RECOVERY TRIAL PROTOCOL:

Region-Specific Appendix for the European Union

Summary

This region-specific appendix provides further details of RECOVERY trial procedures in the European Union, and should be read together with the core RECOVERY protocol. This appendix includes information relating to region-specific eligibility criteria, trial procedures, governance, and safety information.

The European Clinical Research Alliance on Infectious Diseases (Ecraid) is the Regional Coordinating Centre for RECOVERY in the EU. Ecraid can be contacted with questions about the protocol or trial procedures.

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ABBREVIATIONS

CAP	Community-acquired pneumonia
COVID-19	Corona Virus Disease 2019, the disease caused by SARS-CoV-2
CT	Computed Tomography
CTIS	Clinical Trial Information System
CTR	Clinical Trial Regulation
DMC	Data Monitoring Committee
Ecraid	European Clinical Research Alliance on Infectious Diseases
eCRF	Electronic Case Report Form
EEA	European Economic Area
EMA	European Medicine Agency
EU	European Union
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
ICH	International Council for Harmonisation
RSA	Region-Specific Appendix
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SmPC	Summary of Product Characteristics

1. VERSION HISTORY

The version of this EU Region-Specific Appendix (RSA) is given in the footer and in the table below. The current versions of the EU RSA and core protocol should always be used, and can be confirmed by checking the study website (www.recoverytrial.net). This EU RSA will not necessarily be updated with core protocol amendments if they have no impact on this document (so the current EU RSA can be used with subsequent core protocol versions).

EU RSA Version	Date	Brief Description of Changes
1.0	24-Jan-2024	Initial version. Aligned with core protocol V27.0 (13-Sep-2023)

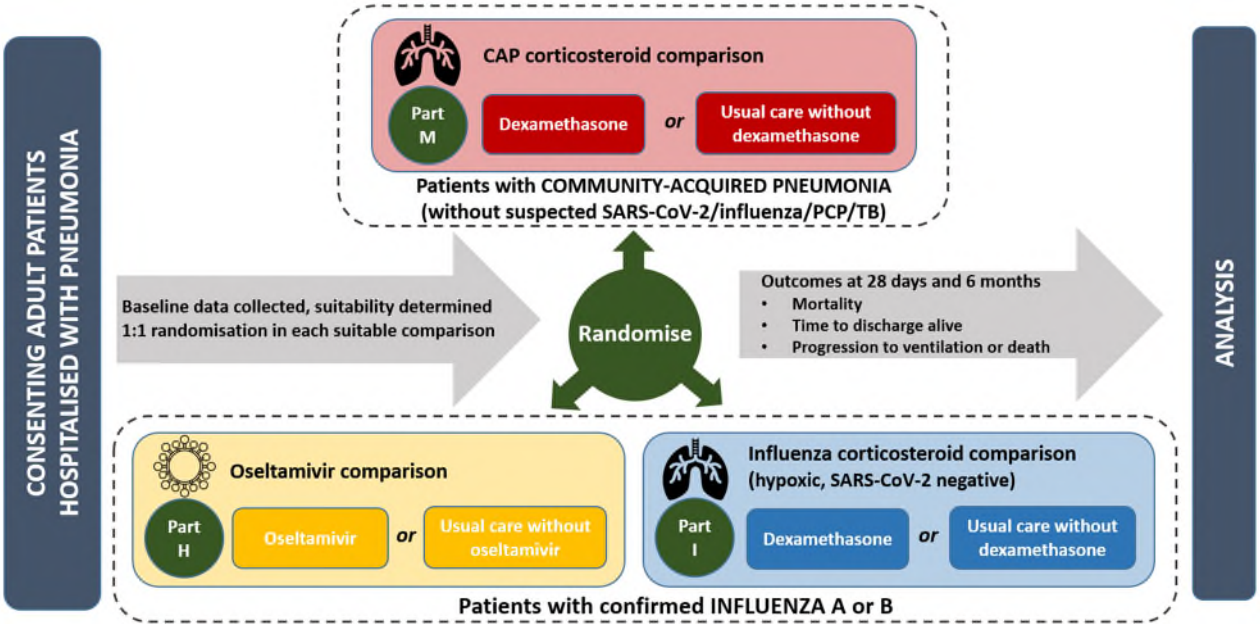
2. EU CONTEXT

The core protocol describes a multinational randomised trial among patients hospitalised for pneumonia, including COVID-19, influenza, and community-acquired pneumonia related to other pathogens. The trial is being conducted in EU countries as well as in other countries around the world, although no COVID-19 treatments are currently being evaluated in the EU.

