Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

HSE Interim Guidance for the Pharmacological Management of Patients Hospitalised with COVID-19.

This document is intended for use by healthcare professionals only.

This guidance is specific to the management of hospitalised patients with COVID-19 disease.

While the guidance is intended to strengthen clinical management of these patients it does not replace clinical judgment or specialist consultation. Paediatric specialist input should be sought for the management of paediatric patients.

This guidance should be read in conjunction with the National HSE Infection Prevention and Control (IPC) Guidance for Possible or Confirmed COVID-19 .

This guidance document is informed by the following published evidence and evidence-based guidelines:

COVID-19 ERG *Rapid Evidence Reviews* (available from: http://www.ncpe.ie/research/covid-19/):

- *Clinical evidence for the use of antivirals in the treatment of COVID-19 v14*.
- *Tocilizumab in the management of COVID-19 v6*.
- *Clinical evidence for the use of intravenous immunoglobulin in the treatment of COVID19 v3.*
- *Clinical evidence for thromboprophylaxis in the management of COVID-19 v1.*

World Health Organisation Guidance:

- *Therapeutics and COVID-19: living guideline (*available from: https://www.who.int/publications/i/item/therapeutics-and-covid-19-living-guideline).
- *Corticosteroids for COVID-19. Living Guidance.* (available online at: https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1).

Background

Many pharmacological therapies are being used or being considered for the treatment of coronavirus disease 2019 (COVID-19). Given the rapidity of emerging evidence, the HSE identified the need to develop evidence-based guidance to support clinicians and other health-care professionals in decisions about treatment and management of patients with COVID-19.

Emerging Evidence

The evidence continues to emerge for the use of pharmacological therapies in the management of COVID-19. Participation in clinical trials, where available, should be strongly encouraged so that reliable and relevant evidence is available to inform evidence-based guidance and support clinicians and other healthcare professionals in the management of patients with COVID-19. The WHO includes the following commentary on emerging evidence in the *Therapeutics and COVID-19: living guideline:*

"*The unprecedented volume of planned and ongoing studies for COVID-19 interventions – 2801 RCTs as of 1 November 2020 – implies that more reliable and relevant evidence will emerge to inform policy and practice. An overview of registered and ongoing trials for COVID-19 therapeutics is available from the Infectious Diseases Data Observatory, through their living systematic review of COVID-19 clinical trial registrations and the WHO website (https://www.covid-nma.com/dataviz/). Whereas most of these studies are small and of variable methodological quality, a number of large, international platform trials (e.g. RECOVERY, SOLIDARITY and DISCOVERY) are better equipped to provide robust evidence for a number of potential treatment options. Such trials can also adapt their design, recruitment strategies and selection of interventions based on new insights, exemplified by the uncertainties outlined above.*"

Table 1 Summary of recommendations.

A number of models have been developed internationally to categorise COVID-19 disease severity. In Ireland, the HSE National Clinical Programme for Respiratory Medicine/Irish Thoracic Society developed the COVID Respiratory Scale (CRS), available from: https://hse.drsteevenslibrary.ie/c.php?g=679077&p=4866795#appendix1%20021. The CRS is used in this HSE interim guidance document.

Intervention	Disease Severity	Recommendation
VTE Prophylaxis	All hospitalised patients with COVID-19.	Risk assessment and provision of appropriate VTE prophylaxis and patient information is recommended for all patients hospitalised with COVID-19. Refer to the *HSE COVID 19 Interim Clinical Guidance for VTE protocol and Patient Information for Acute Hospitals* (available from: https://hse.drsteevenslibrary.ie/c.php?g=679077&p=4866382).
Remdesivir (see **Section 2.1**)	Hospitalised but not requiring supplemental oxygen. (**CRS A not on oxygen**)	Remdesivir is not indicated for hospitalised patients not requiring supplemental oxygen.
	Hospitalised requiring supplemental oxygen +/- high-flow oxygen +/- non-invasive ventilation. **(CRS A on oxygen/B/C1/C2)**	Use of remdesivir should be primarily in the setting of an approved clinical trial. If treatment is being considered outside of a clinical trial, it must only be initiated after consultant-level discussion in a multidisciplinary setting with patient engagement. *Refer to **Section 2.1** for further information.*
	Hospitalised requiring supplemental oxygen with invasive ventilatory support. **(CRS D)**	Remdesivir is not indicated for patients requiring invasive forms of ventilatory support at the start of treatment.
Systemic corticosteroids (see **Section 3.1**)	Hospitalised but not requiring supplemental oxygen. (**CRS A not on oxygen**)	[#]Systemic corticosteroids are not recommended.
	Hospitalised requiring supplemental oxygen +/- high-flow oxygen +/- non-invasive ventilation. **(CRS A on oxygen/B/C1/C2)**	Systemic corticosteroids are recommended. *Refer to **Section 3.1** for further information.*
	Hospitalised requiring supplemental oxygen with invasive ventilator support. **(CRS D)**	Systemic corticosteroids are recommended. *Refer to **Section 3.1** for further information.*

