Consensus Framework for the Optimal Delivery of Bispecific Antibodies for patients with Multiple Myeloma

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A pathway document produced by the Equity in Multiple Myeloma Bispecific Research and Access (EMMBRAce) Bispecific Antibody Implementation Group

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The information contained in this guidance is a consensus of the development and consultation groups' views on current treatment. It should be used in conjunction with any local policies/procedures/guidelines and should be approved for use according to the trust clinical governance process. Care has been taken in the preparation of the information contained in the guidance. Nevertheless, any person seeking to consult the guidance, apply its recommendations or use its content is expected to use independent, personal medical and/or clinical judgement in the context of the individual clinical circumstances, or to seek out the supervision of a qualified clinician.

The group makes no representation or guarantee of any kind whatsoever regarding the guidance content or its use or application and disclaim any responsibility for its use or application in any way. To enable the guideline to stay relevant, it is envisaged that this document will be updated or reviewed periodically. As such these are 'living' documents – designed to be updated based on recently published evidence or experience. Thus, feedback on any of the guidelines is welcomed.

Please email **uclh.emmbrace.queries@nhs.net** with any comments, suggestions or queries.

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Glossary

AC	Ambulatory Care
ACU	Ambulatory Care Unit
BM	Bone marrow
BP	Blood pressure
BsAb	Bispecific Antibody
CMV	Cytomegalovirus
COVID-19	Coronavirus disease 2019
CRS	Cytokine release syndrome
ECOG	Eastern Cooperative Oncology Group
FBC	Full blood count
HR	Heart rate
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICE	Immune effector cell-associated encephalopathy
Ig/IG	Immunoglobulin
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IRR	Immune-related reaction
IVIG	Intravenous Immunoglobulin
LDH	Lactate dehydrogenase
LFT	Liver function test
Mab	Monoclonal antibody
MDT	Multidisciplinary Team
MM	Multiple Myeloma
OPA	Outpatient appointment
PCR	Polymerase chain reaction
PS	Performance status
RR	Respiratory rate
SACT	Systemic anti-cancer therapy
SCIG	Subcutaneous Immunoglobulin
SFLC	Serum free light chain
SmPC	Summary of product and characteristics
SPEP	Serum protein electrophoresis
SpR	Specialist registrar
Treatment Plan	Chemotherapy prescription / plan
U&E	Urine and electrolytes

1. Introduction

Bispecific antibodies (BsAbs) are an effective treatment for patients with multiple myeloma (MM). However, they need to be administered in a safe environment due to the risks of Cytokine Release Syndrome (CRS), immune-related neurotoxicities (ICANS) and severe infections.

This guidance has been created by a multi-disciplinary group of health care professionals from a variety of geographical locations to provide guidance for centres that are involved in the delivering bispecific antibodies to MM patients. The intention is to allow more centres to be able to deliver this treatment and widen access to patients in a safe and efficient manner. This guidance does not seek to replace SmPC or other guidelines.

2. Recommendations to be a Bispecific Antibody Treatment Centre

The following consensus statements were agreed for centres delivering bispecific antibodies in the UK. There are no formal criteria listed in the SmPC and so this document serves as a recommendation to best practice. Step-up dosing can be undertaken either as an in-patient or out-patient. Out-patient dosing for the step-up phase should only be undertaken by hospitals that have performed a risk assessment and have approved protocols in place.

1) The treating centre has access to in-patient beds that has specialist Haematology input available 24 hours per day 7 days per week. This is required irrespective of delivering in-patient or out-patient step up dosing.

2) If the centre has an approved standard operating protocol for out-patient/ ambulatory step-up dosing, this should include access to in-patient beds in case of adverse events (e.g. CRS or ICANS)

3) Centres should ensure an adequate supply of Tocilizumab (anti-IL6 receptor antibody), or alternative is available at treating locations e.g. inpatient ward, day unit or ambulatory care unit. Local guidelines should describe when this should be used (a recommended approach is described in section 9 and 10). The decision to give Tocilizumab +/- corticosteroids should be made by appropriately trained medical staff with Consultant input as required.

4) Centres delivering step-up dosing must have access to critical care beds in case of grade ≥3 CRS or ICANS. It is recommended for centres to discuss with local critical care units on the CRS/ICANS management pathways prior to initiating the service.

5) Centres should have access to neurology input in case of high grade ICANS or other neurotoxicities that have been associated with T-cell immunotherapies.

6) Centres should have access to microbiology and virology advice with the ability to access blood PCR testing for CMV or others in case of atypical infections.

