetitiveclinical or electrical seizures withut return to baseline in betwee
Motor Findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/Cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimagining, decerebrate or decorticate posturing, cranial nerve VI palsy,

				papilledema, or Cushing triad
ICE score definitions				
Orientation	Orientation to year, month. City, Hospital			4 points
Naming	Ability to name 3 objects (eg. Point to clock, pen, button)			3 points
Following commands	Ability to follow simple commands (eg.”Show me 2 fingers” or “Close your eyes and stick out your tongue”			1 point
Writing	Ability to write a standard sentence (eg. “Our national bird is the bald eagle”)			1 point
Attention	Ability to count backwards from 100 to 10			1 point

ICANS grade is detrmined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE socre of 3 who has a generalised seizure is classified as grade 3 ICANS

The management of ICANS is based on the toxicity grade as outlined in Table 4.

Table 5. Management and follow up of ICANS

ASTCT grading	MANAGEMENT
General measures	• **Neurology referral for all grades of ICANS** • Fundoscopic exam to exclude papilloedema. • Monitor closely (Regular neuro observations and ICE scale every 6 hours) • One-to-one nursing care if required. • 30◦ bed elevation to minimise aspiration risk and improve cerebral venous flow. • IV hydration • Rigorous control of blood pressure and electrolytes (particularly sodium, calcium and magnesium). Use bolus/maintenance 0.9% normal saline to keep sodium ≥140mMol/L. • Give **levetiracetam 500** mg every 12 hours (oral or IV)*. • Assess swallowing, withhold oral intake/medicines and convert medication to IV if compromised. • Avoid CNS depressants as much as possible. In case of agitation, low dose of lorazepam (0.25 to 0.5 mg IV every 8 hours) or haloperidol (0.5 mg IV every 6 hours) can be used.
Grade 1	• General measures as above. • Increase **levetiracetam** 1 g every 12 hours (oral or IV)*. • If no improvement within 24 hours, manage as per Grade 2 ICANS.
Grade 2	• General measures as above • Perform urgent CT Brain and arrange MRI brain. • Urgent Critical Care Outreach referral. • Following brain imaging specifically excluding cerebral oedema, perform a diagnostic lumbar puncture (LP) with measurement of opening pressure and samples for microbiology. • Discuss with neurology and request EEG if required. EEG to be requested directly by contacting neurophysiology. **If concurrent CRS:** • Give Tocilizumab 8 mg/kg IV.

	• Repeat tocilizumab every 8 hours if no response; maximum of 3 doses in a 24-hour period. Maximum total of 4 doses if no clinical improvement in the signs and symptoms of ICANS. **If no-improvement in ICANS after 24 hours of tocilizumab** administer Dexamethasone 10 mg IV every 6 hours. • For patients not responding to high dose steroids /tocilizumab, add **Anakinra**. Initial dose 2 mg/kg/d, escalated daily based on response to 4 mg/kg/d and 8 mg/kg/d as per NUH HLH guidelines **(3111- Guideline for the management of adult patients with a suspected diagnosis of Haemophagocytic Lymphohistiocytosis).** **If no concurrent CRS** • Administer Dexamethasone 10 mg IV every 6 hours. If no improvement within 24 hours after starting dexamethasone add Anakinra as above. • If the patient is improving taper corticosteroids and discontinue tocilizumab if administered**. • If unable to exclude CNS infection as a cause for symptoms, consider empirical treatment with merepenem 1g tds IV and acyclovir 10 mg/kg IV.
Grade 3	• General measures, neuro-imaging, LP and EEG as per grade 2 ICANS. • Consider treatment of CNS infection as per grade 2 ICANS. • Discuss with intensive care team and transfer to ITU. If **concurrent CRS** • Administer **Dexamethasone** 10 mg IV every 6 hours and **Tocilizumab** 8 mg/kg IV. If no response add **anakinra** 2mg/kg/day as per ICANS grade 2. Increase dose of Anakinra daily if no response. If **no concurrent CRS** • Administer **Dexamethasone** 10 mg IV every 6 hours and Anakinra 2mg/kg/day as per Grade 2 ICANS . • Request urgent EEG directly by contacting neurophysiology. • If intubated consider cerebral function analysing monitor (CFAM). • Repeat neuroimaging (CT or MRI) after 2-3 days if the patient has persistent Grade ≥3 neurotoxicity. • Patients with status epilepticus should be treated as per current NUH guidelines: http://nuhnet/nuh_documents/Guidelines/Musculoskeletal%20and%20Neurosciences/Neurosciences/2793.pdf#search=epilepticus • Patients with raised intracranial pressure should be treated with steroids as outlined above. The use of hyperventilation hyperosmolar therapies and neurosurgical intervention may be considered by ITU a case by case basis.

