Therapeutics for people with COVID-19

Multiple Technology Appraisal

PART 1 - Community and Hospital for screen and public
CIC information redacted
Redaction update (18/10)
Post committee changes

Technology appraisal committee C

Chair: Stephen O'Brien

Lead team: Stella O'Brien, Iain McGowan, Rachel Elliott

Evidence assessment group: School of Health and Related Research (ScHARR), Sheffield

Technical team: Anuja Chatterjee, Adam Brooke, Ross Dent

Companies: AstraZeneca, Eli Lilly, Gilead, GlaxoSmithKline, Merck Sharp & Dohme, Pfizer, Roche

Overview of the day

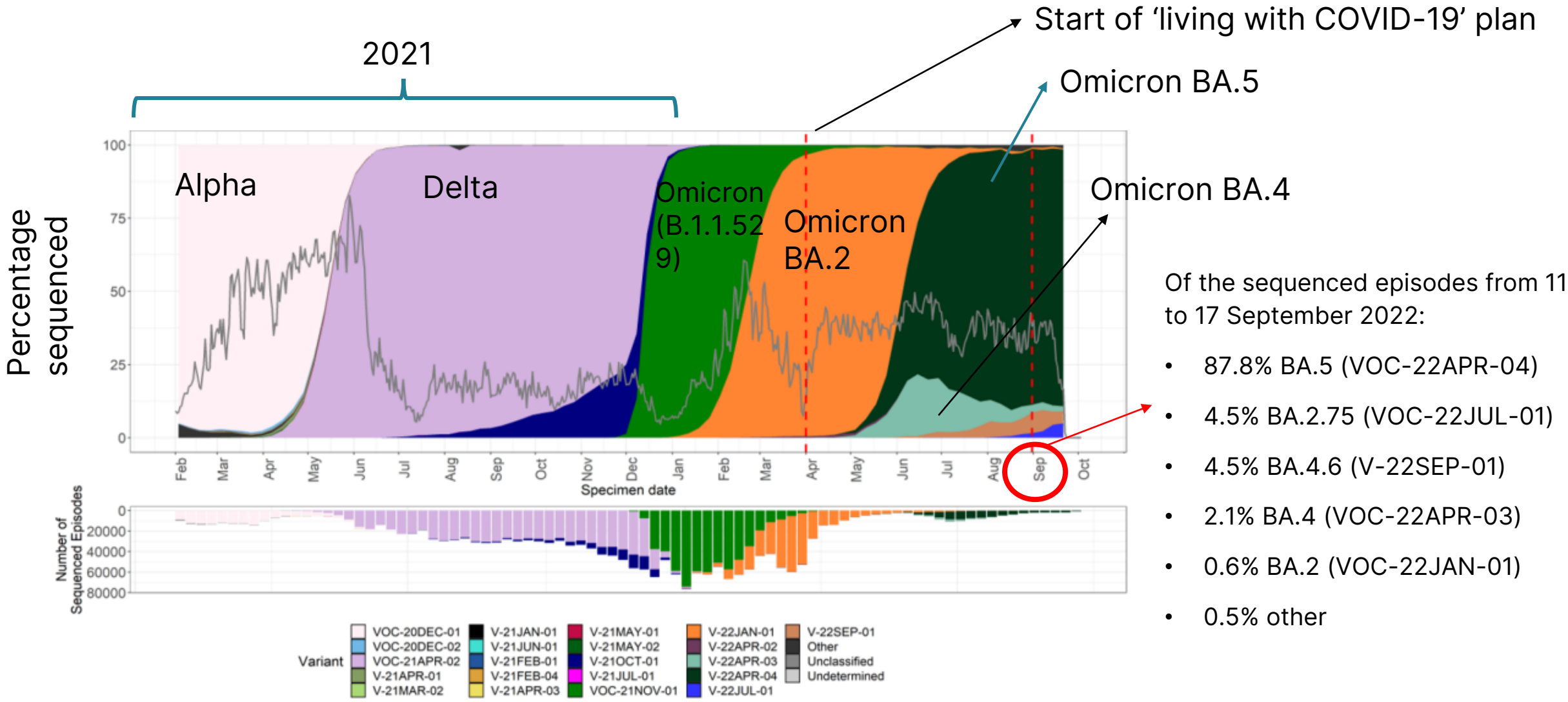
	Chair overview	
Section	**Morning**	
1	General introduction	Public
2.1	Community setting (mild COVID-19) – Part 1	Public
2.2	Community setting – Part 2	Private
	Afternoon – 2PM	
3.1	Hospital setting (severe COVID-19) – Part 1	Public
3.2	Hospital setting – Part 2	Private

Broad themes

- **As the SARS-CoV-2 virus is evolving, the evidence is also evolving**
  - New variants and subvariants have different mortality/hospitalisation profiles
  - Evidence for treatment effectiveness was generated throughout the pandemic – to what extent can in vitro data inform effectiveness against new variants?
- **Different treatments being appraised have different settings and aims**
  - Treatments for severe COVID-19 aim to reduce mortality in hospitals
  - Treatments that reduce risk of progressing to severe COVID-19 aim to reduce hospitalisations, mostly in the community.
    - How should 'high-risk' be defined? (marketing authorisations, PANORAMIC trial, McInnes report)
- **Long term** outcomes and effects of Long-COVID are highly uncertain
- This is an **appraisal** process – assessing treatments within their licenses - not a guideline process
- **An NHS "business as usual" approach for routine commissioning –** are treatments for COVID-19 any different?

COVID-19, Coronavirus-2019; PANORAMIC, Platform Adaptive trial of NOvel antiviRals for eArly treatMent of covid-19 In the Community ; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2

Figure with variant prevalence of available sequenced episodes for England (1 February 2021 to 4 October 2022)