Table 1: Treatments under evaluation in RECOVERY in the EU

Condition	**Randomised comparisons (each vs. usual care alone)**
Influenza	Oseltamivir
	Corticosteroids (dexamethasone)
Community-acquired pneumonia	Corticosteroids (dexamethasone)

Figure 1: RECOVERY Trial design in the EU



2.1 Governance in the EU

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996, the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (R2), EU Clinical Trials Regulation (CTR) [Regulation (EU) No 536/2014], and the General Data Protection Regulation (GDPR) [Regulation (EU) No 2016/679].

RECOVERY is registered with clinicaltrials.gov, study number NCT04381936.

3. EU CORE PROTOCOL CLARIFICATIONS

EU-specific clarifications to the core protocol are listed below, with reference to the sections affected.

3.1 Core protocol Section 2: Design and Procedures

The schedule of assessments for participants in the EU is shown below.

Table 2: RECOVERY Schedule of assessments

Procedure	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D28	D180
Eligibility assessment	X											
Consent	X											
Baseline data collection & randomisation	X											
Concomitant medication assessment	X										X	
Study treatment (oseltamivir)	X	X	X	X	X							
Study treatment (corticosteroids)	X	X	X	X	X	X	X	X	X	X		
28-day follow-up (medical records +/- call to participant)											X	
6-month follow-up (medical records +/- call to participant)												X
Adverse event monitoring*	X	X	X	X	X	X	X	X	X	X		

* Participants are monitored for serious adverse reactions to study treatment by their clinical team

3.2 Core protocol Section 2.1: Eligibility

Patients aged < 18 and patients with COVID-19 are not included in the EU. Patients are eligible for the study in the EU if all of the following are true:

(i) Hospitalised

(ii) Pneumonia syndrome

In general, pneumonia should be suspected when a patient presents with:

a) typical symptoms of a new respiratory infection (e.g. influenza-like illness with fever and muscle pain, or respiratory illness with cough and shortness of breath); and
b) objective evidence of acute lung disease (e.g. consolidation or ground-glass shadowing on X-ray or CT, hypoxia, or compatible clinical examination); and
c) alternative causes have been considered unlikely or excluded (e.g. heart failure).

However, the diagnosis remains a clinical one based on the opinion of the managing doctor (the above criteria are just a guide).

(iii) One of the following diagnoses:

a) Confirmed influenza A or B infection (including patients with SARS-CoV-2 co-infection and/or hospital-acquired infection)
b) Community-acquired pneumonia with planned antibiotic treatment (excluding patients with suspected or confirmed SARS-CoV-2, influenza, active pulmonary tuberculosis or *Pneumocystis jirovecii* pneumonia)

(iv) No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial

(v) Age ≥ 18 years old

In addition, if the attending clinician believes that there is a specific contra-indication to one of the active drug treatment arms (see core protocol Appendix 2) or that the patient should definitely be receiving one of the active drug treatment arms then that arm will not be available.

3.3 Core protocol Section 2.2: Consent

Clarification of consent process
Informed consent will be obtained in accordance with CTR Article 29 by a member of the research team who has completed trial-specific informed consent training and who has been delegated by the principal investigator to perform this role. The criteria for determining capacity should be the same as for routine medical care. If a patient is able to communicate, the consenter should have a discussion with them about the trial and about what participation would involve. If the consenter has doubts about the patient's capacity to provide informed consent, for example their ability to understand the information provided or make an informed decision about participation, the consenter should explore this further (for example, asking them to explain what participation would involve in their own words). If the consenter remains in doubt, they should discuss the patient's capacity with their medical team and/or family to come to a conclusion. If a patient does not have capacity to consent, then legal representative consent is required for the patient to participate in the trial.

If a participant regains capacity after having been enrolled with legal representative consent, their participation in the study will be explained to them as soon as possible. Their rights will be explained (including the right to withdraw from the study), and they will be provided with a copy of the participant information. In order for the participant to continue in the study, they must provide written consent after regaining capacity (in addition to the written consent obtained from their legal representative). This should follow the normal consent procedure.

Country-specific details

Netherlands:
In The Netherlands the legal representative can be (i) the patient's guardian or mentor (ii) the representative appointed in writing by the patient (iii) the spouse, registered partner or life companion (iv) parents (v) adult child(ren) (vi) brother(s) or sister(s) of the patient, with hierarchy of the categories (i-vi). Within categories there is no mandatory order of hierarchy.