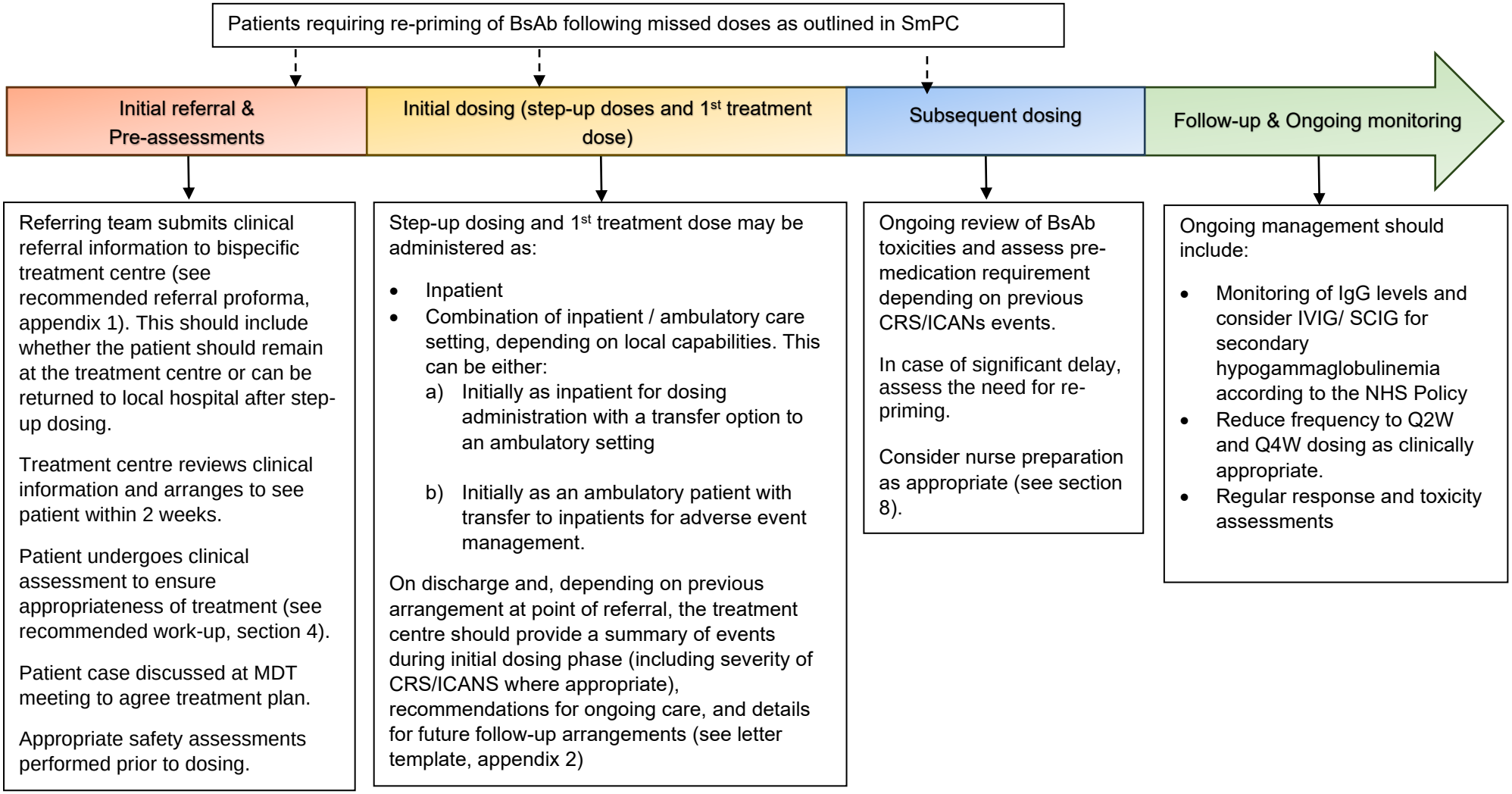
7) Centres should have the resources or shared-care arrangements to facilitate the administration of IVIg and/ or SCIg for secondary hypogammaglobulinemia as per NHS criteria.

8) Adequate training processes with regular updates are required for key staff involved in the pathway. This may include departments outside of immediate haematology care team as per local arrangement e.g. emergency department and critical care unit.

9) Centres should have the following SOPs or shared-care guidelines:

- Treatment protocol for BsAbs
- Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)
- Management of Cytokine Release Syndrome (CRS).

3. Treatment Pathway for Bispecific Antibodies



4. Guidance for Outpatient Clinic Appointments

1st Outpatient clinic:

- Assess suitability for BsAb treatment according to:
  - Prior treatments e.g. PI, IMiD and CD38 Mab exposed
  - Performance status (0-1)
  - Relapsed disease requiring treatment
  - Patient preference

- Document performance status and prior treatments including refractoriness
- Discuss treatment including rationale, logistics (e.g. step-up dosing location), expected efficacy and adverse events which specific mention of CRS, ICANS, Infections and need for Ig replacement
- Discuss alternative treatment options including clinical trials or palliation where appropriate
- Agree on location of ongoing treatment (bispecific treatment centre or local referring hospital) based on local hospital capabilities and patient preference. Where possible, patients should be offered treatment closer to home.
- Where appropriate, all patients should be offered fertility advice and counselled about risks in pregnancy.
- Assess eligibility for step-up dosing to be given via ambulatory care pathway (see appendix 3)
- Complete physical examination including assessment of extramedullary disease and baseline neurological evaluations, including ICE score.
- Document ICE score in medical notes and include baseline handwriting into patient's record so subsequent assessments can be made chronologically for comparison
- Consent patient for treatment. Suggested areas to include are listed in section 6 & 7.
- Book in-patient or ambulatory bed as per local procedure.
- Complete the following baseline investigations:
  - Record Height & Weight
  - Blood tests to include:
    - FBC, renal, bone liver profiles, LDH, SPEP, SFLC, Coagulation screen including fibrinogen, baseline CMV serology, hepatitis serology, HbA1C if diabetes may be possible.
    - If patient is known to be CMV seropositive, send blood PCR for CMV
    - Immunoglobulin levels
    - Restaging with whole-body cross-sectional imaging (e.g. PET-CT/MR or whole body diffusion weighted MRI or low dose whole body CT) to assess for extramedullary disease and fracture risk due to bone disease is recommended. Consider bone marrow biopsy to determine disease burden and cytogenetic analysis for high risk markers as appropriate
    - Advise optimal vaccination schedule e.g. annual 'flu, COVID-19, pneumococcal vaccination ideally pre-treatment.
- Ensure written information is given to patient (e.g. Bispecific antibodies Horizons Infosheet - Myeloma UK) and contact details in case of further questions
- Ensure patient will be/ has been discussed at MDT
- Prescribe:
  - VZV and PJP prophylaxis (e.g. aciclovir, co-trimoxazole or equivalent)
  - Consider Tumour Lysis Syndrome (TLS) prophylaxis for high disease burden.
  - For patients at risk of tumour flare, ensure analgesia is optimised and consider STAT oral dexamethasone 10mg when develop symptoms.
  - For patients receiving ambulatory step-up dosing consider prescribing oral dexamethasone 10mg to be taken immediately if develops symptoms of CRS or ICANS as per local protocols

