



**Health
Information
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An tÚdarás Um Fhaisnéis
agus Cáilíocht Sláinte

Protocol: What is the evidence underpinning the categorisation of “extremely medically vulnerable” groups, who may be at risk of severe illness from COVID-19

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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 will synthesise evidence to inform advice from HIQA to the National Public Health Emergency Team (NPHE). The advice will take account of expert interpretation of the evidence by HIQA's COVID-19 Expert Advisory Group. The evidence synthesis relates to the following policy question outlined by NPHE:

"Based on the available international evidence, is the current definition of what constitutes "extremely medically vulnerable" (i.e., among those who were previously asked to cocoon) in relation to COVID-19 appropriate?"

The following research question was formulated to inform this policy question:

1. What is the evidence underpinning the categorisation of "extremely medically vulnerable" groups who may be at risk of severe illness from COVID-19?

1. Process outline

A standardised approach to the process has been developed and documented to allow for transparency and to aid in project management. Five distinct steps have been identified in the process for completion. These are listed below and described in more detail in Sections 2.1-2.5.

1. Identify document types of interest.
2. Search relevant sources.
3. Screen identified documents.
4. Data extraction and quality appraisal of included documents.
5. Summarise findings.

2. Review process

This review will address the following research question (RQ):

What is the evidence underpinning the categorisation of "extremely medically vulnerable" groups who may be at risk of severe illness from COVID-19?

This RQ was formulated using the PCOS (population, comparator, outcome, study type) framework as detailed in Table 1.

Table 1: Population, outcome, comparator, study type (PCOS)

Population	<p>Groups of individuals of any age who have been categorised by the Health Protection Surveillance Centre (HPSC) as “extremely medically vulnerable” (also referred to as “very high risk”) and may be at risk of severe illness* from COVID-19 (defined as admission to intensive care unit, ventilation or death).</p> <p>The definition of extremely medically vulnerable on the HPSC website encompasses the following groups of individuals:</p> <ol style="list-style-type: none"> 1. people aged ≥ 70 years 2. solid organ transplant recipients 3. people with specific cancers: <ol style="list-style-type: none"> a. people with cancer who are undergoing active chemotherapy or radical radiotherapy for lung cancer b. people with cancers of the blood or bone marrow such as leukaemia, lymphoma or myeloma who are at any stage of treatment c. people having immunotherapy or other continuing antibody treatments for cancer d. people having other targeted cancer treatments which can affect the immune system, such as protein kinase inhibitors or PARP inhibitors e. people who have had bone marrow or stem cell transplants in the last 6 months, or who are still taking immunosuppression drugs. 4. people with severe respiratory conditions including cystic fibrosis, severe asthma, pulmonary fibrosis/ lung fibrosis/ interstitial lung disease and severe COPD 5. people with rare diseases and inborn errors of metabolism that significantly increase the risk of infections (such as SCID, homozygous sickle cell) 6. people on immunosuppression therapies sufficient to significantly increase risk of infection 7. women who are pregnant with significant heart disease, congenital or acquired. <p>Additionally, groups of individuals with renal failure or those on dialysis treatment will be considered as “extremely medically vulnerable”, as defined by the HSE.</p>
Comparator	<p>Groups of individuals of any age who have confirmed SARS-CoV-2 positive by a molecular test (e.g. RT-PCR), but who would not meet</p>