A clinician, even if they are independent of the trial, cannot act as a legal representative in the Netherlands.

France:
In France authorisation can be given by a designated person of trust, this can be any person of full age who may be a parent, a relative or the attending physician. However, the designation of a person of trust should be available in writing, and have been previously signed by the patient and the person of trust. In the absence of a documented person of trust, a family member or, if not available, a person who has close and stable links with the person concerned is able to sign informed consent.

A clinician, even if they are independent of the trial, cannot act as a legal representative in France (unless they were designated as a trusted person when the patient had capacity).

Italy:
In Italy family members can only provide consent for study participation if they have been officially appointed as a legally authorised representative for the patient (via the court).

A clinician, even if they are independent of the trial, cannot act as a legal representative in Italy.

3.4 Core protocol Section 2.3: Baseline information

Patient details: only year of birth and sex will be collected in the EU to comply with GDPR.

3.5 Core protocol Section 2.3.1: Baseline sample collection

No baseline samples will be collected in the EU (even if influenza diagnosis is based on rapid antigen test alone).

3.6 Core protocol Section 2.4: Randomised allocation of treatment for COVID-19

These comparisons are not open in the EU.

3.7 Core protocol section 2.5: Randomised allocation of treatment for Influenza

The baloxavir marboxil comparison (section 2.5.1 Randomisation part G) is not open in the EU.

3.8 Core protocol section 2.7: Administration of allocated treatment

As stated in the core protocol “The patient’s own doctors are free to modify or stop study treatments if they feel it is in the best interests of the patient without the need for the patient to withdraw from the study”, so trial treatment allocation should never override the best interests of the patient.

To clarify, if the attending doctor considers that continuing a trial treatment is no longer in the best interest of the participant for any reason after randomisation, for example because of a suspected adverse reaction, then the treatment should be stopped. Conversely, if the attending doctor considers that a trial treatment becomes indicated after randomisation, then this should be given regardless of randomised allocation. If the participant is allocated corticosteroids in RECOVERY and a different systemic corticosteroid regimen becomes indicated, this should replace the allocated treatment (with trial treatment reintroduced afterwards if needed to complete the planned duration of treatment). For example, if dexamethasone treatment were indicated in a pregnant woman for fetal lung maturation, this should replace prednisolone or hydrocortisone given as part of RECOVERY.

3.9 Core protocol Section 2.8: Collecting follow-up information

Consent will be obtained to access the participant’s medical records held by the admitting hospital. No linkage will be performed to other medical databases.

3.10 Core protocol Section 2.8.1: Follow-up swab samples

No follow-up samples will be collected in the EU.

3.11 Core protocol Section 3: Statistical Analysis

Sample size

RECOVERY comparisons do not have a prospectively determined sample size. Individual comparisons are planned to continue until one of the following occurs:

- Sufficient recruitment has occurred to reliably identify or exclude a moderate benefit of treatment (typically a reduction of one-fifth, based on periodic review of blinded event rate data by the Trial Steering Committee), or
- The Data Monitoring Committee (DMC), after review of unblinded data, consider that there is strong evidence of benefit, evidence of hazard, or no meaningful prospect that further recruitment could provide conclusive proof of a worthwhile benefit of treatment (i.e. futility). The timing of these reviews is determined by the DMC, taking into account all available information about the trial including speed of recruitment, so these need not occur at prespecified intervals or levels of recruitment.

The approach to stopping trial comparisons is described in sections 2.8 and 2.12 of the RECOVERY Statistical Analysis Plan (available on the trial website). There are no predefined criteria that will necessarily lead to the closure of a comparison, as the decision to stop depends on the judgement on the Steering Committee (who have access to blinded outcome data, and who may have received advice from the Data Monitoring Committee based on their review of unblinded data). Previous RECOVERY COVID-19 comparisons have typically required recruitment of 5,000-10,000 participants, and it is estimated that global recruitment of at least 6,000 participants would be required to produce clear results for the current comparisons, as outlined below (this includes recruitment in the EU and the seven non-EU countries currently participating in RECOVERY).