Subsequent outpatient clinic visit:

- Review treatment associated toxicities, specifically document infection history: number, type (bacterial/ viral), antibiotic use, severity (in-patient or out-patient)
- Assess need for ongoing pre-medication (dexamethasone, chlorphenamine and paracetamol) for patients who experienced Grade 2 and above CRS/IRRs in the previous dosing.
- Where appropriate, assess the duration of delay from the last dose to determine next dosing level according to SmPC for respective BsAb.
- Decide on frequency of dosing i.e. Q2W, Q4W based on SmPC and/ or clinical judgement. Consideration to move to less frequent dosing should be made at the time of maximal response in all patients or earlier for frailer patients/ those with poor tolerability (i.e. recurrent infections despite prophylaxis)
- Review functional IgG levels (for patients with IgG paraprotein, this should be subtracted from total IgG) and need for IV/SC immunoglobulin as per local guidelines. For those on IV/SC Immunoglobulin, review infection history and trough IgG levels to optimise dose and frequency of administration.
- Ensure following investigations performed during OPA:
    - Updated weight taken
    - FBC, U&Es, bone profile, LFTs, LDH, SPEP, SFLC
    - Immunoglobulin levels
    - For CMV seropositive patients – send monthly blood PCR for CMV
    - Blood PCR for CMV, Adenovirus and EBV should be considered for patients with atypical infections not responding to standard antibiotics.
- Ensure patient has received optimal vaccination schedule e.g. annual flu, COVID-19, pneumococcal vaccination and additional vaccines as recommended.
- Arrange transfer of care back to local hospital as appropriate

5. Patient Care Pathway for Delivering Bispecific Antibodies in an Ambulatory Care Setting

Referral & Pre-asssement

- Follow pre-assessment checklist as per initial outpatient clinic
- Ensure all criteria for AC pathway are met (See appendix 3 for criteria)
- Provide counselling to patient on ambulatory care pathways, including escalation plan, supportive medication and where appropriate, rescue doses (e.g. dexamethasone)

Ambulatory Care Unit

On treatment days (step-up doses and 1st treatment dose)

- Admit patient in ACU
- Patient will be reviewed by ACU nurse/SpR to ensure patient fit to proceed with BsAb
- Complete observations and SACT toxicity assessment
- If ICE score not done in the preceding 10 days, perform baseline ICE score including handwriting test.
- Once step-up doses given with pre-medication, observe patient for minimum 1-hour post injection.
- Twice daily observations performed (HR, RR, BP, O2 saturations, temperature)
- Provide AC counselling on this visit, including home monitoring.
- Prior to leaving AC the following documents should be given to the patient:
    - Hospital/AC contact numbers
    - BsAb alert card
    - Patient home monitoring guide
    - Where appropriate, education and reminder chart issued to patient
    - Where appropriate, patient counselled on the supply of “Just in Case” dose of dexamethasone
- Ensure patient understood how to take supportive medication whilst in AC

Follow-up days:

- Patient to return to AC for:
    - Daily review by AC nurse/AC doctor
    - Daily review of patient home monitoring booklet
    - Daily bloods (FBC, U+E, LFTs, bone profile, ferritin)
    - Twice daily ICE score including handwriting
    - Twice daily Observations in AC
- Patient can be discharged from AC 48 hours post dose if:
    - no significant adverse events
    - post AC medical review

Discharge
• Ensure advice line number is available to patient • Ensure patient counselled on discharge medicines and continues to carry alert card • Ensure chemo day unit and outpatient clinic appointments booked for subsequent dosing and ongoing review • For patients being repatriated back to referring Trust, ensure discharge letter include summary of events during initial dosing phase (including severity of CRS/ICANS where appropriate), recommendations for ongoing care, and details for future follow-up arrangements.

Monitoring requirements	Frequency	Parameters
Observations	Twice daily	HR, RR, BP, Oxygen saturations, Temperature
ICE score	Twice daily	
Bloods	Daily	FBC, U+E, LFTs, bone profile, ferritin
SACT toxicity assessment	Daily	
Patient home monitoring booklet	Daily	

Admission criteria to hospital:
■ Fever ■ Evidence of CRS ■ Evidence of ICANs ■ Other symptoms requiring admission to hospital (uncontrolled bone pain, diarrhoea, nausea, vomiting etc) ■ Patient unable to cope in AC ■ Patient request for admission

Criteria to return to AC following admission:
■ Patient had <G2 CRS and no ICANS with last dose administered ■ All other AC criteria are met

6. Information for Patients and Carers – Medical Team

The following should be explained to patients:

- How the treatment works in lay terms and how it differs from previous treatments.
- Expected success rates and duration of response of the treatment.
- The likelihood of potential side effects, including what to look for and how these can be managed.
- For patients at risk of tumour flare, counsel patient on bone pain and optimise analgesia. A STAT dose of Dexamethasone 10mg may be given if required.

The following information serves as a summary of the current adverse event data with Elranatamab and Teclistamab. This can be used when consenting patients for treatment.

Elranatamab

- **Efficacy:**

Overall response rate	61% (95% CI: 51.8-69.6)
Progression free survival (PFS)	Median PFS 17.2 months (95% CI, 9.8 - not estimable)
Duration of response (DOR)	71.5% probability of overall response (OR) at 15 months (95% CI, 58.8-80.9); 89.2% probability of ≥ complete response (CR) at 15 months (95% CI, 73.5 – 95.8)
Overall survival (OS)	Median OS, 24.6 months (95% CI, 13.4 - not estimable)

- **Serious adverse events:**

Adverse events	**All grade (%)**	**Grade 3/4 (%)**
Cytokine Release Syndrome*	57.9	0.5
Immune effector cell-associated neurotoxicity syndrome (ICANS)**	3.3	1.1
Pneumonia	37.2	24.6
Sepsis	18.0	12.6
Febrile neutropenia	2.7	2.7
Pyrexia	19.1	4.9
Anaemia	27.3	3.3
Dyspnoea	19.1	4.9

***CRS**
Most patients experienced CRS after the first step-up dose (43.2%) or the second step-up dose (19.1%), with 7.1% of patients having CRS after the first full treatment dose and 1.6% of patients after a subsequent dose. Recurrent CRS occurred in 13.1% of patients. The median time to onset of CRS was 2 (range: 1 to 9) days after the most recent dose, with a median duration of 2 (range: 1 to 19 days) days.