	<p>the criteria for categorisation as “extremely medically vulnerable” (also referred to as “very high risk”) as specified by the HPSC.</p> <p>For studies that utilise data from international disease registries, where classification of the extremely medically vulnerable group is on the basis of greater disease severity (for example, severe vs mild asthma), the comparator will be the lowest disease severity (that is, mild asthma)</p> <p>Subgroups: stratified by age groups (for example, <13 years, 13-69 years, 70+ years) where available.</p>
Outcome	<p>Relative risk/odds ratio/hazard ratio of severe illness from COVID-19 which is defined as admission to intensive care unit, ventilation or death. For community- or population-based studies the baseline risk will also be extracted, if reported.</p>
Study type	<p>Include:</p> <ul style="list-style-type: none"> ▪ Public health guidance and policy documents that provide the evidence sources underpinning the recommendations made. ▪ Reviews that: <ul style="list-style-type: none"> ○ have a defined search strategy ○ include studies from community- or population-based settings. For studies relating to pregnancy, studies from hospital settings are also included ○ include patients of any age ○ specify confirmation of SARS-CoV-2 by a positive molecular test (for example, RT-PCR test) ○ include at least one risk factor (prior to diagnosis) for “extremely medically vulnerable” as defined by the HPSC ○ include the outcome of interest, that is, severe illness from COVID-19 (defined as admission to intensive care unit, ventilation or death). ▪ Original research studies identified in included guidance and policy documents and reviews, which fulfil the study design criteria listed for reviews above. ▪ International disease registries that compare those who are SARS-CoV-2 positive and develop severe illness to those who are SARS-CoV-2 positive and do not develop severe illness. <p>Exclude:</p> <ul style="list-style-type: none"> ▪ Guidance or evidence from general pre-pandemic settings or from other pandemic settings (for example, SARS, MERS, H1N1, seasonal influenza).

	<ul style="list-style-type: none">▪ Reviews and original research studies that do not include community- or population-based settings.▪ Reviews and original research studies that do not specify confirmation of SARS-CoV-2 by a positive molecular test for example, RT-PCR test.▪ Reviews and original research studies that do not include at least one risk factor (prior to diagnosis) for “extremely medically vulnerable” as defined by the HPSC.▪ Reviews and original research studies that do not include relative risk/odds ratio/hazard ratio for the outcome of interest, that is, severe illness from COVID-19 (defined as admission to intensive care unit, ventilation or death).▪ Reviews and original research studies that include animals.
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*Hospital admission was not considered an indication of severe illness as the indication for hospitalisation of patients has changed significantly throughout the pandemic and is largely dependant upon the availability of resources and admission policies within jurisdictions.

2.1 Identify document types of interest

The evidence underpinning the categorisation of “extremely medically vulnerable” groups who may be at risk of severe illness from COVID-19 will be identified from the following document categories:

- a) public health guidance and policy documents
- b) reviews
- c) original research studies
- d) international disease registries.

2.2 Search relevant sources

- a) Public health guidance and policy documents

The websites listed below will be reviewed to identify new or updated public health guidance and policy documents relating to groups that would meet the criteria for being classified as being extremely medically vulnerable (also referred to as very high risk) who may be at risk of severe illness from COVID-19. These were chosen based on widespread use of the organisation’s advice, the country being in a similar phase of pandemic response, guidance being available in English, and or within the working constraints of the HTA team.

- World Health Organization (WHO)
<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance-publications?healthtopics=b6bd35a3-cf4f-4851-8e80-85cb0068335b&publishingoffices=aeebab07-3d0c-4a24-b6ef-7c11b7139e43&healthtopics-hidden=true&publishingoffices-hidden=true>
- European Centre for Disease Prevention and Control (ECDC)
https://www.ecdc.europa.eu/en/search?s=&sort_by=field_ct_publication_date&sort_order=DESC&f%5B0%5D=diseases%3A2942
- Centers for Disease Control and Prevention (CDC)
<https://www.cdc.gov/coronavirus/2019-ncov/whats-new-all.html>
- Public Health England
<https://www.gov.uk/government/collections/coronavirus-covid-19-list-of-guidance>
- National Health Service England

<https://www.england.nhs.uk/coronavirus/publication/page/2/?filter-keyword&filter-category&filter-publication&filter-date-from&filter-date-to&filter-order-by=modified-desc>