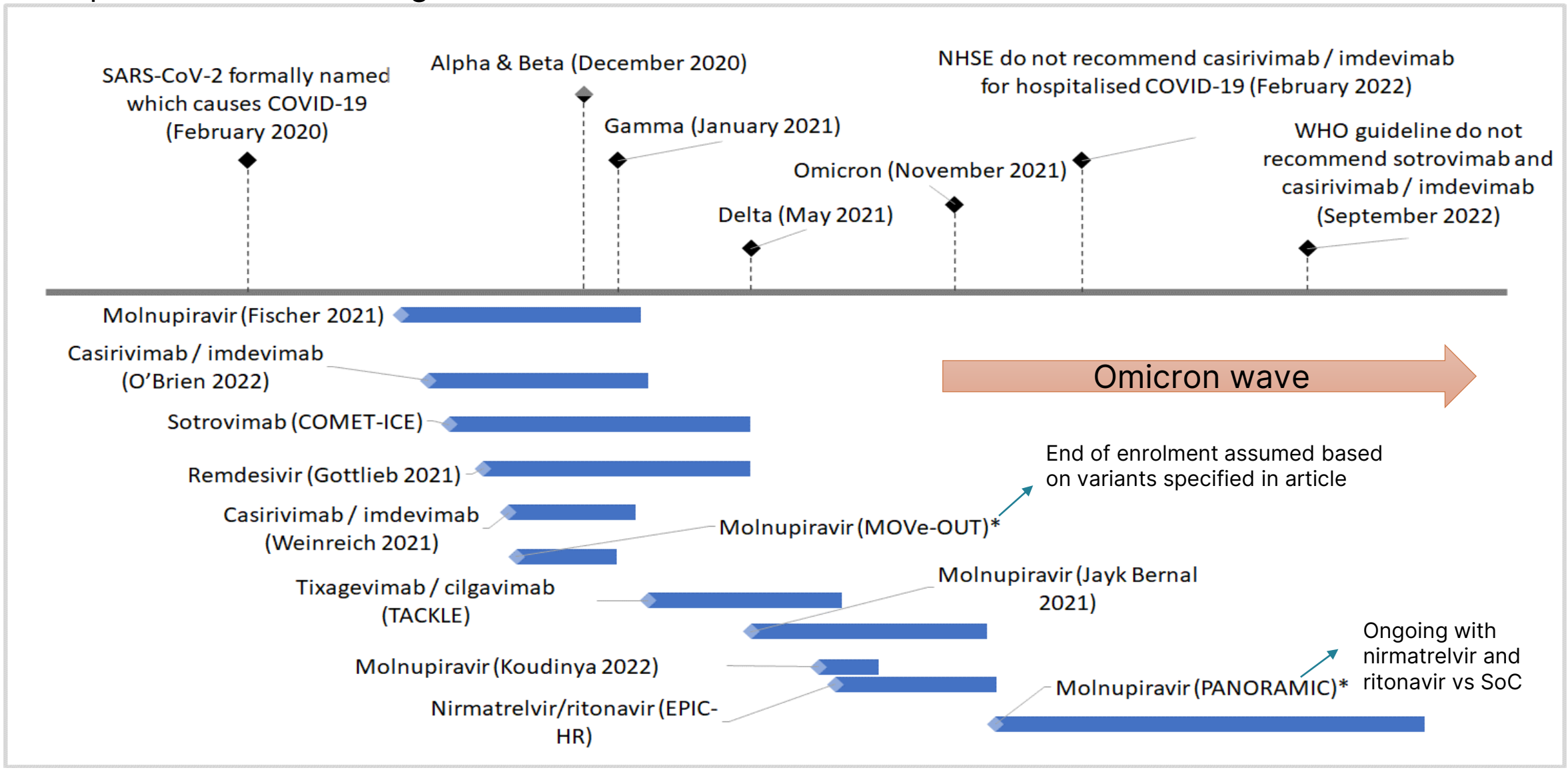
Of the sequenced episodes from 11 to 17 September 2022:

- 87.8% BA.5 (VOC-22APR-04)
- 4.5% BA.2.75 (VOC-22JUL-01)
- 4.5% BA.4.6 (V-22SEP-01)
- 2.1% BA.4 (VOC-22APR-03)
- 0.6% BA.2 (VOC-22JAN-01)
- 0.5% other

Source: UK Health Security Agency, Figure 4 SARS-CoV-2 variants of concern and variants under investigation in England: Technical briefing 46. Vs, Variants; VOC, Variant of concern

Global VOC and clinical trial enrolment dates - Community

All prior to Omicron being declared a VOC



Source: AG report (Table 24 - Trial publications), WHO website for VOC. NHSE, NHS England; SoC, Standard of care; VOC, Variant of concern; WHO, World Health Organisation

COVID-19 treatments being appraised

Antiviral agents: Reduces viral load / lowers progression to severe disease / risk of death

Hospital and community
- Remdesivir (Veklury, Gilead Sciences)

Community
- Molnupiravir (Lagevrio, MSD)
- Nirmatrelvir and ritonavir (Paxlovid, Pfizer)

Monoclonal antibodies: Reduces need for hospital admission / risk of death

Hospital and community
- Casirivimab and imdevimab (Ronapreve, Roche Products)

Community
- Sotrovimab (Xevudy, GSK)
- Tixagevimab and cilgavimab (Evusheld, AstraZeneca)

Anti-inflammatory agents: Treats multisystem inflammatory disease which develops later on in the COVID-19 pathway

(Hospital setting only – severe COVID-19)

- Baricitinib (Olumiant, Eli and Lilly)
- Tocilizumab (RoActemra, Roche Products)

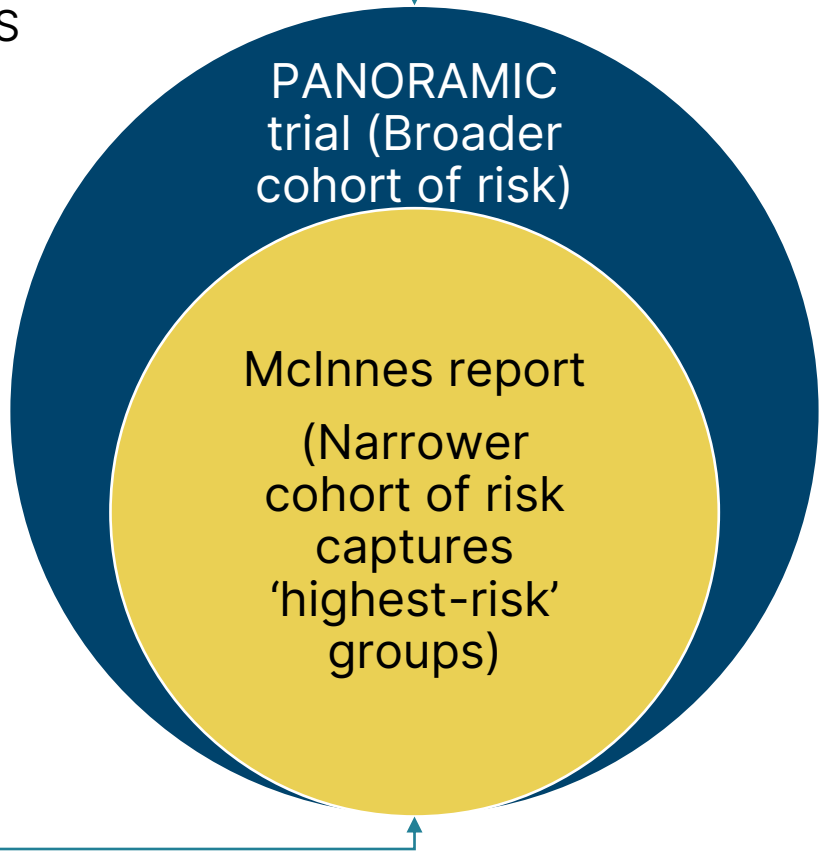
Source: Professional organisation submissions, Marketing authorisations

