Health Technology Assessment (HTA) Expert Advisory Group Meeting (NPHET COVID-19 Support)		
Meeting no. 8 : Monday 25th January 2021 at 11.00am		
(Zoom/video conference)		
MINUTES		
Attendance:		
Chair	Dr Máirín Ryan	Director of Health Technology Assessment (HTA) & Deputy Chief Executive Officer, HIQA
	Prof Karina Butler	Consultant Paediatrician and Infectious Diseases Specialist, Children's Health Ireland & Chair of the National Immunisation Advisory Committee
	Dr Eibhlín Connolly	Deputy Chief Medical Officer, Department of Health
	Prof Máire Connolly	Specialist Public Health Adviser, Department of Health and Professor of Global Health and Development, National University of Ireland, Galway
	Prof Martin Cormican	Consultant Microbiologist & National Clinical Lead, HSE Antimicrobial Resistance and Infection Control Team
	Ms Sinead Creagh	Laboratory Manager at Cork University Hospital & Academy of Clinical Science and Laboratory Medicine
	Dr Ellen Crushell	Consultant Paediatrician, Dean, Faculty of Paediatrics, Royal College of Physicians of Ireland & Co-Clinical Lead, Paediatric/Neonatology National Clinical Programme
	Dr John Cuddihy	Specialist in Public Health Medicine & Interim Director, HSE-Health Protection Surveillance Centre (HPSC)
	Ms Josephine Galway	National Director of Nursing Infection Prevention Control and Antimicrobial Resistance AMRIC Division of Health Protection and Surveillance Centre
	Dr Vida Hamilton	Consultant Anaesthetist & National Clinical Advisor and Group Lead, Acute Hospital Operations Division, HSE
	Dr David Hanlon	General Practitioner & National Clinical Advisor and Group Lead, Primary Care/Clinical Strategy and Programmes, HSE
	Dr Patricia Harrington	Deputy Director, HTA Directorate, HIQA
	Dr Cillian de Gascun	Consultant Virologist & Director of the National Virus Reference Laboratory, University College Dublin
	Dr Derval Igoe	Specialist in Public Health Medicine, HSE- Health Protection Surveillance Centre (HPSC)
	Prof Mary Keogan	Consultant Immunologist, Beaumont Hospital & Clinical Lead, National Clinical Programme for Pathology, HSE
	Dr Siobhán Kennelly	Consultant Geriatrician & National Clinical & Advisory Group Lead, Older Persons, HSE

	Mr Andrew Lynch	Business Manager, Office of the National Clinical Advisor and Group Lead - Mental Health, HSE
	Dr Gerry McCarthy	Consultant in Emergency Medicine, Cork University Hospital & National Clinical Lead, HSE Clinical Programme for Emergency Medicine
	Prof Paddy Mallon	Consultant in Infectious Diseases, St Vincent's University Hospital & HSE Clinical Programme for Infectious Diseases
	Dr Des Murphy	Consultant Respiratory Physician & Clinical Lead, National Clinical Programme for Respiratory Medicine, HSE
	Dr John Murphy	Consultant Paediatrician & Co-National Clinical Lead, HSE Paediatric/Neonatology Clinical Programme
	Dr Sarah M. O'Brien	Specialist in Public Health Medicine, Office of National Clinical Advisor & Group Lead (NCAGL) for Chronic Disease
	Dr Gerard O'Connor	Consultant in Emergency Medicine, Mater Misericordiae University Hospital HSE Clinical Programme for Emergency Medicine
	Ms Michelle O'Neill	Deputy Director, HTA Directorate, HIQA
	Dr Margaret B. O'Sullivan	Specialist in Public Health Medicine, Department of Public Health, HSE South & Chair, National Zoonoses Committee
	Dr Lynda Sisson	Consultant in Occupational Medicine, Dean of Faculty of Occupational Medicine, RCPI & HSE National Clinical Lead for Workplace Health and Well Being
	Prof Susan Smith	Professor of Primary Care Medicine, Royal College of Surgeons in Ireland
	Dr Patrick Stapleton	Consultant Microbiologist, UL Hospitals Group, Limerick & Irish Society of Clinical Microbiologists
	Dr Conor Teljeur	Chief Scientist, HTA Directorate, HIQA
	Dr Lelia Thornton	Specialist in Public Health Medicine, HSE- Health Protection Surveillance Centre (HPSC)
	Ms Anne Tobin	Assessment and Surveillance Manager, Medical Devices, Health Products Regulatory Authority
In attendance	Dr Eamon O Murchu	Senior HTA Research Analyst, HTA Directorate, HIQA
	Dr Karen Cardwell	Postdoctoral Researcher HRB-CICER, HTA Directorate, HIQA
	Dr Paula Byrne	Health Services Researcher, HTA Directorate, HIQA
	Ms Susan Aherne	Health Services Researcher, HTA Directorate, HIQA
	Dr Susan Spillane	Senior HTA Research Analyst, HTA Directorate, HIQA
Secretariat	Ms Debra Spillane	PA to Dr Máirín Ryan, HIQA
Apologies	Dr Jeff Connell	Assistant Director, UCD National Virus Reference Laboratory, University College Dublin
	Dr Lorraine Doherty	National Clinical Director Health Protection, HSE- Health Protection Surveillance Centre (HPSC)