****ICANS:**
The majority of patients had ICANS after the first step-up dose (2.7%), 1 (0.5%) patient had ICANS after the second step-up dose and 1 (0.5%) patient had ICANS after a subsequent dose. Recurrent ICANS occurred in 1.1% of patients. The median time to onset was 3 (range: 1 to 4) days after the most recent dose with a median duration of 2 (range: 1 to 18) days.

- **Other common adverse events:**

Adverse events	All grade (%)	Grade 3/4 (%)
Hypogammaglobulinaemia	14.2	2.7
Upper respiratory tract infection	38.8	5.5
Neutropenia	44.8	43.2
Thrombocytopenia	36.1	26.2
Lymphopenia	30.1	27.9
Injection site reaction	38.3	0
Diarrhoea	37.7	1.1
Nausea	21.3	0
Headache	19.1	0
Peripheral Neuropathy	15.8	1.1

Teclistamab

- **Efficacy:**

Overall response rate	63%
Progression free survival (PFS)	Median PFS 11.4 months (8.8 – 16.4)
Duration of response (DOR)	Median DOR was 24.0 months (95% CI, 17.0 - not estimable)
Overall survival (OS)	Median OS, 22.2 months (95% CI, 15.1 – 29.9)

- **Serious adverse events:**

Adverse events	All grade (%)	Grade 3/4 (%)
Cytokine Release Syndrome*	72	0.6
Immune effector cell-associated neurotoxicity syndrome (ICANS)**	3	0
Pneumonia	28	19
Sepsis	7.9	6.7
Febrile neutropenia	3.6	3.0
Pyrexia	13	1.8
Anaemia	27	0.6
Dyspnoea	13	1.8

*__CRS__
Most patients experienced CRS following Step-up Dose 1 (44%), Step-up Dose 2 (35%), or the initial maintenance dose (24%). Less than 3% of patients developed first occurrence of CRS following subsequent doses of TECVAYLI. CRS events were Grade 1 (50%) and Grade 2 (21%) or Grade 3 (0.6%). The median time to onset of CRS was 2 (Range: 1 to 6) days after the most recent dose, with a median duration of 2 (Range: 1 to 9) days.

**__ICANS:__
The onset of neurologic toxicity can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. The observed time to onset of ICANS ranged from 0 to 21 days after the most recent dose.

- **Other common adverse events:**

Adverse events	All grade (%)	Grade 3/4 (%)
Hypogammaglobulinaemia	75	1.8
Upper respiratory tract infection	37	2.4
Neutropenia	71	64
Thrombocytopenia	40	21
Lymphopenia	35	33
Injection site reaction	38	0.6
Diarrhoea	28	3.6
Nausea	27	0.6
Headache	24	0.6
Peripheral Neuropathy	16	0.6

7. Information for Patients and Carers – Nursing / Pharmacy team

Nursing/pharmacy team should provide the following information to patients during their review if it has not already been provided by the medical team The information provided here and in Appendix 2 are not mutually exclusive and should be used together to provide a holistic approach for patients.

- **Treatment Logistics:**
  - Frequency and location of treatment visits and transport links where applicable.
  - Duration of each treatment session (including monitoring and preparation time).
  - Detailed explanation of how the drug is administered, including the time required for pre-medication and monitoring.
  - Information on step-up dosing and the need for re-escalation if there is a long break in treatment.
  - What to look out for when they go home and who to contact. This should include in case of febrile neutropenia, including visiting the local Accident & Emergency (A&E) department, and the small risk of delayed CRS & neurotoxicity.
  - See section on ambulatory care pathway for counselling for self-monitoring in ambulatory care.

- **Supportive medicines:**
  - Recommendation to have pneumococcal, seasonal flu and COVID-19 vaccinations.
  - Counsel on importance of compliance with prophylactic supportive medication as per local policy. This should include duration of treatment.

- **Care Team Information:**
  - A list of team members and their roles and responsibilities across different care sites (e.g., local hospital, tertiary centre, nursing support team, and out-of-hours team).

- **Alert Card:**
  - An alert card completed with appropriate contact numbers.
  - Patients should be advised to always carry this card and to present it to the triaging nurse if they need to attend A&E.
  - Link to alert cards for BsAbs:
    - Elranatamab: Document (medicines.org.uk)
    - Teclistamab: Document (medicines.org.uk)
    -

Additional Resources

- Bispecific Antibodies Fast Facts in Myeloma

8. Risk Assessment for Safe Handling of Bispecific Antibodies in Clinical Area

The conventional practice in many healthcare settings involves preparing chemotherapies and monoclonal antibodies (mAbs) within pharmacy manufacturing units. As the demand for novel treatments requiring complex aseptic manipulation grows, it is essential to explore different service delivery models to enhance manufacturing capacity. Additionally, the lack of on-site pharmacy manufacturing units or reliance on the commercial compounding services may affect access to BsAbs in some centres.

Bispecific antibodies, once prepared, often have a limited shelf life, posing a logistical challenge for manufacturing units. This necessitates precise timing and coordination of production processes to ensure safe and timely delivery to patients. Furthermore, the risk of doses expiring before use increases the potential for wastage.

