CLINICAL GUIDELINE TITLE	Management of patients with confirmed COVID-19
Version 2	27.03.2020

1) SUMMARY
Please refer to guidelines below.

2) INTRODUCTION
This document is to provide guidance to frontline clinicians caring for patients with COVID-19 and a standardized approach for patients admitted at Imperial College Healthcare NHS Trust.

3) DEFINITIONS
COVID-19: Coronavirus disease 2019

4) SCOPE
This guideline aims to ensure a standardized approach for the treatment of COVID-19 and to provide contact details for specialists who can provide additional advice. It is aimed at all clinical staff and has been compiled by members of the Infection team (Microbiology/Infection Pharmacy/Infectious Diseases) in conjunction with colleagues other medical teams (respiratory, rheumatology, haematology, emergency and intensive care).

5) FULL GUIDELINE
Please refer to guidelines below

6) IMPLEMENTATION

Training required for staff	☐ Yes **X No**
If yes, who will provide training:	
When will training be provided?	
Date for implementation of guideline:	30.03.2020

7) MONITORING / AUDIT

When will this guideline be audited?	TBC
Who will be responsible for auditing this guideline?	Dr Giovanni Satta, Consultant in Infectious Diseases and Medical Microbiology Mr Mark Gilchrist, Consultant Infection Pharmacist
Are there any other specific recommendations for audit?	None

8) REVIEW

Frequency of review	**Please indicate frequency of review:** This is a living document that will be updated in real time as more data emerge. **Person and post responsible for the review:** Dr Giovanni Satta, Consultant in Infectious Diseases and Medical Microbiology Mr Mark Gilchrist, Consultant Infectious Diseases Pharmacist

9) REFERENCES

Please see reference at the end of the document

10) GUIDELINE DETAIL

Start Date:	30.03.2020
Approval Dates	**Name of Divisional group:** **Date of ratification:**
	Name of Directorate group: N/A **Date of ratification:** N/A
Has all relevant legislation, national guidance, recommendations, alerts and Trust action plans been considered, and included as appropriate in the development of this guideline?	**Please list ALL guidance considered:** NHS England Position Statement: Management of COVID-19 in adults with investigational agents A full list of references is provide at the end of the document
Have all relevant stakeholders been included in the development of this guideline?	**Please list all (name and role):** *COVID-19 treatment guidelines working group*: Dr Giovanni Satta, Head of Specialty for Infection Mr Mark Gilchrist, Consultant Infectious Diseases Pharmacist Professor Graham Cooke, NIHR Professor of Infectious Diseases Dr Clare Ross, Head of Specialty for Respiratory Medicine Dr Taryn Youngstein, Consultant Rheumatologist Dr Nichola Cooper, Clinical Senior Lecturer in Haematology Professor Jane Apperley, Professor of Haematology Professor Anastasios Karadimitris, Professor of Haematology Dr Francesca Rubulotta, Consultant in Intensive Care Dr Elizabeth Whittaker, Consultant Paediatric Infectious Diseases Mr Ahmad Al-Abdulla, Specialist Pharmacist
Who will you be notifying of the existence of this guidance?	**Please give names/depts:** All Trust via intranet communication
Related documents	N/A
Author/further information	**Name:** Dr Giovanni Satta **Title:** Consultant in Infectious Diseases and Medical Microbiology **Division:** Pathology/Medicine **Site:** Trust wide **Telephone:** via switchboard

	Trust email address: Giovanni.satta@nhs.net
Document review history	**Next review due:** As deemed necessary
THIS GUIDELINE REPLACES:	N/A

11) INTRANET HOUSEKEEPING

Key words	COVID-19, Treatment, Clinical trials
Which Division/Directorate category does this belong to?	Trust wide
Which specialty should this belong to when appearing on the Source?	Infection, Infectious diseases, Microbiology, Virology

12) EQUALITY IMPACT OF GUIDELINE

Is this guideline anticipated to have any significant equality-related impact on patients, carers or staff?

Yes ☐ **No X**

SUMMARY

This document was developed by members of the Infection team (Microbiology/Infection Pharmacy/Infectious Diseases) in conjunction with colleagues from other medical teams (respiratory, rheumatology, haematology and intensive care) to provide guidance to frontline clinicians caring for patients with COVID-19 and to provide a standardized approach for patients admitted at Imperial College Healthcare NHS Trust.