Mortality

Mortality within 28 days of randomisation is the primary outcome in the community-acquired pneumonia (CAP) comparison, and a co-primary outcome in the influenza comparisons. Estimates of in-hospital mortality in patients hospitalised with CAP and influenza pneumonia vary according to the age groups most affected, location of recruitment (e.g. general ward vs critical care), and dominant strain of influenza, so cannot be predicted with precision. Using plausible ranges of 28-day mortality (3% to 12%),[1–5] table 3 shows the sample sizes required to assess the impact of treatments on the primary outcome of all-cause mortality 28 days after randomisation. With 6,000 patients randomised, the study will have at least 80% power at 2p=0.05 to detect modest decreases in mortality (25-30%) if the in-hospital mortality rate is 6-8% or greater. As a reference, dexamethasone in COVID-19 resulted in a RR for 28-day mortality of 0.64 for those on invasive mechanical ventilation and 0.82 for those on oxygen only.[6]

Table 3: Estimated total sample size for mortality outcomes

Mortality rate in usual care arm	Rate ratio	Required sample size			
		80% power		90% power	
		2p=0.05	2p=0.01	2p=0.05	2p=0.01
3%	0.80	>20,000	>30,000	>30,000	>40,000
	0.75	>10,000	>20,000	>10,000	>20,000
	0.70	9630	>10,000	>10,000	>10,000
6%	0.80	>10,000	>10,000	>10,000	>20,000

	0.75	6940	>10,000	9288	>10,000
	0.70	4688	6976	6276	8886
8%	0.80	8192	>10,000	>10,000	>10,000
	0.75	5108	7602	6838	9682
	0.70	3454	5138	4622	6544
10%	0.80	6426	9564	8602	>10,000
	0.75	4010	5966	5366	7600
	0.70	2712	4036	3628	5140
12%	1.15	5250	7812	7026	9950
	1.20	3276	4876	4386	6210
	1.25	2218	2968	3300	4202

Time to discharge

Time to discharge alive within 28 days is a co-primary outcome for the influenza comparisons. Based on median time to discharge of 8 days,[5] 6,000 patients (3,000 on treatment) will provide at least 90% power at 2p=0.01 to detect a rate ratio of time to discharge of 1.15 on the co-primary outcome of time to discharge alive (table 4) and will allow exploration of the effects among important subgroups of patient (e.g. by age, sex, respiratory status at baseline). As a reference, dexamethasone in COVID-19 resulted in a RR for discharge alive by day 28 of 1.45 for those on invasive mechanical ventilation and 1.16 for those on oxygen only.[6]

Table 4. Estimated sample size for time to discharge outcome

Median time to discharge in usual care arm	Rate ratio	Required sample size			
		80% power		90% power	
		2p=0.05	2p=0.01	2p=0.05	2p=0.01
6 days	1.15	1662	2474	2226	3152
	1.20	976	1454	1308	1852
	1.25	652	970	874	1236
8 days	1.15	1738	2586	2328	3296
	1.20	1018	1516	1364	1930
	1.25	678	1010	908	1286
10 days	1.15	1838	2736	2460	3484
	1.20	1074	1600	1438	2036
	1.25	714	1062	956	1354

Estimated recruitment rate

The time taken to recruit a sufficient number of participants cannot be estimated reliably until these comparisons are well underway (and even then will be difficult for influenza, which has unpredictable epidemiology from year to year and is highly seasonal in temperate regions). Around 190 sites have taken part in RECOVERY COVID-19 comparisons so far. If 150 existing and new RECOVERY sites take part in the CAP and influenza comparisons, with an average recruitment rate of 10-15 participants/site/year/comparison, it will take 3-4 years to recruit 6,000 participants. This rate of recruitment is similar to, or lower than, several previous trials of patients hospitalised with CAP or influenza with similar eligibility to RECOVERY.[1,2,7,8]

3.12 Core protocol Section 4.2: Central assessment and onward reporting of Suspected Severe Adverse Reactions

Events meeting the definition of a Suspected Serious Adverse Reaction as defined in the core protocol, must be reported to the University of Oxford within 24 hours of site personnel becoming aware of the event.

The sponsor and/or local representative will report all Suspected Unexpected Serious Adverse Reactions through the EMA Eudravigilance database and also to the appropriate authorities in European Region, according to the requirements of the Member States and CTR Article 42.

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator will take appropriate urgent safety measures to protect the subjects. In addition, the sponsor will notify the Member States concerned according to CTR Article 54.

Any additional local governance safety reporting requirements are the responsibility of the Principal Investigator at that site.

Annual safety report

The sponsor shall submit annually through CTIS to all Member States concerned a single report on the safety of each investigational medicinal product used in the trial.