	Ms Sarah Lennon	Executive Director, SAGE Advocacy

Proposed Matters for Discussion:

1. **Welcome**

   The Chair welcomed all members.

2. **Apologies & Introductions**

   Apologies as noted above.

3. **Conflicts of Interest**

   No new conflicts raised in advance of or during this meeting.

4. **Minutes**

   The minutes of 25th November 2020 and 18th January 2021 were approved as an accurate reflection of the discussions involved.

5. **Work Programme**

   The group was provided with an overview of the current status of the work programme including:

No.	Review Questions	Status of work
1.	Evidence summary on interventions in an ambulatory setting to prevent progression to severe disease in patients with COVID-19	Drafted
2.	Analysis of factors associated with outbreaks of SARS-CoV-2 in nursing homes in Ireland	Ongoing
3.	Review of international public policy response for weekly update	Ongoing
4.	Measures to support self-isolation and ROM	Ongoing
	Database	Ongoing
	Public health guidance: vulnerable groups LTCFs	Ongoing

6. **Presentation of evidence summary on interventions in an ambulatory setting to prevent progression to severe disease in patients with COVID-19 – key findings**

   The EAG were reminded that NPHET had requested the HIQA evaluation team undertake a review to address the following policy topics:

   "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?"

This request to HIQA from NPHET was agreed on 4 January 2021. In response, HIQA developed a protocol for a rapid evidence summary which was disseminated to the EAG for review in advance. As per the agreed deliverables document, the following research question (RQ) was formulated:

"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?"

The Chair thanked the members for reviewing the draft rapid evidence summary. A presentation was provided on the key points of the rapid evidence summary for the RQ by the Lead Analyst.

The following points were raised as matters for clarification or discussion by the EAG:

The importance of how the findings of the review are presented to the public and to a non-clinical audience was highlighted, as well as the language used, due to the limitations of the findings in terms of safety and the benefit/risk balance. The group emphasised the safety issues associated with numerous interventions included in this review; there are risks associated with all pharmaceutical interventions and the evidence base was extremely limited for all interventions included in this review. It was noted that for all studies the sample size, effect size and clinical relevance should be emphasised. When the effect size is small, the use of the word 'benefit' was questioned.

There was some debate over the inclusion criteria for the review. While one study was identified that technically fulfilled the prespecified inclusion criteria, it was noted that the intervention (neutralised electrolysed saline) does not have any equivalent pharmaceutical grade product available for use. On this basis, it was argued that it was not relevant for inclusion. Separately a distinction was made between the certainty of evidence (based on GRADE summary of findings tables) and the applicability of the evidence to the Irish healthcare system. Inclusion of interventions in the evidence summary did not mean that their use was endorsed.

The group highlighted the importance of employing a rigid approach to the inclusion of studies that relate to therapeutic interventions. It was noted that interventions identified as part of the systematic search should not be excluded because they are not available in Ireland.

The inclusion of preprints was discussed. While it was noted that this was not part of traditional systematic review methodology, it has been a feature of the COVID-19 pandemic due to the urgent requirement for information. Studies published only as preprints are clearly identified within reviews.

It was noted that monoclonal antibodies are time and place specific and that any efficacy estimates may not be generalisable to the new variants of concern.

The difficulty in conducting randomised controlled trials (RCTs) in the primary care setting was noted. This might explain the limited number of RCTs identified for pharmaceutical interventions. It was noted however that NRCTs were also eligible for inclusion, but that no RCTs or NRCTs of non-pharmaceutical interventions were identified. It was agreed that undertaking such trials for non-drug interventions including physiotherapy, lifestyle and psychological interventions is challenging.