This document will be regularly updated as more data emerge. Please make sure that you use the most updated version available on the intranet (you can check which version you are reading at the top of the front page). Also refer to the infection prevention and control guidelines on the intranet regarding the correct personal protective equipment.

In addition to suggested initial management of COVID 19 and laboratory investigations, this guideline covers potential off-label and/or experimental treatment use of medications. It consists of four main sections

1. COVID-19 Suggested management of patients in a general medical ward (level 0-1)
2. COVID-19 Suggested management of patients in intensive care unit (level 2-3)
3. List of potential off-label and/or experimental treatments
4. Clinical trials available at Imperial Healthcare to provide such treatments

1 COVID-19 Suggested management of patients in a general medical ward (level 0-1)

1.1 Diagnostic tests

Initial testing for patients with suspected or confirmed COVID-19 should be done using the Cerner COVID-19 Care Set. If this is used the following tests will be automatically ordered

Initial diagnostic tests	
Haematology / Biochemistry	FBC, U+E, LFT, CRP, BNP, Troponin, Ferritin, D-Dimer, coagulation, HIV test BioAid/ISARIC Blood and RNA This equates to 1 purple top, 2 yellow & 1 blue bottle (the investigations in red)
Microbiology	Blood cultures, Urine MC&S
Radiology	Chest x-ray
Ongoing daily diagnostic tests (if deteriorating patient)	
Haematology / Biochemistry	FBC, U+E, LFT, CRP, Troponin, Ferritin, D-Dimer, coagulation

1.2 General key considerations

From the front door: Early diagnosis, recognition and labs

Suggestive features of COVID 19 infection include:

- **Clinical findings:** cough (frequently dry), chest tightness, chest pain, SOB, myalgia / fatigue, persistent fever, >10% have GI symptoms, beware the elderly can present atypically
- **Bloods**: Leucopenia, elevated CRP
- **Imaging:** Normal or ground glass opacities (often bilateral and involving peripheries and lower lobes)

All suspected patients should be clerked on the Suspected COVID-19 Care Plan on Cerner

All suspected COVID 19 patients should have full investigations from the COVID-19 Investigation Care Set as under diagnostic tests

Routine Care: Your daily ward round

Infection Prevention Control precautions

Isolate - Ensure ?COVID & COVID 19 +ve patients are in appropriate area (side room or cohorted bay) and on the appropriate site (do they need specialist HH services e.g. haemodialysis)
Procedures – avoid or take precautions with potentially aerosol generating procedures – non-essential nebulisers, sputum induction, chest drains for pneumothoraces
Contact precautions – ensure correct PPE worn as per latest guidance

Ward round checklists

Compassion – address anxiety, delirium, palliative care needs (see sheets on ward); keep family updated
Oral intake – consider nutrition; if poor oral intake consider PPI for ulcer prevention
Volume assessment – review fluid balance: cautious filling with crystalloids making sure to not overload in the context of potential ARDS
Imaging and bloods: Review imaging and consider repeat if clinical deterioration; daily bloods if for active management (request via Cerner Careset – see bloods in red under diagnostic tests; no need to repeat BioAid or cultures)
Decision re. escalation/de-escalation: Are there signs of deterioration (i.e. do you want respiratory / ITU / palliative care input) or improvement (can they be stepped down to standard cohort bay?)
Resuscitation – ensure ceilings of care documented and nursing staff aware of any changes
EDD – Set discharge date, identify correct discharge lounge; if hospital transport is needed inform site team; inform patient family re: home isolation precautions; see separate discharge guidance
Drug Chart – Use paracetamol as antipyretic; avoid NSAIDs; avoid nebulisers wherever possible - use an aerochamber and MDI; avoid steroids for COVID but use if absolutely necessary for other conditions
Cannula – Make sure patent and clean
Oxygen – Aim SpO2 $\geq$ 90% in all COVID 19 +ve non-pregnant adults; accurately record the Fi02
Antibiotics – If suspicious of bacterial infection prescribe as per local newly updated ICHT policy and discuss concerns with microbiology team
Thromboprophylaxis – Prophylactic LMWH as per usual ICHT guidelines. Avoid if platelets < 50. If evidence of DIC or acute thrombus contact haematology for advice as necessary

Ceilings of care and managing expectations

- All patients should have resuscitation status clarified at admission
- All patients should have a ceiling of care documented on admission
- It is important to manage the expectations of the patient and their family

1.3 Identify high risk patients

Please note that most **patients tend to deteriorate around day 7-10** since the appearance of clinical symptoms. Increasing evidence suggests that COVID-19 infection can be bi-phasic in a subset of patients:

a) A phase that is directly related to the virus pathogenic effect and corresponds to the flu-like clinical picture of the infection (flu-like) and
b) A relatively late (usually but not always 5-7 days after symptoms start) cytokine release syndrome-like (CRS) hyperinflammatory reaction in the lungs that leads to ARDS. This process appears to be the main reason for the high observed mortality and affects a minority of patients.