GSK, GlaxoSmithKline ; MSD, Merck Sharp & Dohme

There are different high-risk group definitions

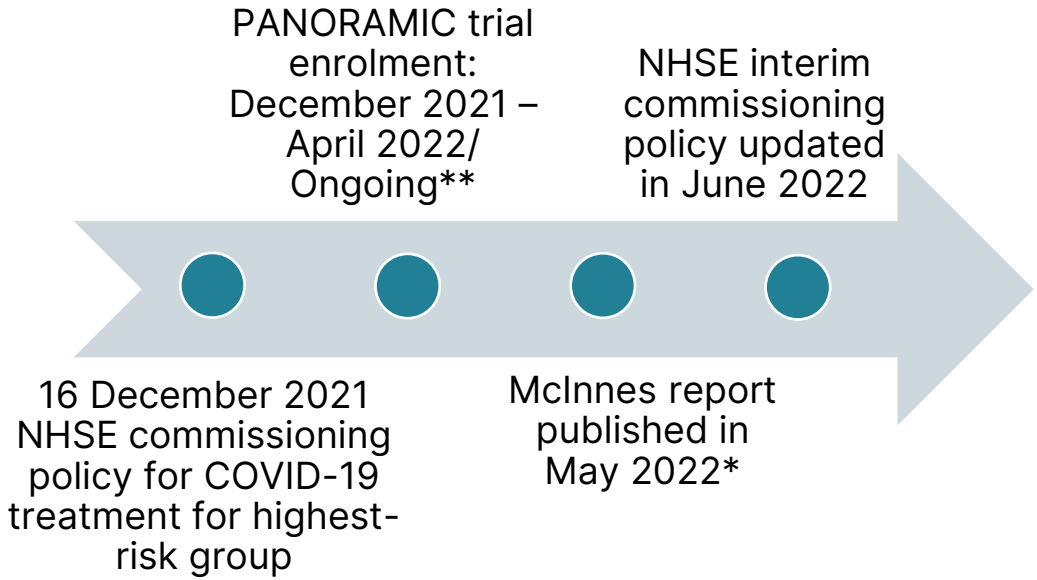
UK clinical trial assessing clinical effectiveness of new antivirals versus NHS standard of care for COVID-19

- regardless of vaccination status, aged 50+ or
- 18+ with pre-existing conditions



Highest risk groups defined using population based studies, literature searches and expert opinion

UK-wide high-risk groups would have enrolled onto the PANORAMIC trial between December 2021-April 2022



Following publication of the NHSE policy, the PANORAMIC trial may not include all people with COVID-19 considered at 'highest-risk' of hospitalisation or death

NICE

Source: *Defining the highest-risk clinical subgroups upon community infection with SARS-CoV-2 when considering the use of neutralising monoclonal antibodies (nMABs) and antiviral drugs: independent advisory group report **www.panoramictrial.org. NHSE, NHS England

Table shows the variable hospitalisation rates for high-risk groups identified

A systematic review was not done to identify risk of hospitalisation rates. The rates identified are from real-world evidence sources that use different definitions of high-risk.

Source	Rate of hospitalisation or death	Which high-risk group does this apply to?
PANORAMIC pre-print (Dec 2021-April 2022)*	96/12484 = 0.77%	Broad high-risk group in UK, includes Omicron wave
GSK: Discover-Now database (interim analysis only) December 2021-April 2022	108/3865 = 2.79%	Highest-risk - people eligible to receive COVID-19 treatment under NHSE policy. Includes Omicron wave
GSK: Targeted review (EMBASE and MEDLINE) Hospitalisation for confirmed COVID-19 December 2021 to August 2022	High-risk population = 5.48% (5 studies N=2027, COVID-19 = 111) COVID-19 related hospitalisation rate (n=98): 5.05%	NHSE policy definition used McInnes highest-risk group in England (?)
AZ: Shields 2022 (January 2021-March 2022)	17.9% Primary immunodeficiency 18.4% Secondary immunodeficiency	Immunocompromised - McInnes subset
OPENSAFELY platform pre-print – Real world study** December 2021-February 2022	87/6020 = 1.4% (receiving molnupiravir and sotrovimab)	People eligible for sotrovimab and molnupiravir NHSE policy McInnes highest-risk group (?)

NICE Source: GSK (GlaxoSmithKline), AZ (AstraZeneca) company submissions, Shields 2022 Front. Immunol. 13:984376. doi: 10.3389/fimmu.2022.984376. Please see slide notes for links to pre-prints (*Butler 2022, **Zheng 2022). NHSE, NHS England

Key issues

Most of the issues impact both settings, all issues impact community setting

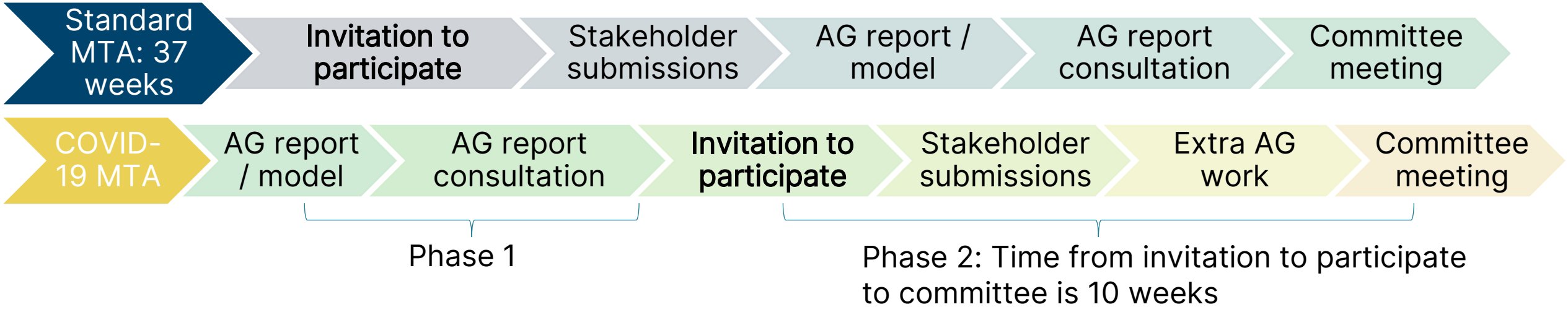
Issue		Applies to community / hospital / both?	Resolved?	ICER impact
	Uncertainty around clinical efficacy			
1	How is 'high-risk' defined and what impact does that have on clinical and cost effectiveness?	Community	No – for discussion	Large
2	How valid are the clinical trial data given the changing nature of SARS-CoV-2?	Both	No – for discussion	Unknown
	Uncaptured benefits?			
3	Are there broader benefits offered by these new treatments other that immediate clinical benefit?	Both	No – for discussion	Unknown
	Modelling inputs			
4	Long-COVID assumptions	Both	Partially	Unknown
5	Utility values	Mainly hospital setting / both	Partially	Small
6	Administration costs	Mainly community setting / both	Partially	Small
7	Hospitalisation costs	Mainly hospital setting / both	Partially	Small

