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Improving Effective and Prompt Management of Cytokine Release Syndrome (CRS) in Clinical Trial Participants across multi-disciplinary teams in a Clinical Trial Site or hospital setting.

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1 Introduction

Cytokine Release Syndrome (CRS) is a type of systemic inflammatory response syndrome, caused by various factors such as infections / specific medications. It emerges when a significant quantity of white blood cells becomes activated, leading to the release of inflammatory cytokines. Consequently, this activation triggers further white blood cell activity, perpetuating the release of inflammatory cytokines.

Effective and timely management of CRS is vital in mitigating potential harm to patients. Therefore, it is imperative to minimise the risk of mismanagement by providing comprehensive training and fostering clear communication among all teams directly involved in the care of patients receiving the Investigational Product (IP) or trial drug.

2 Aim

To ensure that Clinical Research Nurses (CRNs), and other healthcare staff involved in direct care of clinical trial participants, are well-versed in managing Cytokine Release Syndrome (CRS), including the administration of intravenous (IV) Tocilizumab infusion; in both clinical trial sites and hospital settings.

3 Methodology

Clinical trial participants are typically accommodated in the Investigational Medicine Unit (IMU) department at SingHealth or may also be hospitalised as inpatients, necessitating the involvement of various medical teams. Each participant at risk for CRS will receive a printed workflow outlining different grades and management procedures, along with contact information for doctors, CRNs, Clinical Research Coordinators (CRCs), and the Principal Investigator (PI); ensuring prompt identification and early intervention of CRS.

Cytokine Release Syndrome (CRS) and recommended treatments for PROTOCOL: _____

Grade / Symptoms	General recommended treatment
Grade 1 CRS • Fever > 38^{0}C • Nausea • Fatigue • Headache • Myalgia • Malaise	1. Symptomatic treatment 2. Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution, whichever is earlier 3. Monitor fluid balance and administer IV fluids as clinically indicated 4. Standby IV Tocilizumab 8 mg/kg as a single dose for any signs and symptoms present in addition to fever
Grade 2 CRS • Grade 1 symptoms **&** • Oxygen requirement < 40% **OR** • Hypotension responsive to fluids or low dose vasopressor, **OR** • Hypotension NOT requiring vasopressor **and/or** • Hypoxia requiring low dose oxygen by nasal cannula	

Additional Notes: _____

IMU CRN ON-DUTY: _____

*IMU CRN WILL FIRST CONTACT MO-ON-CALL FOR SUSPECTED CRS

CONTACT DOCTORS FOR REVIEW & MANAGEMENT PLANS

1. MO-ON-CALL: _____
2. Reg-ON-CALL: _____

To contact Phase I fellows for advice on CRS management

3. PH 1 FELLOWS: _____

To contact PI if the Phase 1 fellow(s) is/are uncontactable

4. PI: _____

To contact ANY of the following Co-Is if PI is uncontactable

5. Co-I: _____

To contact (insert Dr's name) _ *if ALL the Co-Is are uncontactable*

6. IMU CLINICAL & SCIENTIFIC DIRECTOR
(insert doctor's name and contact number)

All CRNs must undergo training in the administration of IV Tocilizumab, to provide an additional layer of defence alongside the prescribing doctor. This ensures both the drug's suitability for the participant, and safe infusion administration. Given Tocilizumab's high-cost and need for trained administration, as well as close post-administration observation, a competency assessment is mandatory for all CRNs administering IV Tocilizumab. A supply of IV Tocilizumab is provided for every participant at high risk of CRS depending on the trial protocol.

4 Results

When a CRS occurs, the clinical team directly involved in the care of the patient was able to easily identify the grading based on the symptoms manifested. This resulted in prompt intervention by the nursing team and early notification of the PI and relevant medical teams, hence preventing CRS grade escalation/worsening of patient status.

5 Conclusion

Having a visible, clear workflow that is readily available improves response time and early intervention in managing CRS to ensure optimum patient outcome.