Tocilizumab (see **Section 3.2**)	Recently hospitalised patients not in an ICU with rapidly increasing oxygen needs requiring either high-flow oxygen or non-invasive ventilation and significantly increased markers of inflammation. (**Note**: The RECOVERY trial inclusion criterion for inflammation was a CRP≥75 mg/L). **(CRS C1 or C2)**	Intravenous tocilizumab should only be considered for the management of COVID-19 disease in non-ICU patients with an inadequate clinical response to *systemic corticosteroid therapy. Benefit has not been demonstrated with tocilizumab monotherapy, systemic corticosteroids should continue as adjunctive therapy. If treatment is being considered outside of the ICU setting, it should only be initiated after consultant-level discussion in a multidisciplinary setting that includes at least two consultants from critical care medicine, haematology, infection specialists, or respiratory medicine, and with patient engagement (or their relevant person, by phone). *Refer to **Section 3.2** for further information.*
	ICU admission with severe pneumonia and requiring respiratory support. **(CRS C1, C2 and D)**	Intravenous tocilizumab should be considered for the management of COVID-19 disease in ICU patients with an inadequate clinical response to *systemic corticosteroid therapy. Benefit has not been demonstrated with tocilizumab monotherapy, systemic corticosteroids should continue as adjunctive therapy. *Refer to **Section 3.2** for further information.*
Intravenous normal immunoglobulin (IVIg) (see **Section 3.3**)		IVIg is not recommended for the management of [$]COVID-19. **Paediatric Patients** Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV2 (PIMS-TS) has been reported in some cases of COVID-19. All cases of suspected PIMS-TS should be discussed with the Paediatric Infectious Disease team in Children's Health Ireland at Crumlin/Temple Street.
Lopinavir/ritonavir (see **Section 2.2**)		Lopinavir/ritonavir is not recommended for the management of COVID-19.
Hydroxychloroquine +/- Azithromycin (see **Section 2.2**)		Hydroxychloroquine +/- azithromycin is not recommended for the management of COVID-19.

[#]Recommendation does not apply to the use of systemic corticosteroids for indications other than COVID-19 (e.g. exacerbations of asthma or COPD). Patients currently taking corticosteroids for other indications should continue to do so unless advised by their doctor to discontinue. For further information on the use of corticosteroids for indications other than COVID-19, and in both asthma and COPD patients with COVID19, please refer to the HSE COVID-19: Interim Clinical Guidance: Immunosuppressant Therapy, available from: https://hse.drsteevenslibrary.ie/ld.php?content_id=32936271 .

[$]Use in conditions other than COVID-19: Patients being treated with IVIg for conditions where clinical benefit is established should continue to receive IVIg therapy regardless of COVID-19 status, if clinically appropriate to do so. These conditions include immunodeficiencies (primary and secondary) and autoimmune diseases (e.g. neuroinflammatory diseases).

Section 1: Venous Thromboembolism (VTE) Prophylaxis

VTE Prophylaxis
Being hospitalised with COVID-19 is associated with a high risk of venous thromboembolism (VTE). Provision of appropriate prophylaxis and patient information is recommended for all people with COVID-19 admitted to hospital.