	• Use of specific agents to activate safety-switch may be possible in specific CAR-T cell therapies – refer to trial protocol or CAR-T SPC. • If the patient is improving taper corticosteroids and discontinue tocilizumab if administered**.
Grade 4	• General measures, neuro-imaging, LP and EEG as per grade 2 ICANS. • Consider treatment of CNS infection as per grade 2 ICANS. • ITU transfer and consider mechanical ventilation • Consider transfer to neuro-surgical unit in QMC campus. • Status epilepticus and raised intra-cranial pressure to be treated as per grade 3 ICANS. If **concurrent CRS** • Administer **Methyl-prednisolone** 1 g daily for three days and **Tocilizumab** 8 mg/kg IV. Consider **anakinra** 2mg/kg/day as per ICANS grade 2. If **no concurrent CRS** • Administer **Methyl-prednisolone** 1 g daily for three days and Anakinra as per Grade 2 ICANS . • **Cyclophosphamide** (750 -1000 mg/m2) is an alternative for selected refractory cases. • Use of specific agents to activate safety-switch may be possible in specific CAR-T cell therapies – refer to trial protocol or CAR-T SPC. • If the patient is improving taper corticosteroids and discontinue tocilizumab and anakinra if administered**. Wean of anakinra should be done in 2 weeks, discuss with consultant,

*Begin weaning Levetiracetam 7 days after resolution of ICANS. Discuss with Neurology about duration of wean.

**If steroids are required, dose should be tapered quickly (within 7-10 days after resolution to <grade 1. Patients should be monitored closely for recurrence of neurotoxicity symptoms during corticosteroid tapering.

Additional Considerations for ICANS management:

If patient has grade 1-2 ICANS or transfer to ITU for grade 3 ICANS is not imminent then EEG, CT, MRI requests will be made by haematology team.

If patient has grade >3 ICANS and either on ITU or awaiting imminent transfer to ITU, then EEG, CT, MRI requests will be made by ITU staff, and LP performed by ITU.

Fundoscopy and lumbar puncture can be difficult in restless patients/patients with non-dilated pupils. Repeated neuroimaging should be arranged if not feasible. Choice of MRI or CT scan may depend on the neurological status, although MRI is preferred.

6.4. CAR-related HLH grading and management

Haemophagocytic lymphohistiocytosis (HLH) is a rare syndrome of immune dysregulation characterised by fever, hyperinflammation, organ dysfunction, cytopenias and haemophagocytosis. Primary HLH is associated with inherited deficiencies of cytotoxic T-cell and NK cell function, while secondary HLH has additional underlying causes include viral and other infections, immunosuppression, auto-immunity or haematological cancers. Patients with CRS after CAR T cell therapy may have clinical features and laboratory findings that resemble those of HLH/MAS, including high fever; multi-organ dysfunction; CNS disturbances; high serum levels of ferritin, lactate dehydrogenase, soluble CD25, and cytokines (such as IFNγ and IL 6); and low serum levels of fibrinogen.

Typical diagnostic criteria for HLH will not be applicable to CAR-T treated patients as they are very likely to have fevers and cytopenias secondary to CRS. If the patient has ferritin >10 000ng/ml during the CRS and has developed grade ≥3 organ toxicities involving the liver, kidney, or lung, an urgent bone marrow should be performed to assess for the presence of haemophagocytosis. Patients with suspected HLH/MAS should be managed with anti-IL-6 therapy and corticosteroids for grade ≥3 organ toxicities as per the CRS recommendations

Treatment is based on steroids and anakinra as per NUH guidelines (*http://nuhnet/nuh_documents/Guidelines/Cancer and Associated Specialties/Clinical Haematology/3111.pdf*).

If the patient has no improvement clinically or serologically within 48 hrs after commencement of steroids and tocilizumab, additional therapy with Anakinra at 2 milligrams/kilogram/day subcutaneously with response assessed by monitoring fever, blood pressure, cytopaenias and coagulopathy. If there is no response, the dose should escalate daily to 4 milligrams/kilogram/day then to 8 milligrams/kilogram/day daily. The duration of therapy will depend on response and underlying cause but potentially 7-14 days will be required followed by dose de-escalation daily based on clinical response. For refractory HLH/MAS, cyclophosphamide 750 -1000 mg/m2 or etoposide 75 mg/m2 can be considered. Etoposide can be repeated after 4–7 days.

6.5. Reporting of an Adverse Reaction

- Refer to SOP PRB49 Reporting of Adverse Events, Reaction, Incidents and Deviations for the correct procedure to report correctly in the event of an Adverse reaction or incident.
- Consider if there have been other parties involved in the storage, processing and collection of the product implicated in the incident, event or reaction. In this case, this should be reported accordingly to the external party such as the CAR-T manufacturer involved with the product.