MTA process overview for COVID-19

Compressed timelines with assessment group report and model completed first

- The standard steps of an MTA have been followed
- Because of the exceptional nature of COVID-19, the steps were re-sequenced and timelines were shortened (see figure below)

Figure: Comparison of Standard MTA and this COVID-19 MTA process



AG, Assessment group; COVID-19, Coronavirus-2019; MTA, Multiple technology appraisal

Perspective of the evaluation

- Routine NHS commissioning (endemic disease)
- Treatment following diagnosis of COVID-19 either in the community or hospital
- Treatments evaluated using standard NICE methods of Technology Appraisal
    - NHS and Personal Social Services perspective
- Recent clinical effectiveness evidence on currently circulating SARS-CoV-2 variants and their subvariants are being considered
- Exceptionally, committee will consider the clinical evidence for some technologies that do not yet have a GB marketing authorisation. No recommendations on these technologies will be released until GB marketing authorisation is obtained.
- Statement on website about collaboration with Scottish Medicines Consortium/Health Improvement Scotland
- Final recommendations will supersede interim NHS commissioning policies and will be integrated into the NICE rapid guideline on managing COVID-19

COVID-19, Coronavirus-2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Key timelines

	If no consultation
18 October 2022	First appraisal committee meeting
November 2022	Draft final guidance issued for appeal
Dec 22/Jan 23	Final guidance published (if no appeals)

	If consultation
18 October 2022	First appraisal committee meeting
November 2022	Draft guidance consultation
January 2023	**Second appraisal committee meeting**
February 2023	Draft final guidance issued for appeal
March 2023	Final guidance published (if no appeals)

Overview of the day

	Chair overview	
Section	Morning	
1	General introduction	Public
2.1	Community setting (mild COVID-19) – Part 1	Public
2.2	Community setting – Part 2	Private
	Afternoon – 2PM	
3.1	Hospital setting (severe COVID-19) – Part 1	Public
3.2	Hospital setting – Part 2	Private

Section 1 General introduction

- COVID-19 and a constantly changing virus
- Patient and clinical perspectives
- Decision problem & modelling

Section 1 General introduction

- COVID-19 and a constantly changing virus
- Patient and clinical perspectives
- Decision problem & modelling

Background on COVID-19

Causes

- COVID-19 is an acute respiratory illness caused by SARS-CoV-2

Epidemiology

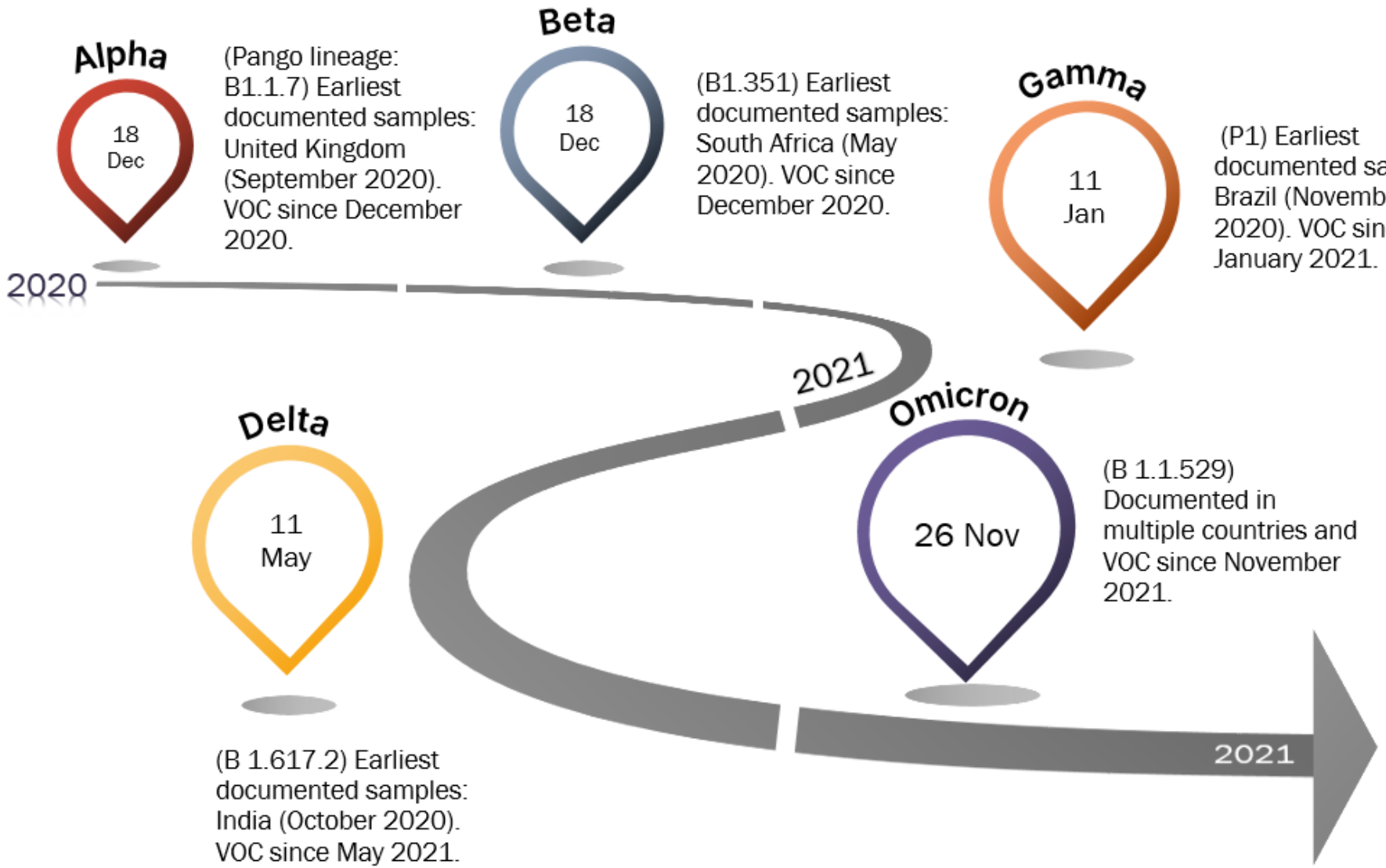
- UK (October 2022) 22 million confirmed COVID-19 cases and over 177,000 deaths*

Symptoms and prognosis

- May start with a cough, fever or breathlessness (viral replication phase with peak of infectiousness and viral shedding). Infection can spread before any symptoms observed
- Infections range from mild and self-limiting to severe
  - if infection is uncontrolled, the body's excess immune response to the virus may result in severe complications (inflammatory phase) accompanied by a high-risk of hospitalisation and death
- In the community, people with severe infections are often hospitalised and may need support with high-flow / low-flow oxygen and treatment in intensive care units
- COVID-19 can progress to post-COVID-19 syndrome / Long-COVID
  - may manifest as debilitating symptoms like fatigue and pain, common long term multisystem effects include dyspnoea, variations in heart rate, dysautonomia