The table below can help in identifying newly admitted patients at high risk of clinical deterioration.

Risk factors for severe COVID-19[1]		
Epidemiological	**Observations**	**Laboratory tests**
Age > 60 years old	Respiratory rate > 24 breaths/min	CRP > 100 mg/L
Pre-existing medical conditions : - Hypertension - Diabetes - Coronary heart disease - Chronic obstructive lung disease Chronic kidney disease	Heart rate > 125 beats/min	Ferritin > 300 ug/L
Immunosuppression or use of biologic agents	SpO2 < 90% on ambient air	Lymphocyte count <0.8 (on admission)
		LDH > 245 U/L
		Troponin >28pg/mL
		CK > twice normal level
		D-dimer >1000 ng/mL

[1] Based on Chinese and Italian data (Zhou et al., and Onder at al., see references at the end)

1.4 How to identify and classify cytokine release syndrome-like (CRS)?

Patients can be classified into 4 main grades as below. The grading is useful for guiding treatment options, in particular when considering treatment with biologics.

CRS Parameter[1]	CRS Grade 1	CRS Grade 2	CRS Grade 3	CRS Grade 4
Fever[2] AND	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
CRP AND/OR	>100mg/L	>100mg/L	>100mg/L	>100mg/L
Hypoxia **SaO2 <94%**	None	Requiring low-flow[3] nasal cannula	Requiring high-flow[4] nasal cannula, face mask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg. CPAP, BiPAP, intubation and mechanical ventilation)

[1]Modified CRS grading from Lee at al., see reference at the end. CRS grade is determined by the more severe event i.e., hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C and hypoxia requiring low-flow nasal but CRP <75 is classified as grade 2 CRS.

[2]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/anakinra or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by CRP and/or hypoxia.

[3]Low-flow nasal cannula is defined as oxygen delivered at <6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics.

[4]High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

2 COVID-19 Suggested management of patients in intensive care unit (level 2-3)

2.1 When to call ICU

- **Anyone with rapidly increasing oxygen requirement**
- **Consider ICU review in anyone with >40% O2**
- **Patients needing >60% O2 should be referred unless clearly improving**

This is especially true if these features are also present:

- Tachycardia
- High RR (>30)
- Unable to complete sentences
- Beware it is reported that work of breathing is often low
- Severe disease can be present even with little increase in work of breathing, so don't be falsely reassured

2.2 Additional diagnostic tests in ICU

Additional diagnostic tests for patients accepted for ICU	
Urgent tests	HBsAg, HBcAb, HCV Ab (HIV test, if not already done) Further tests if indicated: - Repeat blood cultures - Respiratory viral panel - Sputum MC&S - Beta-D-glucan - Legionella and Pneumococcal urinary antigens
Non urgent tests (but useful for patients management)	Chest x-ray CT Chest (if deemed necessary) ECG Thromboelastography (TEG, available at SMH site) Procalcitonin (if indicated) IL-6 (if Tocilizumab is planned) Immunoglobulins profile

The anaesthesia and ICU team have developed a COVID check list for the daily round. Please contact your local ICU team for a copy.

3 List of potential off-label and/or experimental treatments

The following drugs should ONLY be used in the contest of a clinical trial and patients should be enrolled into randomised studies of treatment for COVID-19 (Section 4 below).

