EUnetHTA Joint Action 3 2016-2020

Rolling Collaborative Review (RCR) on Covid-19 treatments

Project ID: **RCR01 - RCRXX**

Project description and planning

This report is part of the project / joint action '724130 / EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014-2020)

Version Log

Version number	Date	Modification	Reason for the modification
V1	25/06/2020	Preliminary draft of Project Plan submitted to EUnetHTA Executive Board Task Force on SARS CoV-2. Preliminary draft of Project Plan submitted to Rolling CR authoring team for review and input.	
V2	30/06/2020	Input from EUnetHTA Executive Board Task Force on SARS CoV-2 and Rolling CR authoring team implemented.	Input from EUnetHTA Executive Board Task Force on SARS CoV-2 and Rolling CR authoring team.

CONTENTS

List of tables

1 Project organisation

1.1 Participants

Table 1-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	Health Technology Wales - HTW	Authors	United Kingdom	Rolling CR on Convalescent plasma/ CPT (Project ID: RCR01)
2.	National Institute of Pharmacy and Nutrition - NIPN	Authors	Hungary	Rolling CR on Lopinavir + Ritonavir (Project ID: RCR02) Rolling CR on Tocilizumab (Project ID: RCR03)
3.	Belgian Health Care Knowledge Centre - KCE	Authors	Belgium	Rolling CR on Camostat (Project ID: RCR04) Rolling CR on Nafamostat (Project ID: RCR05)
4.	Austrian Institute for Health Technology Assessment - AIHTA	Authors	Austria	Rolling CR on Solnatide (Project ID: RCR06) Rolling CR on Anakinra (Project ID: RCR07) Rolling CR on Dexamethasone (Project ID: RCR08)
5.	Agencia Española De Medicamentos Y Productos Sanitarios – AEMPS Andalusian HTA Agency, Ministry of Health - AETSA	Authors	Spain	Rolling CR on APN01 (Project ID: RCR09)
6.	Swiss Network for HTA - SNHTA	Authors	Switzerland	Rolling CR on Darunavir (Project ID: RCR10) Rolling CR on Favipiravir (Project ID: RCR11)
7.	Norwegian Institute of Public Health - NIPH	Authors	Norway	Rolling CR on Sarilumab (Project ID: RCR12) Rolling CR on Interferon (Project ID: RCR13)
8.	Valstybine Vaistu Kontroles Tarnyba (State Medicines Control Agency of Lithuania, SMCA) -VVKT	Authors	Lithuania	Rolling CR on Gimsilumab (Project ID: RCR14) Rolling CR on Canakinumab (Project ID: RCR15)
9.	Department of Epidemiology Lazio Regional Health Service -DEPLazio	Co-Authors	Italy	Table 1 for all Rolling CRs
10.	Austrian Institute for Health Technology Assessment - AIHTA	Project Manager	Austria	Coordination between involved parties throughout the assessment period

1.2 Milestones and Deliverables

Because the topic of this review is of utmost urgent importance for public health, the usual steps and timelines are reduced. As this review is a living document, which is updated regularly, milestones, deliverables and timelines vary from those of EUnetHTA Collaborative Assessments.

Importantly, the project will not include any formal exchange with patient representatives, clinical experts, or manufacturers.

Table 1-2: Milestone and Deliverables

Milestones/Deliverables	Start date	End date
Project duration	Continuous, starting with June 2020	Rolling Collaborative Reviews are terminated in case the monitored product has either entered EMA's marketing authorisation process, is approved or proved irrelevant (not effective or unsafe). In case of marketing authorisation process or approval, a Joint Relative Effectiveness Assessment is eventually produced within EUnetHTA.
Milestone 1: Publication of project plan		**01/07/2020**
Literature searches, Literature screening, Data extraction	Continuous	Continuous
Milestone 2: Data extraction complete	Continuous	10/08/2020
Check of data extraction	10/08/2020	11/08/2020
Data analysis (NMA)	12/08/2020	12/08/2020
Milestone 3: First version of Rolling Collaborative Review complete		12/08/2020
Milestone 4: Publication of Rolling Collaborative Review		**14/08/2020**
Update Literature searches, Literature screening, Data extraction, Check of data extraction	Continuous	Continuous, to be completed each 11th of the month (if no weekend, bank holiday)
Milestone 6: Publication of Rolling Collaborative Review		**15/09/2020**
Milestones 7-X: Publication of Rolling Collaborative Reviews		Each **15th of the month** (if no weekend, bank holiday)