Source: Final Scope, AG report, *https://coronavirus.data.gov.uk/ (Specimens taken up to 19 May 2022, deaths within 28 days of positive test up to 20 May 2022)

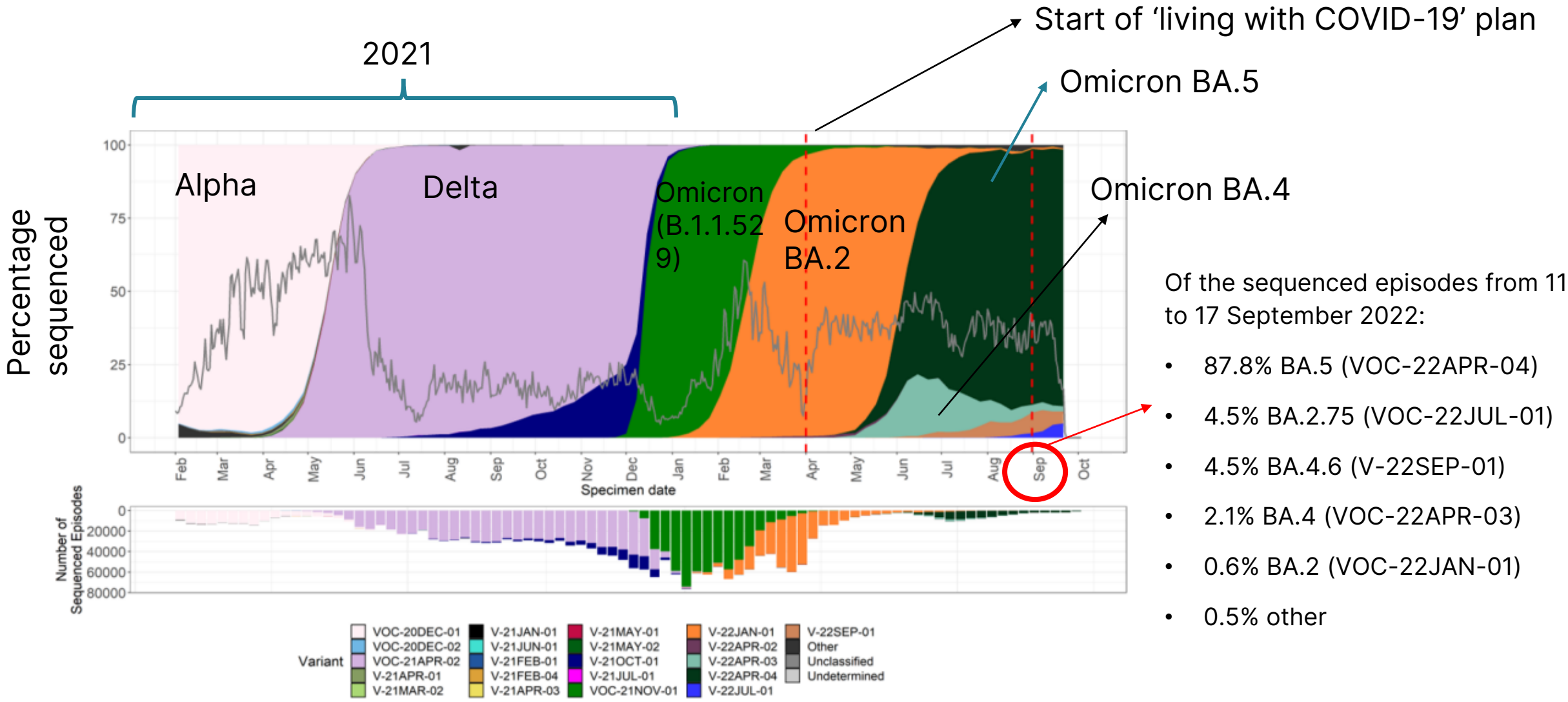
Global COVID-19 timeline of WHO variants of concern



- Only VOC are presented here
- Dates indicate date of designation of a VOC

Source: WHO (https://www.who.int/activities/tracking-SARS-CoV-2-variants) VOC, Variant of concern

Figure with variant prevalence of available sequenced episodes for England (1 February 2021 to 4 October 2022)



Of the sequenced episodes from 11 to 17 September 2022:

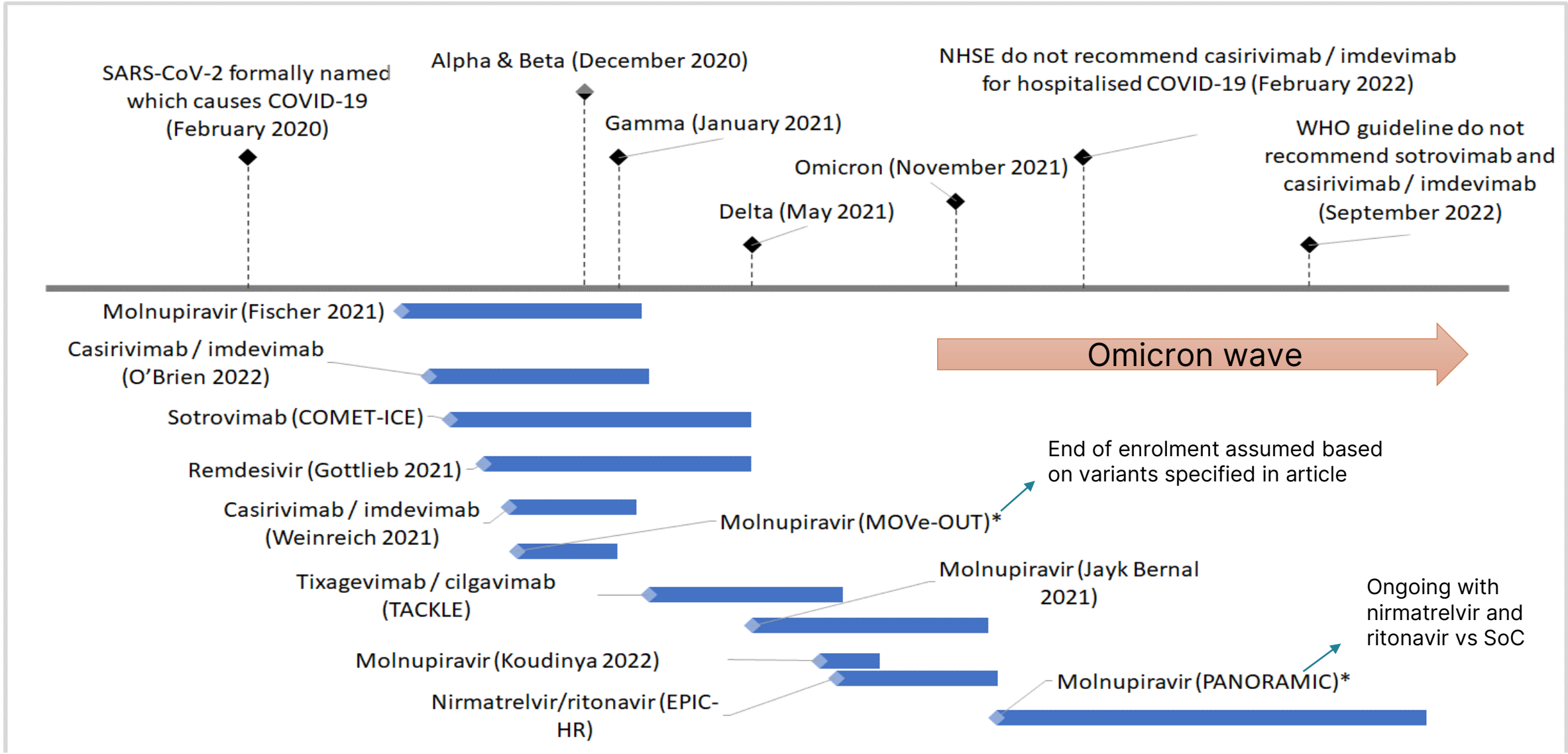
- 87.8% BA.5 (VOC-22APR-04)
- 4.5% BA.2.75 (VOC-22JUL-01)
- 4.5% BA.4.6 (V-22SEP-01)
- 2.1% BA.4 (VOC-22APR-03)
- 0.6% BA.2 (VOC-22JAN-01)
- 0.5% other