7. Endpoints, Expected Results and Limitations of Procedure:

7.1. Endpoint and Expected Results

Resolution of the adverse reaction reported (i.e. CRS and ICANS)
Submission of a report for the event that has occurred and the BMT Quality Manager has been notified. Subsequent investigation is undertaken according to HTA or NUH procedure or as described in SOP PRA04.

7.2. Limitations

7.2.1. **Serious adverse incidents –** contact the BMT Quality Manager as soon as possible (after making the patient safe and minimising clinical risk occurring to patients/staff). Report an incident as per NUH policy. A report must be submitted to the HTA within 24 hours is cells are affected. If QM is not available, contact named HTA reporters below:

Assistant Quality Manager

Laboratory Manager or 'Persons Designate'

Dr JL Byrne (HTA DI, BMT Director, Consultant)

Fletcher Ward Manager or 'Persons Designate'

CAR-T CNS or 'Persons Designate'

7.2.2. Transfer to QMC for neurological treatment. Patient will be transferred from ITU, using hospital transport, ensuring safe transfer

7.2.3. The Consultant assigned to the patient must authorise any planned deviation from the protocol. If consultant is not available, notify Dr JL Byrne for authorisation

7.2.4. Incidents must be reported via the NUH Trust Datix system.

7.2.5. Deviation from the SOP – whether planned or unplanned – must be reported to the BMT Quality Management Group meeting

7.2.6. Reporting requirements may be over-ridden by the requirements of the HTA or NUH trust.

7.2.7. In addition to the reporting measures above, SAE/SARs must be reported to the HTA. An initial report should be submitted as soon as possible. HTA – forms and instructions available at: https://www.hta.gov.uk/policies/serious-adverse-event-or-reaction-saears
The BMT Quality Manager has responsibility for reporting to HTA and undertaking subsequent investigations as required. In the absence of the BMT Quality Manager, the Assistant Quality Manager or Stem Cell Laboratory 'Persons Designate' have the capability to submit a report to the HTA. Please consider if any other parties have been involved in the storage, processing, collection implicated in the incident.

7.2.8. Failure to report an incident is, in itself, an adverse incident and may be investigated as part of the review of the event.

8. Audit:

8.1. Incident reports and deviations from SOP (whether planned or unplanned) are reviewed at the monthly BMT Quality Management Group meeting.

8.2. Incident reports and deviations from SOP (whether planned or unplanned) are reviewed at the monthly BMT Quality Management Group meeting.

8.3. Any cause for concern, will be investigated in an appropriate manner – this may include additional audits

9. Evidence Base of Policies / References:

- PL6 Haemopoietic Stem Cell Transplantation and Cellular Programme Operational Policy and Quality Manual
- PL1 FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration , 8th Edition - also available at *http://www.ebmt.org/jacie-accreditation*
- PL13 Human Tissue (Quality and Safety for Human Application) Regulations 2007, Licensing Standards, also available at *http://www.hta.gov.uk*
- PL7 HTA Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment –also available at *http://www.hta.gov.uk*
- PL14 HTA Code of Practice A - Guiding Principles and Fundamental Principle of Consent - also available at *http://www.hta.gov.uk*
- PL15 HTA Code of Practice G - Donation of allogeneic bone marrow and peripheral blood - also available at *http://www.hta.gov.uk*
- The why, what, and how of the new FACT standards for immune effector cells. Maus and Nikiforow Journal for Immunotherapy of Cancer (2017) 5:36
- FACT Example of Clinical Staff Reference for Immune Effector Cell Toxicity Management – Cytokine Release Syndrome and Neurotoxicity. Examples at : http://www.factwebsite.org/immuneeffectorcells/ downloaded April 2018.
- Long-Term Complications, Immunologic Effects, and Role of Passage for Outcome in Mesenchymal Stromal Cell Therapy. von Bahr et al Biol Blood Marrow Transplant 2012 18: 557-564
- Recent Advances in T-Cell Immunotherapy for Haematological Malignancies Rouce et al Br J Haematol. 2017 March; 176(5): 688–704.
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- Grading of cytokine release syndrome associated with the CAR T cell therapy tisagenlecleucel Porter et al. J Hematol Oncol. 2018;11(1):35
- Schuster et al. Grading and management of cytokine release syndrome in patients treated with tisagenlecleucel in the JULIET trial. Blood Adv, 2020;4(7):1432-1439

10. Training and Competency: (record of staff preparation on procedure described.)

8.4. Training: **Required**

8.5. Competency Assessment: **Required**

8.6. Training & Competency Record

Once they have read the SOP, relevant staff members are to acknowledge the in use SOP on QPulse.