Refer to the *HSE COVID 19 Interim Clinical Guidance for VTE protocol and Patient Information for Acute Hospitals* (available from: https://hse.drsteevenslibrary.ie/c.php?g=679077&p=4866382).

Section 2: Antivirals

Section 2.1 Remdesivir.

At present, prescribing of antivirals for the management of patients with confirmed COVID-19 disease should be **restricted to hospitals only**.

Remdesivir: The HSE recommends that the use of remdesivir for the management of COVID-19 should be primarily in the setting of an ethically approved clinical trial.

However, it is acknowledged that there is an absence of universal access to clinical trials. If treatment is being considered outside of a clinical trial, it must only be initiated after consultant-level discussion in a multidisciplinary setting with patient engagement.

Patients (or their relevant person, by phone) should be adequately informed about the uncertain efficacy and potential toxicities, and given an opportunity to indicate their values and preferences.

Remdesivir Prescribing Information

Clinical Trials
The HSE recommends that the use of remdesivir for the management of COVID-19 should be primarily in the setting of a clinical trial. Information on on-going clinical trials, including those recruiting, is available on the EU CT Register for COVID trials (https://www.clinicaltrialsregister.eu/ctr-search/search?query=covid-19) or www.clinicaltrials.gov.

Treatment outside of a clinical trial

If treatment is being considered outside of a clinical trial, it must only be initiated after consultant-level discussion in a multi-disciplinary setting with patient engagement.

Remdesivir has received a conditional marketing authorisation from the European Commission. This means that the benefits and risks of treatment are under active review, and the product information is updated on a regular basis, to take account of new efficacy and safety information.

Patients (or their relevant person, by phone) should be adequately informed about the uncertain efficacy and potential toxicities, and given the opportunity to indicate their values and preferences.

For full prescribing information refer to the Summary of Prescribing Characteristics (SmPC), available at: https://www.ema.europa.eu/en/medicines/human/EPAR/veklury . **Note:** Remdesivir (Veklury®) is available in two formulations: concentrate for solution for infusion and powder for concentrate for solution for infusion; ensure the correct SmPC is used.

Remdesivir Treatment Criteria for Patients Treated Outside of a Clinical Trial
For full prescribing information refer to the Summary of Prescribing Characteristics (SmPC) for remdesivir. Considering the best available evidence the following criteria, in addition to the prescribing recommendations detailed in the SmPC, should be satisfied if treatment outside of a clinical trial is being considered: • Hospitalised with coronavirus disease 2019 (COVID-19) • Patients with pneumonia requiring supplemental oxygen at the start of treatment (low- or high-flow oxygen or other non-invasive ventilation). Remdesivir is not indicated for patients requiring invasive forms of ventilatory support at the start of treatment. • Multi-disciplinary team assessment should determine if patients not suitable for escalation would benefit from initiation of treatment with remdesivir. • If patients on remdesivir require escalation, continuation of the drug should be considered by multi-disciplinary team assessment.

Duration of Treatment for Patients Treated Outside of a Clinical Trial
The HSE recommends a total duration of 5 days of remdesivir. Available evidence has shown no incremental benefit of 10 days treatment over 5 days. See COVID-19 ERG *Rapid Evidence Review* for "Clinical evidence for the use of antivirals in the treatment of COVID-19 v14" for further information (available from: http://www.ncpe.ie/research/covid-19/).

Access to Remdesivir Supply

1. Clinical Trials: The WHO Solidarity trial is currently open to recruitment across multiple acute hospitals in Ireland. The trial is an international collaboration amongst WHO and participating international member countries and researchers to evaluate potential COVID-19 treatments. Remdesivir is included as an arm in this study.

2. On 15th December 2020, the HPRA confirmed that the Compassionate Use Programme for remdesivir has now closed. Requests for further information should be directed to the manufacturer, contact details are:
   - Gilead UK Med Info; email: UKMed.Info@gilead.com
   - UKICOVID-19; email: UKICOVID-19@gilead.com

3. Consult with the hospital Pharmacy Department for other supply access.

Section 2.2 Other antivirals.