In such cases, centres can consider preparing BsAbs directly in the clinical area by a trained nursing or pharmacy team using closed system transfer devices (CSTDs). This strategy not only mitigates the reliance on external sources but also ensures efficient preparation of BsAbs while optimising resources within the healthcare facilities.

The benefits of preparing these drugs in the clinical area include:

- waste reduction as doses are prepared immediately prior to administration
- increase pharmacy aseptic capacity to focus on handling of cytotoxic or complex drugs
- reduce patient waiting times
- support weekend service for maintenance doses
- enabling care closer to home
- improved overall patient experience

Considerations for preparation of BsAb in clinical area should include:

- Assessment of handling risks such as risk of internal exposure and risk of toxicity
- Assessment of preparation risks, including risk assessment against NPSA alert 20 risk, storage and location of preparation and device compatibility
- Practical considerations such as staff capacity, wastage and cost analysis
- Governance review of procedure for preparing BsAb in clinical area
- Staff communication and training
- Monitoring and audit of ongoing safety and service provision

9. Management and Mitigation of Cytokine Release Syndrome

Cytokine release syndrome (CRS) is a well-recognized adverse effect of BsAbs, characterised by a spectrum of symptoms ranging from persistent culture-negative fevers to hypoxia, hypotension, and coagulopathy.

The onset of CRS is most common during the priming doses and to a lesser extent, the initial full treatment dose. In intravenous BsAb therapies, CRS typically emerges within 24 hours, while subcutaneous BsAb therapies may induce CRS 2-3 days post-dosing[1,2]. Consequently, patients should undergo vigilant monitoring for at least 48 hours following each step-up dose and 24-48hrs after the first full dose of BsAb.

The grading of CRS in BsAbs aligns with the American Society for Transplantation and Cellular Therapy (ASTCT) guidelines [3], which were initially established for chimeric antigen receptor T-cell (CAR-T) therapies.

It is essential to note that patients on clinical trials should adhere to trial specific protocols.

Regular monitoring for cytokine release syndrome (CRS) should occur twice daily, carried out by nursing staff or clinical professionals trained in recognizing CRS symptoms, particularly during the step-up dosing phase and following the initial treatment dose.

Assessment	Notify clinician when:
Temperature	≥38◦C
Blood pressure	>140 mmHg or <90mmHg
Heart rate	>120bpm or <60bpm, or arrhythmia
Respiratory rate	>25 breaths per min or <12 breaths per min
Peripheral oxygen saturation	<94% on room air
Urine output	<30mL/hour
Neurological	Tremors or jerky movements in extremities; change in mental status (alertness, orientation, speech, ability to write a sentence, or ICE score of <7)

The following blood panel should be requested as clinically indicated:

Blood panel / test	Frequency
FBC	Daily
Renal Profile	Daily
Liver profile	3 times a week; or daily if CRS suspected
Bone profile	3 times a week; or daily if
Coagulation screen, fibrinogen	Baseline, then once a week; or daily if CRS suspected
LDH	Baseline and as clinically indicated

CRP	As clinically indicated
Ferritin	Daily if CRS suspected
BNP and Troponin	Baseline and as clinically indicated

Anti-IL6 agent remains the mainstay of CRS management and the decision to treat with Tocilizumab +/- corticosteroid should be made at consultant level.

CRS management (based on IMWG guidelines[4])				
Grade & description		**General management**	**Tocilizumab**	**Corticosteroids**
Grade 1	Temperature ≥38°C, no hypotension/ hypoxia	Fever: • Paracetamol • Infection screen; consider CXR • Include prolactin in blood panel • Start empiric broad spectrum antibiotic • Maintenance IV fluids for hydration (if applicable)	Consider Tocilizumab for persistent and refractory fever. The early use of tocilizumab (at the onset of first fever) is also acceptable according to individual patient risk and local protocols. Centres can also consider the use of prophylactic tocilizumab in patients at high risk of severe CRS or to reduce the number of hospital admissions in out-patient protocols. If there is no clinical improvement following tocilizumab, follow guidance for Grade 2.	Consider STAT dose of Dexamethasone 10mg PO in the following if required: • Ambulatory setting • Perceived delay in accessing emergency care • Bone pain (tumour flare), if not controlled with analgesia
Grade 2	Temperature ≥38°C Hypotension not requiring vasopressors Hypoxia requiring low-flow nasal cannula or blow-by	Fever: Manage fever and constitutional symptoms as per Grade 1 CRS Hypotension: IV bolus 500-100mL normal saline (can give 2nd bolus of 500mls if systolic BP remains <90mmHg)	Start IV tocilizumab 8mg/kg (max 800mg). If there is no clinical improvement with 6-8 hours; dose can be repeated and add corticosteroid. Consider transfer to intensive-care-unit and an echocardiogram if	Consider if no clinical improvement after 6-8 hours of 1st dose of Tocilizumab. Recommendation: Dexamethasone 10mg IV 6-hourly

		Hypoxia: Prescribe supplemental oxygen	hypotension persists despite fluid resuscitation and tocilizumab.	
Grade 3	Temperature ≥38°C Hypotension requiring a vasopressor with or without vasopressin Hypoxia Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Fever: Manage fever and constitutional symptoms as per Grade 1 CRS	Start IV tocilizumab 8mg/kg (max 800mg). If there is no clinical improvement within 6-8 hours; repeat tocilizumab dose. Consider anakinra if no clinical improvement after two doses of tocilizumab and regular high-dose corticosteroid	Start Dexamethasone 10mg IV 6-hourly If there is no clinical improvement within 6-8 hours; increase dose to 20mg IV 6-hourly or start Methylprednisolone IV 1mg/kg every 12 hours
		Hypotension: IV fluid boluses as needed, as per Grade 2 CRS. Transfer to ICU for vasopressors, consider echocardiogram, haemodynamic monitoring as per Grade 2 CRS		
		Hypoxia: Prescribe supplemental oxygen (high-flow oxygen delivery)		
Grade 4	Temperature ≥38°C Hypotension Requiring multiple vasopressors (excluding vasopressin) Hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	Fever: Manage fever and constitutional symptoms as per Grade 1 CRS	Start IV tocilizumab 8mg/kg (max 800mg). If there is no clinical improvement within 6-8 hours; repeat tocilizumab dose. Consider anakinra if no clinical improvement after two doses of tocilizumab and regular corticosteroid	Start Methylprednisolone IV 1gram OD once a day for 3 days
		Hypotension: IV fluid boluses as needed, as per Grade 2 CRS. Transfer to ICU for vasopressors, consider echocardiogram, haemodynamic monitoring as per Grade 2 CRS		
		Hypoxia: Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)		

