RECOVERY EU Protocol Synopsis
Based on Core Protocol V27.0 (2023-09-13) and EU Region-Specific Appendix V1.0 (2024-01-24)

Short Title	RECOVERY
Full Title	Randomised Evaluation of COVID-19 Therapy (Note RECOVERY started in the UK in 2020 as a COVID-19 platform trial, and now includes other causes of pneumonia. No COVID-19 treatments evaluations are currently planned in the EU)
Registration	EudraCT 2020-001113-21 Clinical Trials.gov NCT04381936 ISRCTN50189673
Website	www.recoverytrial.net
Background	Platform trials have been essential to improve the treatment of people hospitalised with COVID-19 and RECOVERY is the largest of these, having recruited over 48,000 patients. It is now open in seven countries worldwide, and since 2020 it has provided clear results for twelve COVID-19 treatments, showing that four are life-saving, and eight are ineffective (www.recoverytrial.net/results). In contrast, there has been little progress in recent decades in the treatment of patients hospitalised with influenza or community-acquired pneumonia caused by other pathogens (CAP). RECOVERY is now evaluating treatments for these types of pneumonia, including at sites in the EU. RECOVERY and other trials showed the benefit of corticosteroids, such as dexamethasone, in hypoxic patients with COVID-19. Reducing immune-mediated lung damage with corticosteroids may provide similar benefits in patients with influenza or CAP, but evidence from previous trials is inadequate to guide treatment. Neuraminidase inhibitors (NAIs), such as oseltamivir, are antivirals that reduce the duration of influenza symptoms when given early after the onset of mild infection. They are frequently used in patients hospitalised with severe influenza, but there is no reliable evidence that they improve outcomes in this setting. During the pandemic, randomised trials showed that antivirals for COVID-19 could be effective in early infection but have little or no benefit in sicker, hospitalised patients. Evidence from adequately powered, randomised controlled trials is needed to resolve these questions, and guide the care of hospitalised patients with influenza and CAP.
Treatment comparisons	**Influenza** 1) **Oseltamivir*** (oral 75mg twice daily for 5 days) versus usual care 2) **Dexamethasone†** (oral/iv 6mg once daily for 10 days) versus usual care **Community-acquired pneumonia** 1) **Dexamethasone†** (oral/iv 6mg once daily for 10 days) versus usual care * Dose reduced in renal impairment, as described in the protocol † Pregnant or breastfeeding women should receive prednisolone (oral 40mg once daily) or hydrocortisone (iv 160mg once daily) instead of dexamethasone
Eligibility criteria	**1.** Hospitalised patients aged ≥18 years **2.** Pneumonia syndrome (clinical diagnosis, in general based on a) typical symptoms of new respiratory infection, b) objective evidence of acute lung disease [e.g. hypoxia or compatible imaging or clinical examination], and c) alternative causes considered unlikely) **3.** One of the following diagnoses: a) Confirmed influenza A or B infection b) Community-acquired pneumonia with planned antibiotic treatment (without suspected or confirmed SARS-CoV-2, influenza, active pulmonary tuberculosis, or *Pneumocystis* pneumonia) **4.** No medical history that might, in the opinion of the patient's doctor, put the patient at significant risk if he/she were to participate in the trial **5.** No reason that the trial treatment definitely should, or should not, be given in the opinion of the patient's doctor (this only affects eligibility for the relevant comparison)
Comparison-specific eligibility criteria	**Oseltamivir comparison** • Patients who received an NAI (e.g. oseltamivir, zanamivir) for the current illness are excluded **Influenza dexamethasone comparison** • Patients in this comparison must be hypoxic, with supplemental O_2 or O_2 saturations <92% • Patients with SARS-CoV-2 co-infection are excluded

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Trial Design	• Randomised, open-label, phase 3 platform trial • Each comparison has 1:1 allocation to study treatment versus usual care without that treatment • Patients can enter ≥1 comparison if eligible, and all are independent (i.e. a factorial design) • RECOVERY is an adaptive trial, so new treatment comparisons may be added in future	
Population	**Patients with influenza**	**Patients with CAP**
Primary outcomes	• All-cause mortality within 28 days • Time to discharge within 28 days	• All-cause mortality within 28 days
Secondary outcomes	• Progression to invasive ventilation or extracorporeal membrane oxygenation (ECMO) or death	• Time to discharge within 28 days • Progression to invasive ventilation, ECMO or death
Subsidiary and safety outcomes	• Primary and secondary outcomes above assessed at 6 months • Cause-specific mortality • Use of non-invasive ventilatory support • Infections (categorised by site and type of infecting organism) • Thrombosis, bleeding, new cardiac arrhythmia, seizures • Acute liver injury, acute kidney injury, renal replacement therapy • Metabolic complications (ketoacidosis, hyper/hypoglycaemia)	
Follow-up	• At 28 days (from medical notes, plus telephone call to participant if needed to confirm details) • At 6 months (via telephone call to participant) No other contact is required with participants during the trial. No biological sample collection.	
Sample size	RECOVERY is an adaptive trial and does not have a fixed sample size. Individual comparisons are planned to continue until: • Sufficient recruitment has occurred, based on review of blinded outcome data, to reliably identify or exclude a moderate benefit of treatment, or • There is strong evidence of benefit, or emerging evidence of hazard, based on Data Monitoring Committee review of unblinded data (as described in the protocol and statistical analysis plan) Previous RECOVERY comparisons have typically required recruitment of 5,000-10,000 participants.	
Trial duration	There is no current planned trial end-date, as RECOVERY is designed as perpetual platform trial	
Trial sites	>200 trial sites across the UK, European Union (the Netherlands, France, Italy), Asia (India, Nepal, Vietnam, Indonesia) and Africa (South Africa and Ghana)	
Ethical considerations and benefit-risk analysis	The study treatments for influenza and CAP have marketing authorisation in the EU and have been used for decades in the treatment of hospitalised patients. However, use remains very variable between countries and between individual clinicians. Corticosteroids have several known potential side-effects, in particular an increased risk of secondary infections and hyperglycaemia. Despite this they are standard care for hospitalised patients with other acute respiratory conditions such as COPD, asthma and COVID-19. Physicians looking after acute inpatients will be familiar with the risks of corticosteroids, and will monitor patients according to usual practice. NAIs are considered to have a good safety profile, with few serious side-effects. However, there is no reliable evidence of benefit in hospitalised patients, and without randomised evidence it is possible they could have hazards that are currently unrecognised. If a patient's doctor considers a study treatment is indicated or contraindicated for any reason, the patient is not eligible for inclusion in that comparison. After enrolment, a doctor may start or stop a study treatment if there has been a change in the benefit-risk balance for their patient. Patients admitted to hospital with influenza or CAP have a substantial risk of death, so even a moderate benefit, or hazard, of treatment is important to identify. Only large-scale randomised trials are likely to provide clear evidence to inform global treatment of these common diseases.	

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