3.13 Core protocol section 4.4: Role of the Data Monitoring Committee

A DMC charter is available as addition to protocol section 4.4

3.14 Core protocol Section 5.2: Training and monitoring

Standardised procedures will be in place to train staff before site initiation, which may include face-to-face meetings, online meetings, and online self-study materials. A site initiation teleconference or visit will usually be conducted before site activation. At least one monitoring visit will be conducted during the recruitment period, and additional monitoring visits will be performed based on recruitment rate or other indications. Email and telephone communication will supplement site visits.

As described in the core protocol, the study will use a risk-based monitoring approach. A representative of Ecraid, or a local representative at request of Ecraid, will monitor the study according to a detailed monitoring plan. A monitoring report will be prepared following each site visit and reviewed by the management committee if appropriate. A follow up letter will be sent to the principal investigator and research coordinator at the site and will be filed in the investigator site file.

Medical records, any other relevant source documents and the site investigator file must be made available to the monitor for these visits during the course of the study and at the completion of the study as needed.

The sponsor will notify the Member States concerned in case of a serious breach of the CTR and of the version of the protocol applicable at the time of the breach through CTIS without undue delay but not later than seven days of becoming aware of that breach.

3.15 Core protocol Section 5.3: Data Management

Data collected for the RECOVERY study will be entered into secure, password protected web-based eCRFs designed by programmers at the Central Coordinating Office, and will be stored on servers located in the United Kingdom. Each subject is allocated a unique trial number. In the EU, the only direct identifiers recorded in the database will be sex and year of birth. Data management and transfer within and outside of the EEA will comply with GDPR requirements. The Project Managers of Ecraid will monitor data entry.

The RECOVERY Data Management Plan contains details of data management, privacy and protection within the RECOVERY study, and was produced in accordance with University of Oxford and Nuffield Department of Population Health data management policies.

3.16 Core protocol Section 6.5: Supply of study treatments

All medicinal products being evaluated in the EU have marketing authorisation and will be managed according to core protocol section 6.5.1. These treatments will be supplied by site pharmacies and will be stored, labelled, and accounted for as required for routine clinical use.

3.17 Core protocol Section 6.6: End of trial

RECOVERY is planned as a perpetual platform trial for patients admitted to hospital with pneumonia, and promising new treatments may be added to the trial in future. There is no planned end date, but the trial may be terminated at the discretion of the sponsor, for example because of inadequate funding or recruitment. The trial may also be terminated in specific countries at the request of the Member State.

3.18 Core protocol Section 6.7: Publications and reports

Data sharing

Core protocol section 6.7 states that the Trial Steering Committee will establish a process to facilitate the use of study data by independent external researchers. This has been established via the Infectious Diseases Data Observatory (IDDO), an organisation that hosts a dedicated, GDPR-compliant platform for data-sharing. Applications to access to study data should be made via IDDO, and will be reviewed by a data access committee. Details of the process can be found on the IDDO website https://www.iddo.org/covid19/data-sharing/accessing-data.

4. JUSTIFICATION OF LOW INTERVENTION STATUS

RECOVERY is a low intervention clinical trial according to the criteria defined by the CTR:

a) the investigational medicinal products, excluding placebos, are authorized;
b) according to the protocol of the clinical trial, (i) the investigational medicinal products are used in accordance with the terms of the marketing authorization; or (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and
c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.

All the medicinal products being evaluated in the EU have standard marketing authorisation by the European Medicines Agency (EMA). The safety profile of the treatments has been established in clinical trials and experience from routine use, as described in the Summary of Product Characteristics (SmPC). Scientific evidence for the use of the treatments in influenza

and CAP is outlined in core protocol Appendix 1. Additional monitoring poses minimal burden on participants, consisting of 1-2 phone calls following discharge.