10. Management and Mitigation of Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) and Other Neurological Complications

Management of ICANS in patients undergoing bispecific antibody therapy involves a multifaceted approach aimed at early detection, supportive care, and targeted interventions to mitigate the severity of neurological symptoms. ICANS manifests as a range of neurological complications, from mild confusion and headache to severe symptoms such as seizures, cerebral oedema, and coma.

Early Detection and Monitoring:

- **Baseline Assessment:**
  Before initiating bispecific antibody therapy, a thorough neurological baseline assessment should be conducted. This includes cognitive function tests and documentation of any pre-existing neurological conditions.

- **Regular Monitoring:**
  During the therapy, particularly during the step-up dosing phase and following the initial full dose, patients should be monitored twice daily for signs of ICANS. Monitoring should be performed by clinical professionals trained in recognising ICANS symptoms, such as headache, confusion, aphasia, altered consciousness, motor weakness, and seizures.

Grading and Documentation:

- **Grading of ICANS:**
  ICANS should be graded based on established criteria, such as the American Society for Transplantation and Cellular Therapy (ASTCT) guidelines, which provide a structured framework for evaluating and managing neurotoxicity.

- **ICE Score:**
  The Immune Effector Cell-Associated Encephalopathy (ICE) score should be performed twice daily by trained nursing staff and/or clinical team. Clinical findings and ICE scores should be documented in the medical record. If ICANS is suspected, the consulting physician in charge must be informed immediately, and management decisions should be made at the consultant level. It is important to remember that the timeline for and severity of ICANS varies therefore staff must be vigilant when any patient who has received a bispecific antibody develops neurological symptoms, even post discharge.

ICE score grading as per ASTCT[3]:

Orientation	Orientation to year, month, city and hospital	4 points (1 point for each correct answer)
Naming	Ability to name 3 objects *e.g. point to clock, pen, button etc*	3 points (1 point for each correct answer)
Following commands	Ability to follow simple commands *e.g. show me 2 fingers*	1 point
Writing	Ability to write a standard sentence	1 point
Attention	Ability to count backwards from 100 to 10	1 point

ASTCT ICANS Consensus Grading for Adults[3]:

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 generalised that resolves rapidly or non-convulsive 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 oedema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Notify clinician when:

- Tremors or jerky movement in extremities
- Change in mental status (alertness, orientation, speech, ability to write a sentence)
- ICE score of <7

ICANS management – specific details according to IMWG guidance[5]		
ICANS grading and ICE score		**Management**
Grade 1	ICE score 7-9	Observe Consider: • Dexamethasone 10mg PO/IV in high-risk patients • Levetiracetam 250mg PO/IV BD • Neurology consultation, if available

Grade 2	ICE score 3-6	Start Dexamethasone 10mg PO/IV 12-hourly. If no improvement after 48 hours: • Increase dexamethasone dose to 20mg PO/IV 6-hourly • Start Levetiracetam 500mg PO/IV BD • Consider anakinra • Fundoscopic exam to assess for papilloedema • MRI of the brain with and with contrast (CT brain if MRI of the brain is not feasible) • Perform EEG; if EEG shoes non-convulsive status epilepticus, seek urgent advice from Neurology team
Grade 3	ICE score 0-2	Start Dexamethasone 10mg PO/IV 6-hourly. If no improvement after 24 hours: • Increase dexamethasone dose to 20mg PO/IV 6-hourly or; Methylprednisolone 1-2g/day • Start Levetiracetam 500mg PO/IV BD • Consider anakinra • Fundoscopic exam to assess for papilloedema • MRI of the brain with and with contrast (CT brain if MRI of the brain is not feasible) • Perform EEG; if EEG shoes non-convulsive status epilepticus, seek urgent advice from Neurology team • Consider diagnostic lumbar puncture with measurement of opening pressure where possible • Transfer patient to ICU
Grade 4	ICE score 0	Transfer patient to ICU Start Dexamethasone 10mg PO/IV 6-hourly. • If refractory to dexamethasone, start methylprednisolone 2mg/kg IV 12-hourly • Consider anakinra • Start Levetiracetam 500mg PO/IV BD • MRI of the brain with and with contrast (CT brain if MRI of the brain is not feasible) • Perform EEG; if EEG shows non-convulsive status epilepticus, seek urgent advice from Neurology team • Consider diagnostic lumbar puncture with measurement of opening pressure where possible.