2 Project Outline

2.1 Project Background

The aim of this EUnetHTA Rolling Collaborative Review is

- to inform health policy at the national/regional and at the European level at an early stage in the life-cycle of therapies which interventions are currently undergoing clinical trials,
- to monitor (ongoing studies and their results) permanently - in the format of a Living Document - potential therapies against covid-19,

- to present comparative data on effectiveness and safety of potential therapies and
- to support preparations for an evidence-based purchasing of regional/ national health politicians, if necessary.

To avoid redundancies and duplication, the EUnetHTA Rolling Collaborative Review will reuse sources from international initiatives to collect information and data on covid-19 treatments.

The scope of the Rolling Collaborative Review is of descriptive nature. These **EUnetHTA Rolling Collaborative Reviews are not meant to substitute a joint Relative Effectiveness Assessment (REA)** adhering to the agreed procedures, aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the Marketing Authorization Holder (MAH).

2.2 Project Method and Scope

2.2.1 Approach and Method

Table 2-1: Project approach and method

Project approach and method
Three main sources of information support the continuous review: • **Table 1** (Summary of findings/ SoF – efficacy and safety) is based on (peer reviewed) published RCTs based on the PROSPERO registered protocol for a network meta-analysis/ NMA (http://www.fvcalabria.unicz.it/COVID-19/REVIEW/comparative%20effectiveness%20of%20pharmacological%20interventions%20for%20COVID_19_%20a%20living%20systematic%20review.pdf/) [1]. • **Table 2** is based on published (peer reviewed) observational studies for safety results. Sources: https://www.ncbi.nlm.nih.gov/research/coronavirus/docsum?filters=topics.General%20Info [2] and https://www.fhi.no/en/qk/systematic-reviews-hta/map/ [3]. • **Table 3** is based on clinical trial registries: Inclusion criteria: RCTs or CTs only; ClinicalTrials.gov; EudraCT Register

Table 2-2: Planned literature search strategy

Literature search strategy
Table 1: The following electronic databases are searched for randomised controlled trials (RCTs): • Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library. • MEDLINE, accessed via OVID. • Embase, accessed via OVID. The searches will cover from the inception of each database and will be updated on a daily basis using auto-alerts when possible. Search strategies including a combination of controlled vocabulary and free text terms will be developed. We will revise the strategy appropriately for each database to take account of differences in controlled vocabulary and syntax rules. We will apply no restriction on language of publication.

We will also search medRxiv Health Sciences and bioRxiv Biology, which provide open access to preprints of preliminary reports of work that have not been peer-reviewed.

Inclusion criteria: randomised controlled trials (RCTs)

See details: http://deplazio.net/farmacicovid/index.html [4]

In the context of the living systematic review, we will follow key conferences that are to be held and we will search conference proceedings when published.

Table 2: The following secondary sources are searched for observational studies:

- https://www.ncbi.nlm.nih.gov/research/coronavirus/docsum?filters=topics.General%20Info [2]
- https://www.fhi.no/en/qk/systematic-reviews-hta/map/ [3]

The searches will cover individual therapeutics (generic and brand name, if available).

Inclusion criteria: comparative or single-arm prospective studies and registries, > 50 patients,
Exclusion criteria: retrospective studies, case reports.

Table 3: In addition to the sources and strategies described above, we will screen registries of ongoing studies (RCTs):

- ClinicalTrials.gov: https://clinicaltrials.gov/
- ISRCTN: https://www.isrctn.com/
- European Clinical Trials Registry: https://www.clinicaltrialsregister.eu/