5. STRUCTURED RISK ANALYSIS

1 Oseltamivir	
Registration	Oseltamivir received EU marketing authorisation in 2002, and is registered for the treatment of influenza. www.ema.europa.eu/en/medicines/human/EPAR/tamiflu
Use in influenza	Information about the use of oseltamivir for influenza is summarised in core protocol Appendix 1.
Use in RECOVERY	**Dose & route** • 75mg twice daily by mouth or nasogastric tube In patients with renal impairment the dose is adjusted as follows: • eGFR ≥30 mL/min/1.73m^2: dose as in normal renal function • eGFR ≥10 <30 mL/min/1.73m^2: 75 mg once daily • eGFR <10 mL/min/1.73m^2: 75 mg as a single dose on day 1 Dosing in normal renal function follows the SmPC. Dosing in renal impairment follows the UK Renal Drug Database monograph, which advises dose adjustment that differs from the SmPC due to clinical experience and established tolerability of oseltamivir. **Duration** • 5 days, increased to 10 days in patients considered to be immunosuppressed by their managing doctor. Treatment is to be completed at home if the patient is discharged before the end of the course.
Possible risks & mitigation	**Adverse effects of treatment** Undesirable effects and safety profile are summarised in section 4.8 of the SmPC. Participants will be informed about common side effects such as headache, nausea and vomiting. Oseltamivir is rarely associated with life-threatening adverse reactions, including anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis and fulminant hepatitis, which have been reported in <1 in 1000 patients. The risk of death among patients hospitalised with influenza ranges from 2% to over 20% depending on severity, meaning that the plausible benefits of oseltamivir (e.g. reducing the risk of death by 10-20%) would substantially outweigh the risks of treatment. It is possible that oseltamivir may have unrecognised adverse effects in acutely unwell patients, as there have been few randomised trials in this setting. In addition to reporting of suspected serious adverse reactions, other important safety outcomes will be recorded in all participants and monitored by the DMC, as outlined in core protocol section 4.3. **Drug-drug interactions** None are expected

2 Corticosteroids	
Registration	The corticosteroids used in RECOVERY (dexamethasone, prednisolone and hydrocortisone) have been authorised in the EU by national medicines authorities for several decades. They are authorised for use in a variety of allergic, infectious and inflammatory conditions.
Use in influenza and CAP	Information about corticosteroid use in influenza and CAP is summarised in core protocol appendix 1.
Use in RECOVERY	**Dose and route** • Dexamethasone 6mg once daily by mouth, nasogastric tube or intravenous infusion Pregnant and breastfeeding women should receive an alternative corticosteroid producing less fetal/infant exposure, either: • Prednisolone 40mg once daily by mouth or nasogastric tube, or • Hydrocortisone 160mg once daily by intravenous infusion The doses of these three drugs are chosen to have equivalent glucocorticoid activity, and are typical doses used in the treatment of patients with acute respiratory conditions such as COVID-19, and exacerbations of COPD and asthma, as outlined in the SmPCs. **Duration** • 10 days Treatment is to be stopped on discharge if this occurs before the end of the course
Possible risks & mitigation	**Adverse effects of treatment** The adverse effect profile of corticosteroids is well known and includes several potentially serious reactions, as described in SmPC section 4.8. These include immunosuppression with increased risk of secondary infections, hyperglycaemia, peptic ulceration, fluid retention, and psychiatric reactions. Participants will be informed of these, along with common non-serious side effects such as nausea, insomnia, and appetite suppression **Drug-drug interactions** Drugs that inhibit CYP3A4 are expected to increase exposure to corticosteroids and so may increase the risks of systemic side effects. The immunosuppressive effects of corticosteroids may be enhanced in patients receiving other immunosuppressive treatments. The risk of gastrointestinal bleeding is increased in patients receiving non-steroidal anti-inflammatory drugs. Corticosteroids are some of the most commonly used treatments in hospitalised patients and acute physicians are familiar with their important adverse effects. Consequently, the risk-benefit balance for each potential participant is best determined by their managing doctor, considering both the severity of disease and the individual risk of corticosteroid side effects. If the managing doctor thinks the potential risks of corticosteroid treatment outweigh the potential benefits then the participant will not be eligible for the corticosteroid comparison. However, the risk of death in patients hospitalised with influenza or

	CAP is high (ranging from 2% to over 20% depending on severity) and the plausible benefits of corticosteroids are substantial (e.g. in hypoxic patients with COVID-19 mortality is reduced by 20%), so uniform exclusion criteria are not appropriate. To mitigate the risks of corticosteroid treatment, clinical trial staff involved in identifying participants will receive training about potential adverse effects and drug-drug interactions. Management of these should be individualised and determined by the patient's managing doctors in line with usual clinical practice. Training will highlight possible approaches to risk mitigation and monitoring, including blood glucose monitoring in patients with diabetes, use of gastroprotection in patients at higher risk of peptic ulceration, and mitigation of potential drug-drug interactions (e.g. possible suspension or replacement of drugs that inhibit CYP3A4 if appropriate). In addition to reporting of suspected serious adverse reactions, other important safety outcomes will be recorded in all participants and monitored by the DMC, as outlined in core protocol section 4.3. This includes secondary infection, gastrointestinal bleeding and hyperglycaemia, which are potential adverse effects of corticosteroids.

6. REFERENCES

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