Lopinavir/ritonavir: Not recommended as a therapeutic agent due to evidence indicating a lack of benefit in patients hospitalised with COVID-19.

Hydroxychloroquine: Not recommended as a therapeutic agent due to evidence indicating a lack of benefit in patients hospitalised with COVID-19.

Azithromycin: Not recommended in combination with hydroxychloroquine in the context of COVID-19 due to its lack of proven clinical efficacy and safety concerns in COVID-19.

Section 3: Immunomodulators

Section 3.1 Systemic Corticosteroids.

Summary Guidance for the use of Systemic Corticosteroids in the Management of Patients with Severe COVID-19.

- Emerging high quality evidence, including randomised controlled trials[1-4] and one meta-analysis of randomised trials[5], suggests that corticosteroids may provide benefit in the management of severe COVID-19. There is evidence of no benefit, and possible harm, for the use of corticosteroids in patients with non-severe COVID-19 not requiring respiratory support.

- A meta-analysis of seven randomised trials (1,703 patients) published by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group concluded that administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality in hospitalised, critically ill patients with COVID-19.[5]

- The corticosteroids used in the trials included in the WHO meta-analysis were dexamethasone (3 trials, 1,282 patients), hydrocortisone (3 trials, 374 patients) and methylprednisolone (1 trial, 47 patients).[5] Further details of the meta-analysis are available online at: https://jamanetwork.com/journals/jama/fullarticle/2770279

- The results of a subgroup analysis of the RECOVERY trial for dexamethasone suggests that the relative effects of systemic corticosteroids is related to the level of respiratory support received at randomisation. Evidence of benefit was limited to patients with severe COVID-19 requiring respiratory support. The RECOVERY trial reported that dexamethasone did not provide benefit over usual care in patients not receiving respiratory support at randomisation (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55) and the results were consistent with possible harm in this subgroup.[1]

- The potential for adverse events resulting from systemic corticosteroid therapy must be considered before initiating therapy in patients with COVID-19. The WHO REACT Working Group did not conduct a meta-analysis of serious adverse events as there were inconsistencies in the reporting and definitions used in the clinical trials included in the meta-analysis.[5] The WHO clinical guideline panel concluded that "harms, in the context of the mortality reduction in severe COVID-19, are minor".[5]

- The HSE recommend that the use of systemic corticosteroids in a defined cohort of patients* infected with COVID-19 should only be considered after consultant-level discussion in a multidisciplinary setting (*see patient selection criteria below).

- This guidance does not apply to the use of systemic corticosteroids for indications other than COVID-19 (e.g. exacerbations of asthma or COPD). Patients currently taking corticosteroids for other indications should continue to do so unless advised by their doctor to discontinue. For further information on the use of corticosteroids for indications other than COVID-19, and in both asthma and COPD patients with COVID-19, please refer to the *HSE COVID-19: Interim Clinical Guidance: Immunosuppressant Therapy,* available from: https://hse.drsteevenslibrary.ie/ld.php?content_id=32936271 .

Patient Selection for systemic corticosteroid therapy (with input from specialist multidisciplinary team)
1. Systemic corticosteroid therapy should only be considered for the management of COVID-19 disease in hospitalised patients requiring: - Mechanical ventilation **(CRS D)** **OR** - Supplemental oxygen but who are not mechanically ventilated **(CRS A on oxygen, B, C1, C2)** (The above definitions correspond to the HSE National Clinical Programme for Respiratory Medicine/Irish Thoracic Society COVID Respiratory Scale (CRS) categories B, C or D; the CRS is available from https://hse.drsteevenslibrary.ie/c.php?g=679077&p=4866795#appendix1%20021) *Systemic corticosteroids should **not** be used for the management of patients with COVID-19 who do not require respiratory support, unless another indication for corticosteroid therapy exists* **AND** 2. Exclusion of contraindications to systemic corticosteroid therapy including acute severe infection from sources other than SARS-CoV2. **AND** 3. If treatment is being considered, it must only be initiated after consultant-level discussion in a multidisciplinary setting.