- Health Protection Scotland <https://www.hps.scot.nhs.uk/a-to-z-of-topics/covid-19/>
- Public Health Agency of Northern Ireland
<https://www.publichealth.hscni.net/>
<https://www.publichealth.hscni.net/covid-19-coronavirus/guidance-professionals-and-organisations>
<https://www.publichealth.hscni.net/covid-19-coronavirus/guidance-hsc-staff-healthcare-workers-and-care-providers/guidance-healthcare>
- Australian Government Department of Health
<https://www.health.gov.au/resources>
- Government of Canada
<https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/guidance-documents.html>
<https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/awareness-resources.html>
<https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection.html>
- Ministry of Health New Zealand
<https://www.health.govt.nz/our-work/diseases-and-conditions/covid-19-novel-coronavirus>
- Federal Office of Public Health, Switzerland
<https://www.bag.admin.ch/bag/en/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov.html>
- Norwegian Institute of Public Health (NIPH)
<https://www.fhi.no/en/id/infectious-diseases/coronavirus/>
- Ministry of Health Singapore
<https://www.moh.gov.sg/covid-19/advisories-for-various-sectors>
- Federal Ministry of Education, Science and Research, Austria
<https://www.bmbwf.gv.at/Ministerium/Informationspflicht/corona.html>
- Government of the Netherlands, National Institute for Public Health and Environment, Netherlands
<https://ici.rivm.nl/langdurig-neusverkouden-kinderen>
<https://www.rijksoverheid.nl/onderwerpen/coronavirus-covid-19/ouders-scholieren-en-studenten-kinderopvang-en-onderwijs>
- Ministry of Education and Training, Belgium
<https://onderwijs.vlaanderen.be/nl/update-corona-akkoord-over-draaiboeken-2020-2021>

- Ministry for Health, and Ministry for Education and Vocational Education, Spain
<https://www.educacionyfp.gob.es/portada.html>
- Ministry for National Education, France
<https://www.education.gouv.fr/>
- Ministry of Education, Science and Culture, Iceland
<https://www.government.is/ministries/ministry-of-education-science-and-culture/>
- National Board of Health, Ministry of Children and Education, Denmark
<https://www.uvm.dk/aktuelt/nyheder/uvm/2020/jul/200701-regler-og-retningslinjer-fra-den-1--august-er-nu-udstedt-i-ny-bekendtgoerelse>
<https://www.sst.dk/da/Udgivelser/2020/Genaabning-af-skoler>
- Federal Ministry of Health, Robert Koch Institut, Germany
<https://www.zusammengegencorona.de/en/>
https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2020/19/Art_03.html?n=13490888
- Public Health Agency of Sweden
<https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/>

b) Reviews

A systematic literature search will be conducted in PubMed, Embase, Europe PMC and NHS Evidence to identify evidence underpinning the categorisation of “extremely medically vulnerable” groups who may be at risk of severe illness from COVID-19. 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; pre-prints will not be included if sufficient peer-reviewed evidence is available. The detailed search strategy is presented in Appendix 1.

c) Evidence from original research studies

Original research studies that provide evidence underpinning the categorisation of “extremely medically vulnerable” groups who may be at risk of severe illness from COVID-19 will be identified from public health guidance and policy documents and reviews.

d) International disease registries

International disease registries, identified through reviewing of guidance and policy documents, reviews and original studies that compare those who are SARS-CoV-2 positive and develop severe illness to those who are SARS-CoV-2 positive and do not develop severe illness.

2.3 Screen identified documents

All potentially eligible documents identified in the search will be screened against the PCOS (Table 1) by one reviewer. Public health guidance and policy documents will be checked to ensure that: (i) the document relates to extremely medically vulnerable (very high risk) groups who may be at risk of severe illness from COVID-19; (ii) the evidence underpinning the recommendations made is referenced within the document; (iii) the recommendations relate to the SARS-CoV-2 pandemic and not general pre-pandemic settings (for example SARS, MERS, H1N1, seasonal influenza).

Reviews identified through searching of databases, and original research studies identified through public health guidance, policy documents and reviews, will be exported to Covidence. Documents will only be included where full texts are available. No language or date restrictions will be applied. Where websites or documents are not readily available in English, titles will be screened for relevant keywords using the language of the document; full page translations will not be performed at screening stage. Where documents are considered for inclusion in the evidence summary they will be translated via Google Translate; this translation will be noted as a potential caveat.

2.4 Data extraction and quality appraisal of included documents

Data extraction templates are detailed in Appendix 2.

