Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Protocol

Interventions in an ambulatory setting to prevent progression to severe disease in COVID-19 patients

Published: 5 February 2021

Revision Record	
Revision Date	**Description of change**

1. Purpose and aim

The purpose of this protocol is to outline the process by which the Health Information and Quality Authority's (HIQA's) Health Technology Assessment (HTA) Team identifies and reviews relevant SARS-CoV-2 evidence. This review will inform advice that is provided to the National Public Health Emergency Team (NPHET), in their response to the COVID-19 pandemic. HIQA's HTA team develops evidence summaries based on specific research questions (RQs). This protocol details the process to be undertaken to inform the policy question relating to community-based interventions to prevent progression to severe disease in COVID-19 patients.

2. Process outline

It is important that a standardised approach to the process is developed and documented, to allow for transparency and to mitigate risks which may arise due to changes in staff delivering and or receiving the information.

Five distinct steps in the process have been identified. These are listed below and described in more detail in sections 3-9:

1. Develop research question and formulate PICO/POS
2. Search relevant databases.
3. Screen identified studies to match relevant clinical question.
4. Data extraction and quality appraisal of included studies.
5. Summarise findings.
6. Apply an 'Evidence to Advice' framework to these findings to produce evidence-based advice.
7. This advice is then provided to NPHET.

3. Research question and PICOS

This evidence summary will address the following policy question:

> **"**What is the emerging evidence in relation to (i) pharmaceutical and (ii) lifestyle interventions post diagnosis of COVID-19 in the community aimed at minimising progression to severe disease?**"**

The following research question was developed to address this policy question:

> What is the evidence on the effectiveness of (i) pharmaceutical and (ii) non-pharmaceutical interventions in the community setting aimed at reducing progression to severe disease in individuals with confirmed or suspected COVID-19?

Both pharmaceutical and non-pharmaceutical interventions are included. Non-pharmaceutical interventions are categorised as lifestyle interventions (such as smoking cessation and dietary modifications), physiotherapy and respiratory interventions, psychological interventions, organisational interventions (such as community-based assessments and prediction rules) and technological interventions (such as pulse oximetry).

A limited scoping of the literature was conducted in advance of this protocol and a large number of pharmaceutical interventions were identified as prospective candidates for the treatment of COVID-19. For the purpose of this evidence summary, only studies with published effectiveness data will be included; ongoing studies without interim or preliminary results will be excluded. Studies that enrolled patients from both inpatient and outpatient settings will be excluded unless they report disaggregated data relating to the outpatient group.

Table 1 outlines the population, intervention, comparator, outcomes, study design (PICOS) criteria for study selection.

Table 1. PICOS criteria

Population(s)	Individuals of any age who are not hospitalised (community-dwelling individuals and residents of long term care facilities or other residential centres) who have been diagnosed with confirmed or suspected COVID-19. Subgroups include: ▪ children (≤18 years) ▪ vulnerable groups (≥70 years of age, individuals with underlying conditions such as chronic respiratory or cardiac disease) ▪ residents of long term care facilities ▪ RT-PCR diagnosed versus clinically diagnosed cases.
Intervention(s)	Any intervention that aims to reduce the progression of COVID-19, including: ▪ pharmaceutical interventions ▪ physiotherapy interventions ▪ respiratory therapy interventions ▪ psychological therapy interventions ▪ lifestyle interventions (including smoking cessation, dietary changes, alcohol reduction) ▪ organisational interventions (including the use of prediction rules, community assessment centres) ▪ technological interventions (including pulse oximetry, peak flow meters).
Comparator(s)	Placebo, no intervention or head-to-head comparison with alternative included intervention(s).
Outcome(s)	Primary outcome: Hospitalisation Secondary outcomes: ▪ mortality

	▪ duration of illness/self-reported recovery ▪ ICU admission ▪ clinical outcomes including the need for supplemental oxygen, mechanical ventilation ▪ safety outcomes, including serious adverse events and death.
Study design(s)	▪ randomised controlled trials (RCTs), non-randomised controlled trials (NRCTs) ▪ systematic reviews and meta-analyses of RCTS and or NRCTs. The following studies will be excluded: ▪ ongoing RCTs without published results ▪ RCTs that did not reach any study endpoint ▪ RCTs that included interventions that regulatory agencies (such as the EMA, FDA, MHRA) have issued warnings against (such as hydroxychloroquine).

Key: EMA – European Medicines Agency; FDA – Food and Drug Agency (USA); MHRA – Medicines and Healthcare products Regulatory Agency

4. Search of relevant databases

The following databases will be searched using the search strategy defined in Appendix 1:

- PubMed
- Embase
- Europe PMC (for the retrieval of preprints).

PubMed underwent substantial changes in early 2020, including updates to its search algorithm. This has led to searches conducted in 'new' PubMed yielding different results to that of 'old' PubMed. All reasonable efforts have been made to ensure that all relevant evidence from PubMed is retrieved during the searching process. The search for this research question has been conducted exclusively in 'new' PubMed.