Key Prescribing Recommendations for Systemic Corticosteroids (Adapted from WHO Clinical Guideline: *Corticosteroids for COVID-19*) *Refer to Summary of Product Characteristics of respective medicinal products for full prescribing information.*	
Systemic (i.e. intravenous or oral) corticosteroid therapy (e.g. dexamethasone orally or intravenously or hydrocortisone intravenously) for 7 to 10 days.	
Recommended Dexamethasone Dose Schedule:	Dexamethasone 6mg orally daily for 7 to 10 days. **OR** Dexamethasone phosphate 8mg (equivalent to dexamethasone 6.6mg) intravenously daily for 7 to 10 days [#] *[#]In the RECOVERY trial dexamethasone was prescribed as dexamethasone base*[7] *Dexamethasone phosphate (salt) 4mg in 1ml injection is equivalent to dexamethasone (base) 3.3mg in 1ml injection.*[8,9] *Check with local pharmacy department for formulation available.* *No conversion is required for oral formulations of dexamethasone*.
Recommended Hydrocortisone Dose Schedule:	Hydrocortisone 50mg every 6 to 8 hours intravenously for 7 to 10 days.[6,10]

Considerations for Route of Administration Based on Level of Care (*All patients must satisfy the criteria for systemic corticosteroid therapy regardless of level of care)*	Intensive Care Unit (ICU) Patients: Hospitalised patients requiring escalation to ICU within 24 hours of admission and not already commenced on dexamethasone should be considered for treatment with intravenous hydrocortisone. Non-ICU Patients: Hospitalised patients not requiring admission to an ICU should be considered for treatment with parenteral corticosteroids (dexamethasone or hydrocortisone) for the first 48hours followed by a review to oral therapy. (*Expert Opinion of Guideline Development Group*)

Additional Considerations for Prescribing Systemic Corticosteroids.

1. The optimal dose and duration of corticosteroid treatment was not assessed in the WHO Group meta-analysis. There was no evidence suggesting that *higher doses of corticosteroids were associated with greater benefit than lower dose corticosteroids.[5]

   **The WHO Group applied the following a priori cut-offs to define high-dose corticosteroids: dexamethasone 15mg per day, hydrocortisone 400mg per day, and methylprednisolone 1mg/kg per day.*[5]

2. The evidence for use of corticosteroids in the management of paediatric or pregnant patients with severe COVID-19 disease is lacking and specialist advice should be sought for the appropriate clinical management of these patients.

3. Suspected co-infection with pathogens other than SARS-CoV2 should be investigated and treated empirically as per local antimicrobial policy with consideration of the principles of antimicrobial stewardship (Further information available from: https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/guidance/infectionpreventionandcontrolguidance/antimicrobialstewardship/ .

4. For patients prescribed systemic corticosteroids at the time of hospital admission, the dose should be increased to a dose therapeutically equivalent to that detailed in the *Key Prescribing Recommendations for Systemic Corticosteroids* table above. Corticosteroid anti-inflammatory dose equivalencies[11] are:
   a. Dexamethasone base 6 mg
   b. ≡ Hydrocortisone 160 mg
   c. ≡ Methylprednisolone 32 mg
   d. ≡ Prednisolone 40 mg

   Once the course of treatment with systemic corticosteroids indicated for COVID 19 is completed, assess clinical need to recommence the previous corticosteroid prescription.

5. Response to systemic corticosteroid therapy should include monitoring of relevant laboratory markers of inflammation and clinical parameters.

6. Patients with COVID-19 who are receiving corticosteroids must be monitored for adverse effects (e.g. hyperglycaemia, secondary infections; see Summary of Product Characteristics for full information on adverse events). Consideration needs to be given to the need for appropriate gastroprotection according to local hospital policy.

7. Use of systemic corticosteroids may increase the risk of reactivation of latent infections (e.g., hepatitis B virus, herpes viruses, and tuberculosis).

8. The safety and efficacy of corticosteroids in combination with other COVID-19 therapies (e.g. remdesivir) is not confirmed.