Potential off-label and/or experimental treatments include (as per NHS England document, *Position Statement: Management of COVID-19 in adults with investigational agents*) New options will be added as evidence emerges			
	Classification	**Potential mechanism of action**	**Side effects**
Lopinavir/ritonavir (Kaletra) (ORAL only)	Off-label	Protease inhibitor developed for HIV, a completely unrelated virus. In vitro data for both MERS and SARS-CoV are variable but suggest low potency inhibition at clinically achievable concentrations	QT prolongation, ALT elevations, diarrhoea
Hydroxychloroquine (ORAL only)	Off-label	Effective inhibition of SARS-CoV replication in vitro due to various mechanisms	QT prolongation
Interferon beta (nebulized)	Off-label	Immunomodulatory effect Unpublished in vitro data indicate that SARS-CoV is more susceptible to IFN- β-1a and - 1b than to IFN- α.	Depression, injection site reaction, flu like syndrome
Remdesivir (IV only)	Experimental	Nucleotide prodrug with activity against a number of unrelated RNA viruses. Potent inhibition of SARS-CoV, MERS-CoV and	Nausea, vomiting, ALT elevations

		bat coronaviruses with pandemic potential in human airway epithelial cells in vitro, with sub-micromolar EC50 values.	
Tocilizumab or similar analogues (IV only)	Off-label	Monoclonal antibody to IL6 receptor/treats cytokine release syndrome	ALT elevations
Anakinra (SC only)	Off-label	Recombinant and slightly modified version of the human interleukin 1 receptor antagonist protein/ selective cytokine blockade	Injection site reaction, flu like syndrome

4 Clinical trials available at Imperial Healthcare to provide such treatments

The following interventional clinical trials and national observational studies are active in the UK for recruitment for hospitalised patients:

a. **RECOVERY trial** (UK study; standard of care versus lopinavir/ritonavir vs. interferon beta-1a vs. dexamethasone vs hydroxychloroquine)
b. **REMAP-CAP** (international critical care study, UK sites; expanded to include COVID-19-specific arms for standard of care versus lopinavir/ritonavir and standard of care versus interferon-beta-1a, and interleukin-1 receptor antagonist (Anakinra)
c. **ISARIC-CCP** UK Case Record Forms (CRF) are available for the collection of standardised clinical data on suspected or confirmed cases of COVID-19

The following interventional clinical trials and national observational studies are emerging or proposed in the UK:

a. **DISCOVERY trial** (WHO pan-European; standard of care versus standard of care + remdesivir versus standard of care + lopinavir/ritonavir versus standard-of-care + lopinavir/ritonavir + Interferon beta-1a)
b. Proposal to amend the **REALIST trial** (acute respiratory distress syndrome) to include patients with COVID-19 / HLH and use of anakinra or tocilizumab
c. **ACTT** trial (remdesivir versus standard-of-care)
d. **Gilead sponsored trial** (remdesivir, 5 days versus 10 days)
e. **Roche sponsored trial** (tocilizumab in patients with severe COVID-19 pneumonia)

4.1 Which patient and which suggested clinical trial?

There is currently an understandable lack of clear or properly controlled randomised controlled study data to guide therapies for COVID-19. COVI-19 is a bi-phasic illness. There is an initial period of several days where there is progressive viral replication within the respiratory tract. In a proportion of patients there is then a second phase characterised by cytokine and development of acute respiratory distress syndrome. Cumulative clinical observation and evidence suggests that antiviral strategies should be deployed early before there is viral replicative escape within the lung. Once cytokine storm/ARDS ensues immunosuppressive approaches are considered. **See Flowchart in the next page.**