It was asked if evidence had been found regarding Vitamin D. There has been strong public and GP interest in the use of Vitamin D as an immunomodulator. While eligible for inclusion, no relevant trials were identified in the search. It was noted that there is a difference between population-based cross sectional studies and controlled trials of an intervention - this specific research question related to the use of interventions in patients who had already been diagnosed with COVID-19. Interest was expressed in a further research question specific to this issue to provide an objective evidence-based review, so that there could be clarity regarding its potential role, if any, and particularly to identify population subgroups likely to benefit. It was noted that while there are good theoretical arguments for its use, despite extensive research, no clear role has been identified for vitamin D in other populations including those with with asthma and in the management of chronic viral infections. A distinction was noted relating to individuals who are vitamin D deficient. It was also noted that Vitamin D deficiency has been associated with deprivation.

The difficulty in administering infusions in the community was highlighted, given the poor infrastructure in those settings, although it was noted that there would be potential for them to be administed in the community hubs.

The use of corticosteroids in the community was discussed. It was acknowledged that many COVID-19 patients may also suffer from COPD. The use of corticosteroids in such patients would not be considered inappropriate as they are routinely used for infective exacerbations of COPD, the symptoms of which overlap with the symptoms of COVID-19’

It was noted that while not licensed, ivermectin is used in Ireland for range of indications on a named-patient basis. However, it was noted that high doses pose significant safety concerns.

The importance of this review was highlighted in terms of documenting the current level of evidence, given the significant interest among clinicians and the public.

The potential use of pulse oximetry as an intervention in the community was discussed by the group. It was noted that no controlled trials were identified for this intervention.

It was noted that the HPRA is willing to help with communication of safety risks if required.

The Chair noted that clarifications would be made to the draft rapid evidence summary report where necessary based on the above points. The draft was otherwise accepted by the EAG as a fair reflection of the rapid evidence synthesis that was undertaken.

7. Advice: interventions in an ambulatory setting to prevent progression to severe disease in patients with COVID-19 *(for discussion)*

In the context of this evidence, the EAG was asked for their input in order to formulate the advice. Suggested issues to be considered included the: evidence-bar that must be met for any of these interventions to be implemented; whether there is a higher evidence bar with respect to safety for pharmaceutical interventions, and particularly given a proposed use to prevention deterioration; applicability of the data to the Irish healthcare system; applicability of the data to different population subgroups; relevance of the regulatory status of the interventions to decision-making; potential resource issues associated with the implementation of any of the interventions; any other context from Ireland relevant to the formulation of this advice.

Feedback on advice from EAG:

- The EAG were in agreement that evidence regarding the effectiveness of therapeutic interventions, particularly for pharmaceutical treatments, must be subject to the highest standards of rigour. It was noted that trials included in the present review are severely limited with respect to the certainty, quantity, and applicability of the evidence and are insufficient to inform decision-making on treatment options for COVID-19 in Ireland. The EAG were in agreement that there is currently no evidence of benefit associated with the treatments considered within the present review and there is insufficient information on whether any of these may be safely used in the treatment of COVID-19. Furthermore, some of the interventions investigated within the trials would not be considered applicable to the Irish setting due to differences in the standard of care and or on the basis of safety concerns.

- A distinction was drawn between interventions for which there is no evidence in any setting versus those for which there is evidence in another setting (for example, acute care). Evidence in relation to the potential to cause harm should include trial data, but should be supported by the broader literature with respect to that intervention. The usual requirements for robust clinical governance would have to be adhered to for any treatment used in the community, along with strong evidence of effectiveness and safety.

- In consideration of the fact that evidence exists in support of the use of corticosteroids to treat hospitalised patients with severe COVID-19, it was noted that no evidence was identified for the use of corticosteroids to treat COVID-19 in the community. While there are anecdotal reports of corticosteroids being used in the community, it was highlighted that evidence of benefit for dexamethasone in the RECOVERY clinical trial was limited to patients with severe disease requiring supplemental oxygen. Moreover, there was evidence that dexamethasone might increase mortality in hospitalised patients who do not require supplemental oxygen.

- While none of the pharmaceutical interventions identified in the review are currently licensed for the treatment of COVID-19, it was noted that Schedule 1 of the Medicinal Products Regulations 2007 includes an exemption for practitioners to prescribe unauthorised

medicinal products for individual patients under their direct responsibility, in order to fulfil the special needs of those patients.

- It was noted that where treatments outlined in the identified trials may technically be acquired for off-label use on an individual patient basis, the doses used within some of the trials represent higher doses than those used in clinical practice for other indications, thus raising further safety concerns.