9. The benefits of co-administration of dexamethasone and remdesivir are under investigation in clinical trials. Based on the metabolism and clearance of both agents a clinically significant interaction is unlikely.[12]

Refer to the Summary of Product Characteristics and drug-drug interaction databases (e.g. Stockley's Interaction Checker) to check for drug-drug interactions. The University of Liverpool have developed an online database for checking drug-drug interactions with the experimental COVID-19 specific medicinal products; available online at www.covid19-druginteractions.org .

References for Section 3.1 Systemic Corticosteroids

1. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. N Engl J Med. DOI: 10.1056/NEJMoa2021436.
2. Dequin PF, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. Published online September 2, 2020. doi:10.1001/jama.2020.16761.
3. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. *JAMA.* Published online September 02, 2020. doi:10.1001/jama.2020.17021.
4. The Writing Committee for the REMAP-CAP Investigators. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. *JAMA.* Published online September 02, 2020. doi:10.1001/jama.2020.17022.
5. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA.* Published online September 02, 2020. doi:10.1001/jama.2020.17023
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7. Randomised Evaluation of COVID-19 thERapY (RECOVERY) Clinical Trial Protocol. 2020. Available online at: https://www.recoverytrial.net/files/recovery-protocol-v7-0-2020-06-18.pdf . Accessed 20 July 2020.
8. Medicines Complete. Injectable Drugs Guide: Dexamethasone. Available online at: https://www.medicinescomplete.com/ . Accessed 20 July 2020.
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11. Joint Formulary Committee. (2020). *British national formulary*. Available online at: https://www.medicinescomplete.com/ . Accessed 09 Sep 2020.
12. University of Liverpool. COVID-19 Drug Interactions. Available online at: www.covid19-druginteractions.org . Accessed 02 Sep 2020.

Section 3.2 Intravenous Tocilizumab.

Summary Guidance for the use of Tocilizumab in the Management of Patients with Severe COVID-19.

- This guidance is informed by the COVID-19 ERG Rapid Evidence Review: *Tocilizumab in the management of COVID-19 v6* (available from: http://www.ncpe.ie/research/covid-19/).

- The HSE recommends the use of tocilizumab in a defined cohort of patients infected with COVID-19. See below for patient selection criteria.

- HSE guidance for the use of tocilizumab in the intensive care unit (ICU) setting is informed by the REMAP-CAP trial which demonstrates benefit with the use of tocilizumab, in combination with systemic corticosteroids and standard of care, in critically ill patients with COVID-19 receiving organ support (respiratory or cardiac) in an ICU.

- HSE guidance for the use of tocilizumab in the non-ICU setting is informed by preliminary reports from the RECOVERY study. Preliminary reports from the RECOVERY study suggests possible benefit in a subset of hospitalised patients with severe COVID-19 outside of the ICU setting who demonstrate evidence of progressive COVID-19 characterised by an inflammatory phenotype (CRP ≥75 mg/L) and hypoxaemia (oxygen saturation <92% on air or requiring oxygen therapy). Full publication of the RECOVERY trial will help inform future HSE recommendations.

- Use of tocilizumab outside of the ICU setting should only be considered after consultant-level discussion in a multidisciplinary setting that includes at least two consultants from critical care medicine, haematology, infection specialists, or respiratory medicine, and with patient engagement (or their relevant person, by phone).

- The potential for adverse events resulting from intravenous tocilizumab therapy must be considered before initiating therapy in patients with COVID-19. Notably, no new safety signals associated with intravenous tocilizumab were reported from the EMPACTA trial, the REMAP-CAP trial, or the preliminary report from the RECOVERY trial.

- Patients should continue to be enrolled in clinical trials, including trials to assess the safety and efficacy of IL6 -inhibitors compared to other immunomodulatory agents, wherever possible. Information on on-going clinical trials, including those recruiting, is available on the EU CT Register for COVID trials (https://www.clinicaltrialsregister.eu/ctrsearch/search?query=covid-19) or www.clinicaltrials.gov .

- There is a limited global supply of intravenous tocilizumab and judicious consideration before use is advised. Use should be restricted to clinical scenarios with potential for treatment benefit.

- The use of tocilizumab in the management of COVID-19 is off-label. Off-label use of medicines should be managed under existing local hospital governance arrangements. The State Claims Agency advise that if a clinician should prescribe and/or administer an off-label medication with the explicit knowledge and authority of the hospital, the Clinical Indemnity Scheme will indemnify the hospital/clinician.