Appendix 1: Referral Form Template

MYELOMA BISPECIFIC ANTIBODY TREATMENT REFERRAL FORM

PATIENT DETAILS		
Surname:	**Forename:**	**NHS number:**
DOB:	**Interpreter required:**	**Ethnicity / Race:**
Referring GP Details **Address and Tel No:**	Yes ☐ No ☐ If yes, preferred language:	☐ Asian / Asian British ☐ Black, Black British, Caribbean or African ☐ Mixed or multiple ethnic groups ☐ White ☐ Other ethnic group ☐ Not disclosed

I have informed the patient this is a referral for treatment of bispecific antibody treatment	☐

PLEASE PROVIDE FOLLOWING INFORMATION:
FISH result (if applicable):
Myeloma ISS stage at diagnosis (please tick one) I ☐ II ☐ III ☐
Performance status (please tick one) 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐
Relevant comorbidities:

PLEASE OUTLINE PREVIOUS TREATMENT AND RESPONSES:			
Start Date	**Treatment regimen**	**Best response**	**Refractory?***

* Refractory: progression on or within 60 days of last dose of regimen

PLEASE PROVIDE SUMMARY OF CURRENT CLINICAL CONDITION:							
PLEASE PROVIDE MOST RECENT BLOOD RESULTS:						**DATE:**	
Hb (g/L)		WCC (x10^9/L)		Neutrophils (x10^9/L)		Platelets (x10^9/L)	
sCr (µmol/L)		eGFR (ml/min)		Paraprotein (g/L)		sFLC	Kappa: Lambda:

	PLEASE TICK
Does patient have recent imaging (within last 3-months)? *If Yes – please provide copy of scan report with referral form*	Yes ☐ No ☐
Does patient have evidence of any CNS myeloma?	Yes ☐ No ☐
Does patient have any blood abnormalities or require G-CSF support? *If Yes – please provide information in additional information section below:*	Yes ☐ No ☐

PLEASE PROVIDE VACCINATION HISTORY (IF APPLICABLE):
ADDITIONAL INFORMATION:

Appendix 2: Letter Template for Repatriation to Referring Centre

Trust Consultant Name
Specialist Trust Details
Contact details
Date

Trust Consultant Name
Trust Details
Contact details

Cc:
GP Practice Name
Surgery Address
Contact Details

Dear Dr

Patient full name:	
Patient DOB:	
Patient NHS number:	

The above patient with relapsed multiple myeloma received *[insert drug name]* during this admission, with the following dosing administration:

	Date
1st priming dose	
2nd priming dose	
1st treatment dose	

Summary of Bispecific-antibody-specific events from this admission:

Patient experienced CRS during inpatient stay	*Yes / No*
Is yes to above, provide details of CRS event, including grading and dates	
Patient experienced ICANS during inpatient stay	*Yes / No*
Is yes to above, provide details of CRS event, including grading and dates	
Number of Tocilizumab doses used to manage CRS / ICANS	
Number of doses of corticosteroid used to manage CRS / ICANS, including dosage:	

General Recommendations to reduce the risk of severe infections:

1. Patient should continue to receive HSV prophylaxis and PCP prophylaxis whilst on treatment
2. Consider IV/ SC immunoglobulin treatment for secondary hypogammaglobulinemia according to the NHS criteria
3. Refer to Summary of Product Characteristics for guidance on missed doses and refer to specialist centre for re-priming where appropriate.

Specific Recommendations:

Details of any follow-up arranged:

Please do not hesitate to contact us for any assistance.

Yours sincerely,

[insert name and position]

Appendix 3: Criteria for BsAb administration in ambulatory care

MM specific criteria:	**General Ambulatory criteria:**
1. ECOG <2 2. Adequate BM function (can be supported with blood products or GCSF): • Platelet count ≥ $30x10^9$L • Absolute neutrophils count ≥$1x10^9$L • Haemoglobin≥80g/L 3. Creatinine clearance >30ml/min 4. Adequate liver function (bilirubin ≤2× upper limit of normal, ALT ≤2.5× ULN) 5. No evidence of extramedullary disease 6. <60% Plasma cells in BM prior to commencing treatment 7. No evidence of CNS disease or active plasma cell leukaemia 8. No other significant co-morbidities	• Patient has a carer to remain with them for entire duration of Ambulatory stay • Patient and/or carer must understand spoken and written English • Patient is independent for mobility • Patient is off antibiotics and apyrexial for 24 hours or more • Patient must have access to a mobile phone • Patient needs to be able to take own medication, monitor own temperature, and be compliant with care • Patients must have an address to be discharged to and have a GP • No clinical signs of an infection

Appendix 4: Ambulatory Care Patient Information

Dear Patient,

You are about to start treatment with a bispecific antibody for multiple myeloma. Whilst this treatment can be very effective, it is important to monitor for side effects that may occur during the first few doses.

The instructions set out below are for the first 10 days after you start your bispecific antibody treatment. This is because the risk of cytokine release syndrome (CRS) is greatest in the first 10 days of treatment. Symptoms of CRS include a high temperature or confusion.

Please complete your home monitoring record three times per day for 2 days after each of your first three treatments. If you have a temperature of 38°C or higher, answer yes to any of the questions or notice that your handwriting is shaky you **must** ring the advice line and come to the hospital for assessment. The hospital team will tell you where to go for assessment. You must tell the team you have received a bispecific antibody and are at risk of CRS.

Please bring this record with you each time you visit the hospital during your first 10 days of treatment.

If you have been given a "Just in Case" dose of dexamethasone and your temperature is 38°C or higher between 17:00 and 09:00 you should take these tablets before you make your way to the hospital for assessment. **Please inform the team on arrival that you have taken the dexamethasone tablets.**

You should only take these tablets if you get a high temperature within the first 10 days of your first dose of treatment. The team on the advice line will give you further information on this.

Advice line number:

Ambulatory care unit phone number:

Template for CRS and ICE Home Monitoring Record:

Circle as appropriate: Dose 1 (step up dose 1) / Dose 2 (step up dose 2) / Dose 3 (first full dose)

Date of treatment:_____

Please record your temperature and a sample of your handwriting three times per day for 48 hours after your first dose. We recommend you do this at breakfast time, midday and before you go to bed. If you start to feel unwell check your temperature again.