NICE

Source: UK Health Security Agency, Figure 4 SARS-CoV-2 variants of concern and variants under investigation in England: Technical briefing 46. Vs, Variants; VOC, Variant of concern

Global VOC and clinical trial enrolment dates - Community

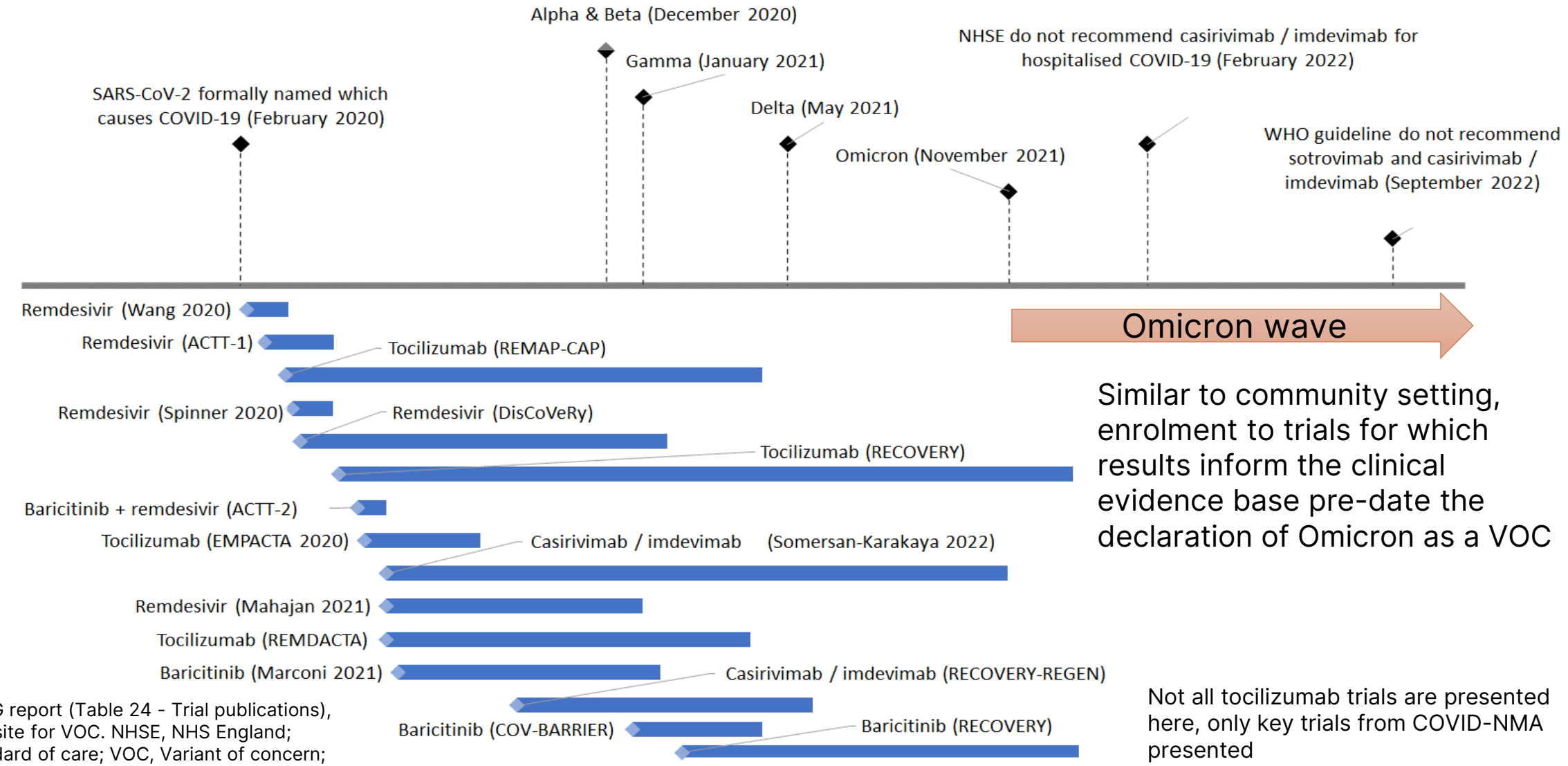
Most of the community trials pre-date the declaration of Omicron as a VOC



Source: AG report (Table 24 - Trial publications), WHO website for VOC. NHSE, NHS England; SoC, Standard of care; VOC, Variant of concern; WHO, World Health Organisation