Patient Selection for Intravenous Tocilizumab (with input from specialist multidisciplinary team)
1. Intravenous tocilizumab should only be considered for the management of COVID-19 disease in hospitalised patients with an inadequate clinical response to *systemic corticosteroid therapy requiring: a. ICU admission with severe pneumonia and requiring respiratory support **(CRS C1, C2 and D)** **OR** b. Recently hospitalised patients not in an ICU with rapidly increasing oxygen needs requiring either high-flow oxygen or non-invasive ventilation and significantly increased markers of inflammation. **(CRS C1 or C2)** **Note**: The RECOVERY trial inclusion criterion for inflammation was a CRP≥75 mg/L *The HSE National Clinical Programme for Respiratory Medicine/Irish Thoracic Society CRS is available from https://hse.drsteevenslibrary.ie/c.php?g=679077&p=4866795#appendix1%20021* If treatment is being considered outside of the ICU setting, it should only be initiated after consultant-level discussion in a multidisciplinary setting that includes at least two consultants from critical care medicine, haematology, infection specialists, or respiratory medicine, and with patient engagement (or their relevant person, by phone). **AND** 2. Exclusion of contraindications to intravenous tocilizumab, including acute severe infection from sources other than SARS-CoV2^.

*Refer to ***Section 3.1***.

^Suspected co-infection with pathogens other than SARS-CoV2 should be investigated and treated empirically as per local antimicrobial policy with consideration of the principles of antimicrobial stewardship (Further information available from: https://www.hpsc.ie/az/respiratory/coronavirus/novelcoronavirus/guidance/infectionpreventionandcontrolguidance/antimicrobialstewardship/ .

Key Prescribing Information for Intravenous Tocilizumab Adapted from Summary of Product Characteristics[1] for tocilizumab (RoActemra®) and the REMAP-CAP study protocol[2]. Refer to the Summary of Product Characteristics[3] for tocilizumab for full prescribing information.	
Recommended Dose Schedule in Adults (Specialist Paediatric advice required for patients aged under 18 years old)	- Benefit has not been demonstrated with tocilizumab monotherapy, systemic corticosteroids should continue as adjunctive therapy. - Tocilizumab should be administered as a single intravenous infusion at a dose of 8mg/kg (maximum 800mg per dose). - Dose rounding to the nearest whole vial is recommended. Vial sizes available may include 80mg, 200mg, and 400mg. - In exceptional circumstances, one additional dose may be considered no sooner than 12 hours after the initial dose if there has not been sufficient clinical improvement. - The decision to administer a second dose must only be made following consultant-level multidisciplinary specialist input and not considered routine clinical practice. - A maximum of two doses per course is recommended; subject to drug access.
Method of Administration for Adult Patients >30kg (Specialist Paediatric advice required for patients aged under 18 years old)	- Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 100 mL infusion bag, equal to the volume of RoActemra® concentrate required for the patients dose, under aseptic conditions.[3] - The required amount of RoActemra® concentrate (0.4 mL/kg) should be withdrawn from the vial and placed in the 100 mL infusion bag. This should be a final volume of 100 mL. To mix the solution, gently invert the infusion bag to avoid foaming.[3] - After dilution, RoActemra® should be administered as an intravenous infusion over 1 hour.[3]

[1] Summary of Product Charateristics. RoActemra 20 mg/mL concentrate for solution for infusion. Available online from: https://www.medicines.ie/medicines/roactemra-20-mg-ml-concentrate-for-solution-for-infusion--33648/spc .
[2] REMAP-CAP Study Protocol. *Domain-Specific Appendix: COVID-19 Immune Modulation Therapy.* Available online from: https://www.remapcap.org/protocol-documents .

Section 3.3 Other Immunomodulators.

Intravenous Normal Immunoglobulin (IVIg) for COVID-19
IVIg is not recommended for the management of COVID-19 infection due to a lack of evidence. There is evidence of micro-emboli in the COVID-19 disease process and consideration must be made of the risk:benefit ratio of the potential pro-thrombotic effect of IVIg.