Day 1 / 2 / 3

Date:

CRS score			
Time of day	Temperature	Do you feel dizzy or confused?	Do you have any difficulty breathing?
Morning			
Midday			
Evening			
Morning	Write a sentence		
Midday	Write a sentence		
Evening	Write a sentence		

Appendix 5: Risk Assessment Template for Preparation of Monoclonal Antibodies in Clinical Area

Generic (RINN) name		
Brand name(s)		
Route of administration	IV ☐ SC ☐ IM ☐ Other:	
Formulation	Liquid ☐ Powder ☐	
Vehicle	Sodium chloride 0.9% ☐ Glucose 5% ☐ Neat ☐ Other:	
Vial size(s) & strength(s)		
Standard Dose		
Dose preparation	Max.dose (mg) =	Max. no. of vials required =
Treatment indication	SACT ☐ Rescue treatment ☐	
Product	Licensed ☐ Unlicensed ☐	
Origin of MAB	Murine ☐ Chimeric ☐ Humanised ☐ Human ☐	

Section 1	**Yes / No**
Is it conjugated to a cytotoxic or radiolabelled agent?	Y / N
Are there handling risks which demonstrate that it is carcinogenic to humans?	Y / N
Is it a known human genotoxic or mutagenic agent?	Y / N
Is serial dilution required for preparation?	Y / N
Is the maximum number of vials required to make up a dose ≥ 10 vials?	Y / N
If any answers Section 1 are YES, the mAb must be made in the pharmacy aseptic unit. **If all the answers in this section are NO, proceed to Section 2.**	

Section 2	Yes / No
Is the mAb available in different route formulations?	Y / N
Is reconstitution of a powder required?	Y / N
Would the mAb be required for urgent rescue treatment?	Y / N
Is a filter required for preparation? [NB an inline filter for administration is excluded]	Y / N
Are there more than 5 non-touch manipulations involved? (Includes >4 vials per dose)	Y / N
Is the preparation method complex? *Document below the preparation method including the diluent, vehicle and references:*	Y / N
Is there a known risk of teratogenicity or other developmental toxicity? *If yes, document below the identified risks including references:*	Y / N
Other comments:	
If any answers in Section 2 are YES, complete Section 3 and 4. **If all the answers in Section 2 are NO, proceed to Section 4.**	

Section 3
Describe the risk highlighted in Section 2 in terms of cause and consequence.
Explain the controls to mitigate the risk highlighted in Section 2.

Proceed to Section 4.

Section 4: Practical Considerations and Cost/capacity analysis	**Yes / No**
Is there a Medusa IV guide suitable for nurse preparation of mAb? (Note, this is not required for neat S/C drugs in solution) *If no, prepare a pharmacy preparation guide prior to approval for nurse preparation.*	Y / N
Is the CSTD physically compatible with the vial? *Document brand checked:* *Document size which fits:*	Y / N
Additional Notes (including treatment pathway factors):	
Final decision	
Sections 1-3: Risk assessment for preparation of mAbs in clinical area Is mAb suitable for nurse preparation? Yes ☐ No ☐ If Yes: Are any additional mitigation required? If No: Summary of reasons why nurse preparation is not suitable**:**	
Section 4: Practical Considerations and Cost Analysis Nurse Preparation ☐ Outsource Product ☐ Aseptic Manufacture ☐ Summary of decision:	

Risk assessment signatories	**Name + Role**	**Signature**	**Date**
Completed by clinical pharmacist OR pharmacy technician			
Approved by lead pharmacist			
Approved by Lead Chemotherapy nurse (or deputy)			
Chemotherapy Governance Approval			

Appendix 6: Bispecific Pathway Implementation Group

- Adam Forbes, Royal Cornwall Hospitals NHS Trust
- Adrian Shields, University of Birmingham and University Hospitals Birmingham NHS Foundation Trust
- Andrea Preston, Sanius Health Ltd and University Hospitals Bristol & Weston NHS Foundation Trust
- Anish Tailor, University College London Hospital NHS Foundation Trust
- Antoinette Carr, Patient Representative
- Bhuvan Kishore, University Hospitals Birmingham NHS Foundation Trust
- Ceri Bygrave, University Hospital of Wales
- Chantelle Hughes, University College London Hospital NHS Foundation Trust
- Dunsi Bolarinwa, University College London Hospital NHS Foundation Trust
- Emma Williams, Cardiff and Vale University Health Board
- Grant Mehrjou, Cardiff and Vale University Health Board
- Hayder Hussein, University Hospitals Birmingham NHS Foundation Trust
- Helen Parry, University Hospitals Birmingham NHS Foundation Trust
- Jackie Quinn, Belfast City Hospital
- Jane Aston, The Newcastle Upon Tyne Hospitals NHS Foundation Trust
- Jennifer Young, The Newcastle Upon Tyne Hospitals NHS Foundation Trust
- Kamaraj Karunanithi, University Hospitals of North Midlands NHS Trust
- Lesley Symington, NHS Lothian Scotland
- May Low, University College London Hospital NHS Foundation Trust
- Michelle Amos, The Newcastle Upon Tyne Hospitals NHS Foundation Trust
- Neill Storrar, NHS Lothian Scotland
- Nicola Lawton, University Hospitals Birmingham NHS Foundation Trust
- Nicola Parry, University Hospitals Birmingham NHS Foundation Trust
- Peter Baker, Hywel Dda University Health Board
- Pinkie Chambers, University College London Hospital NHS Foundation Trust, Co-Chair
- Rachel Hall, University Hospitals Dorset NHS Foundation Trust
- Rakesh Popat, University College London Hospital NHS Foundation Trust; Co-Chair
- Sandra Quinn, Myeloma UK
- Sarah Henshaw, Nottingham University Hospitals NHS Trust
- Satarupa Choudhuri, The Northern Care Alliance NHS Foundation Trust
- Sumantha Gabriel, The Newcastle Upon Tyne Hospitals NHS Foundation Trust
- Suzanne Stainer, Patient Representative
- Tiffany Chan, Great Western Hospitals NHS Foundation Trust

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