- General practitioners should receive very clear communication that, based on the current evidence, there are no medicines that should be prescribed outside of a clinical trial for the treatment of COVID-19 in the community. There are a range of opportunities for communication, including GP webinars and other fora presented by the Irish College of General Practitioners (ICGP). Such communication, when supported by a comprehensive evidence review such as the one that has been undertaken, will help ensure that individuals do not prescribe or use interventions for the treatment of COVID-19 that do not meet the necessary minimum criteria and practitioners are not criticised for not prescribing these interventions.

- The HSE has established ongoing processes for development of clinical guidance with respect to SARS-CoV-2 infection. This includes guidance for the clinical management of COVID-19 in the acute setting, which is approved for use by the HSE National Clinical Advisor and Group Lead, Acute Hospitals Division. The published guidance is developed by guideline review groups and informed by rapid evidence reviews undertaken by the HSE COVID-19 Evidence Review Group for Medicines. This latter group comprises evidence synthesis practitioners from the National Centre for Pharmacoeconomics (NCPE), Medicines Management Programme (MMP) and the National Medicines Information Centre (NMIC). The HSE COVID-19 Evidence Review Group has also published evidence summaries in relation to specific interventions for both ambulatory and hospital use. These processes are linked with established medicines management and purchasing schemes. While the HIQA review provides information on emerging evidence, it does not supersede the ongoing processes for guidance development and or the reimbursement of medicines as described.

- If evidence of effectiveness should emerge in the future, it is important that due process would apply in decision-making regarding recommendation of a treatment and the reimbursement of any medicine that may be recommended. Additionally, there is currently very poor infrastructure in place for the delivery of infusions in the community generally, with significant additional challenges regarding the delivery of infusions for patients with COVID-19. Thus there are significant concerns regarding availability of resources and feasibility of implementation. With respect to monoclonal antibody treatments, it was noted that SARS-CoV-2 variant resistance may occur; as such, effectiveness evidence may be specific to time and place and may not apply universally as the pandemic evolves.

- The high standard of evidence required for pharmaceutical interventions, particularly in the context of population-level recommendations, was reiterated. Demonstration of a clinically relevant effect size should be required prior to an agent being adopted for use. Concerns

were raised about the pre-prints, that is, manuscript publications which have yet to be formally peer-reviewed, included in the review. It was noted that for some agents, this was the only evidence available, emphasising the lack of robust evidence currently available to inform decision-making.

- It was acknowledged, that conducting controlled clinical trials in the primary care setting during the pandemic is challenging, and as such there may continue to be a lack of robust evidence to inform decision making. This was viewed as particularly relevant to the generation of evidence on non-pharmaceutical interventions.

- It was highlighted that there has been widespread discussion in the media, and among clinicians, regarding the potential use of certain interventions for the treatment of COVID-19 in the community; for instance Vitamin D, corticosteroids, and the use of pulse oximetry by patients. It was agreed that the advice pertains to medicines explicitly for the treatment of COVID-19 and does not pertain to the routine use of these medicines for other indications (for example, use of corticosteroids in patients with an exacerbation of COPD or asthma).

- It was recognised that, as with pharmaceutical interventions, there may be harms associated with non-pharmaceutical interventions. For example, the widespread use of pulse oximetry by patients, in the absence of clinical supervision, may lead to delayed presentation by patients who have been falsely assured by readings that have been incorrectly taken or taken using devices that have not been validated. Alternatively this intervention could contribute to anxiety and additional emergency department attendances in others where their baseline clinical context has not been taken into consideration. It was noted that remote pulse oximetry monitoring of COVID-19 patients in the community has been deployed by at least one hospital, but that this is in the context of validated devices for which there is centralised monitoring and ongoing clinical oversight.

- It was noted that once a medical device has been CE marked, there is no legal impediment to it being placed on the market. However, there are risks with this interpretation as it does not mean that safety and efficacy have been demonstrated.

- The potential role of HSE Community Assessment Hubs was noted. While the evidence review did not identify international literature with respect to such hubs, it was noted that they play an important role in Ireland in terms of patient triage. This can help ensure that those requiring hospital review are promptly referred while providing assurance to other patients, including very anxious patients, that their needs can adequately be met in primary care without ED attendance.

- It was noted that evidence-based advice documents around possible interventions for COVID-19 provide useful support to those in clinical leadership positions and can help prevent dissemination of interventions for which there is no evidence to support their use.

8. Meeting Close

a) AOB

The Chair thanked the EAG members for their contribution to date and acknowledged the valuable feedback provided under short timelines.

b) Date of next meeting: 8th February 2021