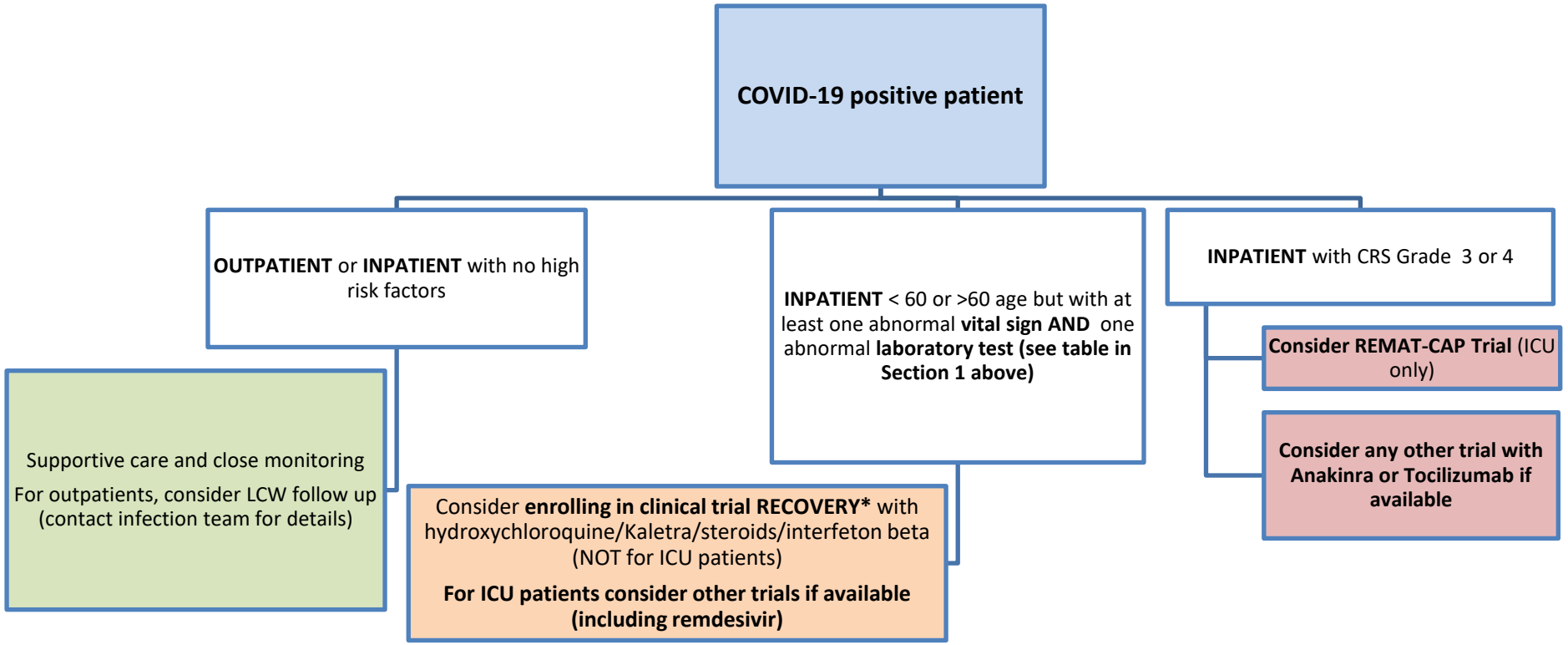
4.2 Compassionate use if not suitable or clinical trial not available

Compassionate use of one of the drugs above may be considered if no clinical trial is available and the pharmacy department has the drug in stock.

All off-label drugs should ALWAYS be discussed with the *COVID-19 treatment guidelines working group* AND final authorization from the *Trust Decision Reference Group*.

The requesting consultant should email members of the COVID-19 group (details in the front page) stating the clinical history and the clinical need and pharmacological agent required.

The Trust has also established a 24/7 clinical decision support service that is designed to support our clinicians when making difficult clinical decisions (including paediatric patients and limited supply and high demand/higher number of patients requiring the drug). Consultants only can contact the service by calling the site practitioner on bleep 5050 (24/7).



*contact the Infection team on how to enrol on a clinical trial

REFERENCES

1. Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 11. pii: S0140-6736(20)30566-3.
2. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA. 2020 Mar 23.
3. Team NCPERE. Vital surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) – China. China CDC Weekly. 2020;2(8):113-22.
4. Lee DW, Santomasso BD, Locke FL at al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-638.
5. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: Interim guidance v1.2. WHO. 13 Mar 2020
6. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centred, retrospective, observational study. Lancet Respir Med. 2020. Epub 2020/02/28. Doi: 10.1016/S2213-2600(20)30079-5. PubMed PMID: 32105632
7. Cao B, Wang, Y, Wen, D, Liu W et al. A Trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. N Engl J Med. Epub 2020/03/18. Doi: 10.1056/nejmoa2001282
8. Ruan Q, Yang K, Wang W, Jiang L and Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Medicine* 2020. Epub 3 Mar 2020. Doi: 10.1007/s00134-020-05991-x
9. Young B, Ong S, Kalimuddin S et al. Epidemiological features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA*. Epub 3 Mar 2020. Doi:10.1001/jama.2020.3204
10. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nature reviews Drug discovery* **19**;149-150 (2020). Doi: 10.1038/d41573-020-00016-0
11. Jin YH, Cai L et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Military Medical Research* **7**;4 (2020). ePub 6 Feb 2020
12. CDC. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html
13. Gautret P, Lagier JC et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicr Agents*. Epub 16 Mar 2020. Doi: 10.1016/.j.ijantimicag.2020.105949
14. NHS England document, Position Statement: Management of COVID-19 in adults with investigational agents), 23 March 2020.
15. MHRA – Press release regarding Chloroquine/Hydroxychloroquine 26 March 2020.