Appendix 1: Brief guideline on ICU management of CAR-T patients

For full guideline see the CAR-T cell Programme Standard Operating Procedure - Management of adverse events related to Chimeric Antigen Receptor T-cells (CAR-T-cells)

The full guideline outlines the indications for the use of tocilizumab/steroids and other treatments for CRS/ICANS

Indications for Outreach review	
Grade 2 cytokine release syndrome (CRS)	Any of: FiO_2 0.24-0.4% brief or persistent hypotension not requiring inotropes
Grade 2 Immune effector cell-associated neurotoxicity syndrome (ICANS)	Any of: ICE score 3-6 Only responding to voice
Any other standard indication	
Indications for ITU review and/or transfer	
Grade ≥3 cytokine release syndrome (CRS)	Any of: FiO2 ≥40% Hypotension not responding to fluid challenges
Grade ≥3 Immune effector cell-associated neurotoxicity syndrome (ICANS)	Any of: ICE score 0-2 Awakens only to tactile stimulus Any clinical seizure regardless of duration Focal or local oedema on CT or MRI Any new hemi- or paraparesis

Management on ICU - general	
Respiratory	Ventilation or NIV as required Target SpO2 88-92% Monitor for effusions – drain as required
Cardiovascular (hypotension unresponsive to fluids)	Insert CVC Use cardiac output monitoring if vasopressors required ECHO to assess LV Function Repeat ECHO if increasing cardiovascular instability after first 24 hours(e.g. additional inotrope or noradrenaline >0.6mcg/kg/hr) Treat CRS as per guideline

Unresponsive hyperpyrexia	Use Arctic Sun or Intravascular cooling device if temp>39.5 for >2 hours
Renal	Send tumour lysis bloods initially daily
Neurology	Neurology referral for all grades of ICANS 4-hourly neuro-obs and GCS (one hourly if decreased conscious level) CT head as soon as possible before/after admission to ICU Discuss need for MRI with haematology team If no cerebral oedema, perform LP with measurement of opening pressure and samples for microbiology (mc&s, HSV, VZV, HHV6 PCR). Request urgent EEG directly by contacting neurophysiology If intubated consider cerebral function analysing monitor (CFAM). Repeat CT every 3-4 days until improving For those with status epilepticus treat as per NUH guideline Treat ICANS as per guideline
Microbiology	Ensure blood cultures and septic screen sent – repeat after 3/7 if still required Send blood for BDG and galactomannan Perform BAL in intubated patients if possible – send for culture, viral panel, galactomannan, PCP PCR Do NOT use Procalcitonin test
Blood samples	Daily FBC, coags, U&E, LFT, Calcium, phosphate, urate, LDH, magnesium, ferritin, CK, fibrinogen, CRP, ferritin
General	IV hydration and careful fluid balance Maintain Hb >80, Platelets >20000/µL, PTT> 14s, Fibrinogen >1g/L For CRS: Paracetamol and anti-histamines up to 4 hourly. For ICANS: 30◦ bed elevation to minimise aspiration and improve cerebral venous flow. Rigorous control of blood pressure and electrolytes Avoid CNS depressants as much as possible

Appendix 2 ICANS grading

ASTCT ICANS Consensus Grading for Adults

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/Cerebral Oedema	N/A	N/A	Focal/Local oedema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Appendix 3 CRS grading

ASTCT Consensus Grading for CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp >38°C	Temp >38°C	Temp >38°C	Temp >38°C
With				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or				
Hypoxia	None	Requiring low-flow nasal cannula	Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Management of Cytokine Release Syndrome

CRS Grade	Treatment
Grade 1	o Supportive care including oral paracetamol and anti-histamines (eg chlorphenamine) up to every 4 hours and IV saline with careful fluid balance. o Assess and treat for neutropenic infections as per neutropenic protocol o Consider tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) for persistent fevers (lasting >3 days).
Grade 2	o Urgent referral for Critical Care Outreach review. o Use tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). o Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen; Maximum total of four doses if no clinical improvement in the signs and symptoms of CRS. o If no improvement within 24 hours after starting tocilizumab, manage as per Grade 3 CRS.
Grade 3	o Discuss with intensive care team and transfer to ITU. Administer tocilizumab as per grade 2 CRS. o If not response to tocilizumab within 24 hours, add dexamethasone 10 mg IV every 6 hours. o If no improvement within 24 hours after starting dexamethasone manage as per Grade 4 CRS.
Grade 4	o Discuss with intensive care team and transfer to ITU, supportive treatment and investigations as per CRS grade 3. o Administer tocilizumab as per grade 2 CRS. o Methylprednisolone 1g/day IV for three days. o If no improvement within 24 hours consider Anakinra as per HLH guidelines. o Use of specific agents to activate safety-switch may be possible in specific CAR-T cell therapies – refer to trial protocol or CAR-T SPC. o If the patient is improving, discontinue tocilizumab and taper corticosteroids*.