Data collected for each document category are:

1. Public health guidance and policy documents: Country or organisation, guidance/document title, URL, date, extremely medically vulnerable groups identified, evidence source.
2. Reviews: study descriptors, population demographics, outcomes relating to extremely medically vulnerable groups, author conclusions.
3. Community and or population based studies: study descriptors, population demographics, outcomes relating to extremely medically vulnerable groups, author conclusions.

4. International disease registries: registry name, disease name, country, population demographics, outcomes reported (specific to severe COVID-19) that compare mild versus severe disease or other relevant within disease classifications.

Risk of bias in systematic reviews will be assessed using AMSTAR-2. The National Heart, Lung and Blood Institute (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies will be used for the appraisal of observational cohort studies.

3 Summarise findings and delivery to relevant contacts

A summary of the evidence underpinning the categorisation of “extremely medically vulnerable” groups who may be at risk of severe illness from COVID-19 will be compiled and sent to the relevant parties. A PRISMA flow chart will be presented.

4 Quality assurance process

The review question will be led by an experienced member of the team. Four team members in total will perform the review. This will permit double checking of documents and data included in the review, and confirmation that the summary accurately reflects the body of literature, while providing cover in the event of illness. All summaries and reviews will be further reviewed by two senior members of the team, to ensure processes are followed and quality maintained; this will also enable cover to be maintained.

5 Review and update

Given the rapidly changing environment, this protocol will be regarded as a live document and amended when required to ensure it reflects any changes made to the outlined processes.

Appendix 1

Search Strategies

Searches ran on 12/10/2020

	PubMed	Hits
A	"coronavirus"[MeSH Terms] OR "coronavirus infections"[MeSH Terms] OR "coronavirus"[All Fields] OR "covid 2019"[All Fields] OR "SARS2"[All Fields] OR "SARS-CoV-2"[All Fields] OR "SARS-CoV-19"[All Fields] OR "coronavirus infection"[All Fields] OR "severe acute respiratory"[All Fields] OR "pneumonia outbreak"[All Fields] OR "novel cov"[All Fields] OR "2019ncov"[All Fields] OR "sars cov2"[All Fields] OR "cov2"[All Fields] OR "ncov"[All Fields] OR "covid-19"[All Fields] OR "covid19"[All Fields] OR "coronaviridae"[All Fields] OR "corona virus"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]	83,152
B	vulnerable OR risk OR "organ transplant"[Text word] OR "transplants"[text word] or "cancer"[Text word] OR "neoplasms"[text word] OR "chemotherapy"[Text word] OR "radiotherapy"[text word] OR leukaemia OR "lymphoma"[text word] OR "myeloma"[Text word] OR "immunotherapy"[text word] OR "protein kinase inhibitors"[text word] OR "parp"[Text word] OR "immunosuppress*"[text word] OR "cystic fibrosis"[text word] OR "severe asthma"[Text word] OR "pulmonary fibrosis"[text word] OR "lung fibrosis"[Text word] OR "interstitial lung diseases"[text word] OR (severe AND COPD) OR SCID OR "homozygous sickle cell"[Text word] OR "steroids"[text word] OR pregnancy OR dialysis OR (renal and failure) OR (renal and disease) OR (kidney and failure)	7,536,802
C	((("systematic review"[Title] OR "systematic literature review"[Title] OR "systematic scoping review"[Title] OR "systematic narrative review"[Title] OR "systematic qualitative review"[Title] OR "systematic evidence review"[Title] OR "systematic quantitative review"[Title] OR "systematic meta review"[Title] OR "systematic critical review"[Title] OR "systematic mixed studies review"[Title] OR "systematic mapping review"[Title] OR "systematic cochrane review"[Title] OR "systematic search and review"[Title] OR "systematic integrative review"[Title]) NOT "comment"[Publication Type]) NOT ("protocol"[Title] OR "protocols"[Title])) NOT "MEDLINE"[Filter]) OR ("cochrane database syst rev"[Journal] AND "review"[Publication Type]) OR "systematic review"[Publication Type] OR ("rapid review"[All Fields] OR "scoping review"[All Fields])	175,085
D	#A and #B and #C	656
E	Filters: from 2020 - 2021	608
	Europe PubMed Central	