Global VOC and key clinical trial enrolment dates - Hospital

Most of the hospital setting trials started earlier than the community setting

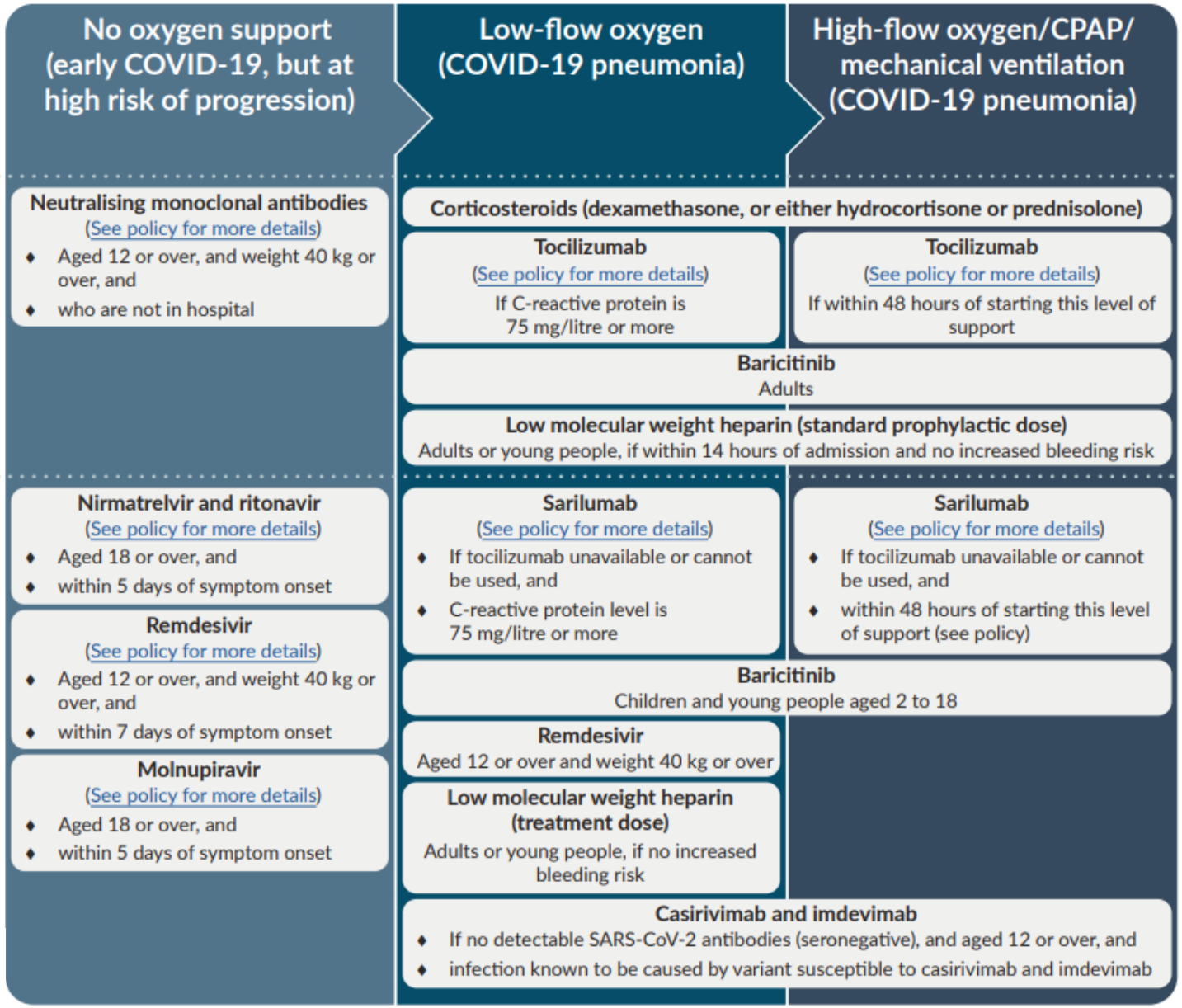


Similar to community setting, enrolment to trials for which results inform the clinical evidence base pre-date the declaration of Omicron as a VOC

Not all tocilizumab trials are presented here, only key trials from COVID-NMA presented

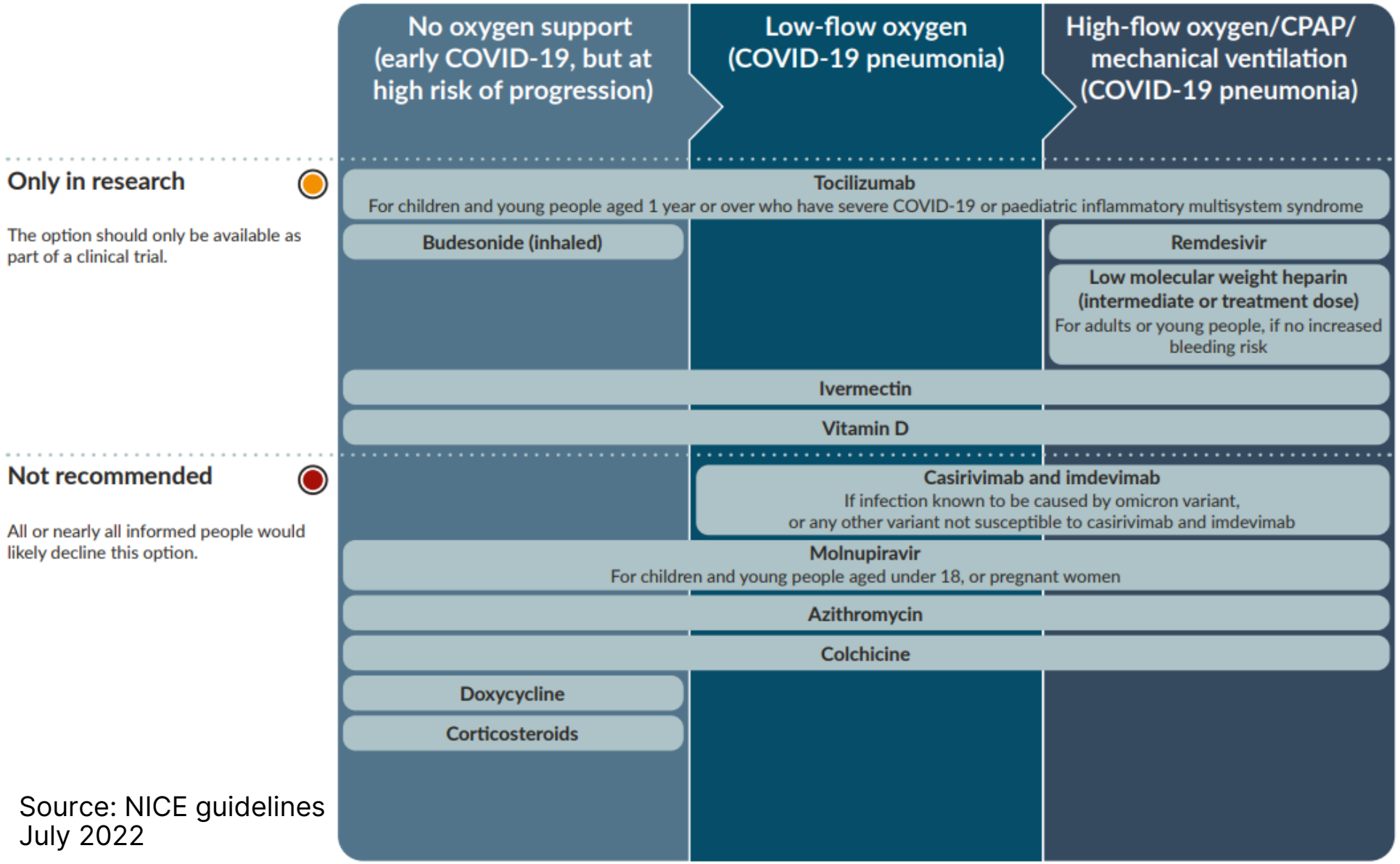
Source: AG report (Table 24 - Trial publications), WHO website for VOC. NHSE, NHS England; SoC, Standard of care; VOC, Variant of concern; WHO, World Health Organisation