Table 2-3: Plan for data extraction

Planned data extraction
Table 1: Data on efficacy and safety from RCTs: **Study selection**: The studies will be selected and data will be extracted independently by two authors: **Data extraction**: Author of the study, year of publication, study design, diagnosis, sample size, average age, gender, disease severity, setting, number of patients assigned to each treatment group, drug name, dosage, duration of treatment and follow-up period, primary and secondary outcomes. **Risk of Bias** (RoB) Assessment according to Cochrane Handbook for Systematic Reviews of Interventions [5]: At least two authors will independently assess the risk of bias of each study. Summary of findings/ SoF will be presented according to GRADE (Certainty of Evidence, see: http://deplazio.net/farmacicovid/index.html [4], but English language). **Table 2**: Data on safety from observational studies (comparative or single-arm prospective studies and registries): **Study selection**: The studies will be selected by two authors, extracted by one author. **Data extraction**: Author of the study, year of publication, study design, sample size, patient population (in-/exclusion criteria), disease severity, setting, drug name, dosage, follow-up period, safety outcomes (adverse events and serious adverse events). **Risk of Bias** (RoB) Assessment with Robins-I: https://training.cochrane.org/handbook/current/chapter-25 [6]. One author will conduct the RoB assessment.

Table 3: Data on (ongoing) studies (RCTs):

Study selection: The trial registries will be searched and the study selection of ongoing, suspended, terminated, withdrawn and completed RCTs will be done by one author.

Data extraction: Sponsor of the study, Trial Identifier, study design, sample size, disease severity, setting, number of patients, intervention drug name and dosage, comparator drug name and dosage, follow-up period, primary and secondary outcomes, status of trial, duration of trial.

2.2.2 Project Scope

The EUnetHTA Guidelines, available at https://www.eunethta.eu/methodology-guidelines/ need to be consulted throughout the assessment process.

Table 2-4: Project Scope: PICO (please see HTA Core Model® for rapid REA)

Description	Project Scope
Population	**Disease** • SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death. **ICD-Codes** (https://www.who.int/classifications/icd/covid19/en) • An emergency ICD-10 code of 'U07.1 COVID-19, virus identified' is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing. • An emergency ICD-10 code of 'U07.2 COVID-19, virus not identified' is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available. • Both U07.1 and U07.2 may be used for mortality coding as cause of death. See the International guidelines for certification and classification (coding) of COVID-19 as cause of death following the link below. • In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1. **MeSH-terms** • COVID-19, Coronavirus Disease 2019 **Target population** (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/) [7] • Asymptomatic or Presymptomatic Infection: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms. • Mild Illness: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging. • Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level. • Severe Illness: Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%. • Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Intervention	• Convalescent plasma/ CPT • Lopinavir + Ritonavir (Kaletra®) • Tocilizumab (Roactemra®) • Camostat (Foipan®) • Nafamostat (Futhan®) • Solnatide • Anakinra (Kineret®) • Dexamethasone • APN01 (rhACE2) • Darunavir (Prezista®) • Favipiravir (Avigan®) • Sarilumab (Kevzara®) • Interferon beta 1a (Novaferon, …) • Gimsilumab • Canakinumab All above mentioned interventions also in combination therapies.
Comparison	Any active treatment, placebo, or standard of care. **Rationale**: Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.
Outcomes	Main outcome: • All-cause Mortality (Survival) Additional Outcomes: Efficacy: • Length of hospital stay, • Viral burden (2019-nCoV RT-PCR negativity), • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study), • Rates of hospitalization and of patients entering ICU, • Duration of mechanical ventilation, • Quality of life. Safety: • Adverse events (AE), • Severe adverse events (SAE), • Withdrawals due to AEs, • Most frequent AEs, • Most frequent SAEs. **Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 [8] (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdf) and A minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection [9].
Study design	Efficacy: randomised controlled trials (RCT) Safety: observational studies (comparative or single-arm prospective studies and registries)

3 Communication and collaboration

3.3 Dissemination plan

The Rolling Collaborative Review will be published on the EUnetHTA website: https://eunethta.eu/services/covid-19/.

All partners and contributors are informed about the publication of the review by the project manager.

This project will be registered on PROSPERO and the authors hope to publish findings in a peer reviewed journal.

3.4 Conflict of interest and confidentiality management

Conflicts of interest will be handled according to the EUnetHTA Conflict of Interest Policy. All individuals participating in this project will sign the standardised Declaration of Interest and Confidentiality Undertaking statements.

Author, co-author(s) and dedicated reviewers who declare a specific conflict of interest will be excluded from the whole work under this specific topic. However, they still may be included in other assessments.

4 References

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