A	((coronavirus OR covid-19 OR "covid 19" OR "SARS-CoV-2") AND ("risk" OR "vulnerable" OR "organ transplant" OR "transplant" OR "cancer" OR "neoplasms" OR "chemotherapy" OR "radiotherapy" OR leukemia OR "lymphoma" OR "myeloma" OR "immunotherapy" OR "protein kinase inhibitors" OR "parp" OR "bone marrow" OR "stem cells" OR "immunosuppress*" OR "cystic fibrosis" OR "severe asthma" OR "pulmonary fibrosis" OR "lung fibrosis" OR "interstitial lung disease" OR "severe COPD" OR "SCID" OR "homozygous sickle cell" OR "steroids" OR "pregnancy" OR "dialysis" OR "kidney failure" OR "renal failure" OR "kidney disease" OR "renal disease")) AND (ABSTRACT:"systematic review" OR TITLE:"systematic review" OR ABSTRACT:"rapid review" OR TITLE:"rapid review") AND (SRC:PPR)	409
EMBASE		
#1	'coronavirus disease 2019'/exp OR 'coronavirus disease 2019' OR 'covid-19' OR 'covid 19' OR 'covid19' OR 'sars-related coronavirus' OR 'coronaviridae' OR 'sars2' OR 'sars-cov-2' OR 'sars-cov-19' OR 'severe acute respiratory syndrome coronavirus 2' OR 'coronavirus infection' OR ('severe acute respiratory' AND 'pneumonia outbreak') OR 'novel cov' OR '2019ncov' OR 'sars cov2' OR 'cov2' OR 'ncov' OR 'corona virus'	84,123
#2	'vulnerable' OR 'risk' OR 'organ transplant' OR 'transplant'/de OR 'cancer'/de OR 'neoplasm'/de OR 'chemotherapy'/de OR 'radiotherapy'/de OR 'leukemia'/de OR 'lymphoma'/de OR 'myeloma'/de OR 'immunotherapy'/de OR 'protein kinase inhibitors'/de OR 'parp'/de OR 'bone marrow'/de OR 'stem cell'/de OR 'immunosuppress*'/de OR 'cystic fibrosis'/de OR ('severe' AND ('asthma'/exp OR 'asthma')) OR 'pulmonary fibrosis'/de OR 'lung fibrosis'/de OR 'interstitial lung disease'/exp OR 'interstitial lung disease' OR 'chronic obstructive lung disease'/exp OR 'chronic obstructive pulmonary disease' OR 'severe combined immunodeficiency'/exp OR 'severe combined immunodeficiency' OR 'SCID' OR 'homozygous sickle cell' OR 'pregnancy'/exp OR 'pregnancy' OR dialysis OR 'kidney failure' OR 'kidney disease'	6,894,565
#3	#1 AND #2	22,274
#4	#3 AND 'systematic review'/de	857
#5	#3 AND 'rapid review'	74
#6	#3 AND 'scoping review'	48
#7	#4 OR #5 OR #6	928
#8	#7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim).	287
	#8 2020 AND 2021	266
NHS Evidence		
A	(coronavirus OR covid 19 OR covid 19 OR SARS CoV 2) AND (risk factor)	5873
B	Limit to systematic reviews and evidence summaries	2442

C	Limit January 2020 to date	302
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Appendix 2

Data extraction templates

Appendix 2.1

Data extraction template for public health guidance and policy documents

Country or organisation Guidance/document title URL Date	Extremely medically vulnerable groups	Evidence source
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Appendix 2.2

Data extraction template for reviews

First author Review type DOI	Number of included studies Extremely medically vulnerable groups identified	Outcomes Author conclusions
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Appendix 2.3

Data extraction template for original research studies

First author Country Design DOI	Setting/Source Sample size Demographics Extremely medically vulnerable groups identified	Outcomes Author conclusions
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Appendix 2.4

Data extraction template for international disease registries

Registry name Country	Population demographics	Outcomes reported (specific to COVID-19)*
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*Comparing mild versus severe disease.

For further information please contact:

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