Paediatric Patients
Reports of Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV2 (PIMS-TS) began to emerge in May 2020; characteristics similar to Kawasaki disease have been reported in some cases. All cases of suspected PIMS-TS should be discussed with the Paediatric Infectious Disease team in Children's Health Ireland at Crumlin/Temple Street.

Use in conditions other than COVID-19
Patients being treated with IVIg for conditions where clinical benefit is established should continue to receive IVIg therapy regardless of COVID-19 status, if clinically appropriate to do so. These conditions include immunodeficiencies (primary and secondary) and autoimmune diseases (e.g. neuroinflammatory diseases).

Appendix 1: A Proposed Core Outcome Measure Set for Clinical Studies of COVID-19 Infection.

Graphic contains recommendations from the WHO Clinical Characterization and Management Working Group, http://www.comet-initiative.org/Studies/Details/1528 . Refer to HSE COVID 19 Dataset specification for additional information on clinical coding detail.
https://www.hse.ie/eng/services/news/newsfeatures/covid19-updates/covid-19-dataset-specification-for-patient-assessment-and-tracking.pdf

Viral burden
Semiquantitative viral RNA of severe acute respiratory syndrome coronavirus 2 as measured by quantitative PCR or cycle threshold; nasopharyngeal swabs are associated with the highest viral load

Survival
All-cause mortality at hospital discharge or at 60 days

Clinical progression
WHO Clinical Progression Scale measured daily over the course of the study

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

Appendix 2: Pregnancy and Antivirals used in COVID-19

Based on the limited available evidence, the clinical characteristics of COVID-19 pneumonia are similar for pregnant and non-pregnant adult patients of similar age.[1,2,3] At present, the approach to prevention, evaluation, diagnosis, and treatment of pregnant women with suspected COVID-19 should be similar to that in non-pregnant individuals. The priority for medical care should be to stabilise the woman's condition with standard therapies.[4] As highlighted in multiple maternal death enquiries from Ireland and the UK, pregnant or postpartum women with medical problems should not be denied investigations and treatment because they are pregnant or breastfeeding and should be treated the same as non-pregnant women unless there is a clear contra-indication.[5]

The management of pregnant women with acute respiratory infection with COVID-19 should be in line with national guidance for non-pregnant patients, as detailed in the main body of this document. The use of pharmacological agents in the treatment of COVID-19 should only be used in a pregnant patient if the potential risk of maternal infection with COVID-19 is considered to be greater than any potential or unknown risks to the mother or the foetus from the drug. If treatment is indicated, pregnant and postpartum women should not be excluded from clinical trials unless there is a clear contra-indication.[5]

The use of pharmacological agents outside of a clinical trial should balance the limited evidence of the safety of these agents in pregnancy with the uncertain efficacy. If treatment is being considered outside of a clinical trial, it must only be initiated after consultant-level discussion with multidisciplinary input with from relevant specialities, including Infectious Diseases / Microbiology / Obstetrics / Respiratory and patient engagement.

Seek pharmacy advice on available products, choice of agent, and potential drug-drug interactions.

There is additional information on COVID-19 in pregnancy available from HPSC: https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/guidance/

Evidence for Safety in Pregnancy: Antivirals used in COVID-19

Remdesivir in pregnancy

Extremely limited information is available on the use of remdesivir in human or animal pregnancy. Nonclinical reproductive toxicity studies demonstrated no adverse effect on embryofetal development when remdesivir was administered to pregnant rats and rabbits at exposure that was 4 times the recommended human dose (RHD).[6] A randomised controlled trial of remdesivir use in the treatment of EBOLA included 6 women who had a positive pregnancy test (timing of exposure is unreported). No information on adverse pregnancy outcomes is described.[7]

A number of case reports[8-10] and two case series including 17[11] and 67[12] women, have described the use of remdesivir in pregnant women.[11,12] No particular concerns have been reported in relation to the safety of remdesivir in pregnancy; however the absence of data on the use of remdesivir in the first trimester limits these conclusions.

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Appendix 3: Guideline Development Group

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