An additional search of publications from select international public health agencies, institutional websites, clinical trial registries and desktop searching was conducted, including but not limited to the following:

- rolling collaborative reviews conducted by the European Network of HTA (EUnetHTA) (https://eunethta.eu/Covid-19-treatment/)
- evidence summaries of COVID-19 treatments conducted by the National Institute for Health and Care Excellence (NICE, UK) (https://www.nice.org.uk/Covid-19#rapid-es)
- the Canadian Agency for Drugs and Technologies in Health (CADTH) Covid-19 Evidence Portal (https://Covid.cadth.ca/)

- HTA Austria's Horizon Scanning System (HSS) for Covid-19 interventions (https://eprints.aihta.at/1234/)
- COVID-19 treatment guidelines conducted by the National Institutes of Health (NIH, USA) (https://www.Covid19treatmentguidelines.nih.gov/)
- US National Library of Medicine clinical trials database (https://clinicaltrials.gov/)
- Google and Google Scholar (https://scholar.google.com/).

5. Screening of identified studies to match clinical question

All potentially eligible papers identified in the search strategy will be exported to Endnote and single screened against the PICOS, as outlined in the associated standard operating procedure, using Covidence software. Full texts will be single screened. No language restrictions will be applied. Non-English studies will be translated via Google translate, and this will be noted as a potential caveat.

6. Data extraction and appraisal of included studies

For each study included, data on the study design, participant demographics and clinically relevant data will be extracted as required. A template for the data extraction table is provided in Appendix 2.

If the paper has not been peer reviewed, this will be noted. For randomised controlled trials (RCTs) the Cochrane risk of bias tool version 2 (RoB 2[1]) will be used. ROBINS-I tool (Risk of bias in non-randomised studies of interventions) will be used for quality appraisal of non-randomised studies. The AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews[2]) will be used to appraise systematic reviews. Grading of Recommendations Assessment, Development and Evaluation (GRADE[3]) will be used to evaluate the quality of the body of evidence by outcome.

Data from pre-print publications may contain errors and or older data, which may be corrected and or updated when the final published version becomes available in a peer-reviewed journal. Prior to the final version of an evidence summary being published on the HIQA website, pre-print publications will be checked to identify if final published versions have become available since the original search was conducted. Any discrepancies identified will be corrected.

7. Summarise findings

A descriptive overview of the identified evidence to date for will be compiled and or a meta-analysis where appropriate and sent to the relevant parties in word format. A PRISMA flow chart will be presented where appropriate.

8. Evidence to Advice framework

Following completion of the evidence review, findings are applied to HIQA's 'Evidence to Advice' framework in conjunction with advice and input from the EAG. The development of advice is a key component of HIQA's evidence synthesis process.

9. Quality assurance process

Each review question will be led by an experienced systematic reviewer. A second reviewer will be assigned to assist and to provide cover in the event of illness. The second reviewer will be required to read all the key studies and check that the summary accurately reflects the body of literature. All summaries will be reviewed by a senior member of the team, to ensure processes are followed and quality maintained, this will also enable cover to be maintained.

10. Timelines

This evidence summary will be conducted in line with the processes and timelines outlined for Phase 2 of HIQA's COVID-19 response. Work will commence on 4 January 2021 and a final draft will be completed by 21 January 2021. Draft outputs from the evidence summary will be circulated to the COVID-19 Expert Advisory Group for review, with a view to providing advice to NPHET on 26 January 2021.

Appendix 1

Search strategy: PubMed

PubMed	Search strategy
1	"coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "COVID-19"
2	(general practi* or family practi* or family physician* or primary health* or primary care*).ti,ab. or "primary health care"[Mesh] or "family practice"[Mesh] or "physicians, family"[Mesh] or "ambulatory care"[Mesh]
3	#1 and #2 Filters: Humans

Search strategy: Embase

Embase	Search strategy
1	('coronavirinae'/exp OR 'coronavirinae' OR 'coronaviridae infection'/exp OR 'coronaviridae infection' OR 'coronavirus disease 2019'/exp OR 'coronavirus'/exp OR coronavirus OR 'coronavirus infection'/de) NOT [medline]/lim AND 'human'/de
2	((((general AND practi* OR 'family'/exp OR family) AND practi* OR 'family'/exp OR family) AND physician* OR primary) AND health* OR primary) AND care* OR 'primary health care'/exp OR 'primary health care' OR 'general practice'/exp OR 'general practice' OR 'general practitioner'/exp OR 'general practitioner' OR 'ambulatory care'/exp OR 'ambulatory care'
3	#1 and #2 Filters: Humans

Search strategy: Europe PMC

(("coronavirus" OR "coronavirus" OR "COVID-19") AND ("general practice" OR "general practise" OR "family practice" OR "family practise" OR "family physician" OR "primary health" OR "primary care" OR "primary health care" OR "ambulatory care")) AND (SRC:PPR).

Appendix 2. Data extraction template

Study characteristics	PICO	Patient demographics Clinical characteristics	Primary outcome results
Author Country Study design Setting	Population(s) Intervention(s) Comparator(s) Outcome(s)	Patient demographics (Intervention: N=x participants, mean age=x, X%=male; Control: N=x participants, mean age=x, X%=male) Clinical characteristics (Intervention: asymptomatic/mild/moderate; Control: asymptomatic/mild/moderate).	Primary outcome results

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