COVID-19 treatments – NICE guidelines



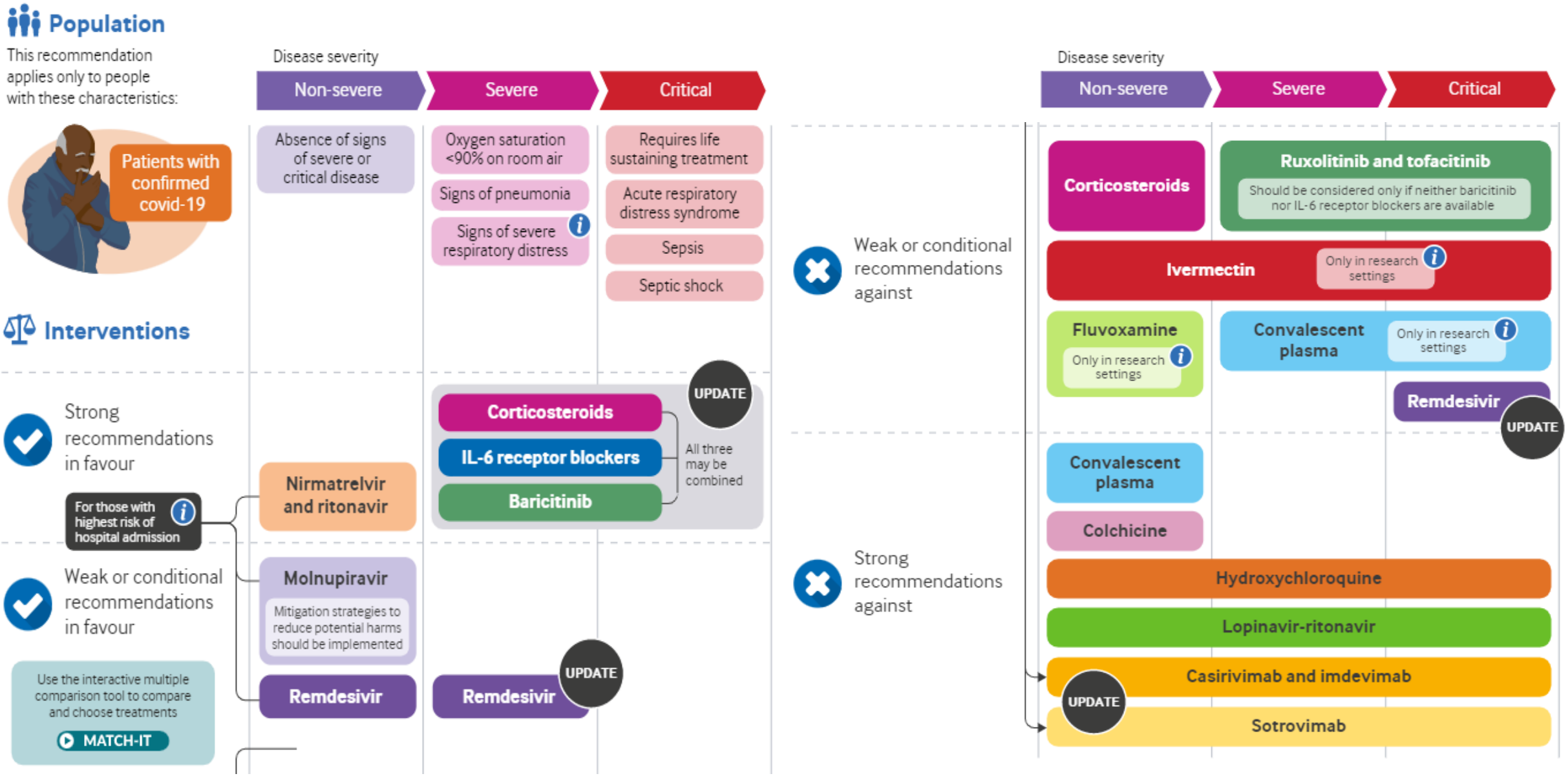
Source: NICE guidelines
July 2022

COVID-19 treatments – NICE guidelines



Source: NICE guidelines July 2022

COVID-19 treatments – WHO guidelines (September 2022)



A living WHO guideline on drugs for covid-19 – 16 September 2022, BMJ 2020;370:m3379

Table shows the recent evidence for reduced efficacy against Omicron

	Evidence	WHO Guidelines (16 September 2022)	NHSE interim policy (Version 6)	MHRA
1.Casirivimab / imdevimab (cas/imd) 2.Sotrovimab	WHO: Meaningful reduction of in vitro neutralization activity strongly suggests absence of clinical effectiveness of monoclonal antibodies such as sotrovimab and casirivimab-imdevimab.	1. Strongly recommend against cas / imd for people with COVID-19 2. Strongly recommend against sotrovimab for people with non-severe COVID-19	1. Commissioning policy withdrawn 2. Commissioning policy for first line use for high-risk non-hospitalised	No subvariant specific marketing authorisation
Tixagevimab / cilgavimab	Focosi and Tuccori 2022* discuss sources showing reduced efficacy against Omicron	No recommendations for high-risk community setting	No commissioning policy	No UK marketing authorisation

WHO: Assays showing loss of neutralisation effect of sotrovimab and casirivimab/imdevimab are sufficient to rule out clinical efficacy, but not sufficient to rule them back in for other variants

NICE

FDA: 'Due to the high frequency of variants circulating within the United States that are not susceptible to the following mAbs, the treatments below are not currently authorized in any U.S. region until further notice by FDA and may not be administered for the treatment of COVID-19 under the EUA':

- REGEN-COV (casirivimab and imdevimab)
- Sotrovimab

*Focosi D, Tuccori M. Pathogens. 2022 Jul 22;11(8):823. (Paragraph 3), https://www.fda.gov, WHO: https://app.magicapp.org/#/guideline/nBkO1E/rec/LA69PM

Section 1 General introduction

- COVID-19 and a constantly changing virus
- Patient and clinical perspectives
- Decision problem & modelling

Patient perspectives (1/5)

Submissions received from 13 organisations, many ran their own surveys

Table: Overview of the patient organisations and their information sources

Patient organisations	Data collection methods for responses
Joint submissions from Blood Cancer UK, Anthony Nolan, Myeloma UK, Leukaemia Care, Lymphoma Action, Chronic Lymphocytic Leukaemia Support	• Leukaemia Care survey: 568 responses, 8% who tested positive received hospital treatment, 37% in community not contacted following positive test, 82.6% community treated said they felt better after the treatment • Other sources include: case studies, patient and carer submissions, research study of 560 people with myeloma
Down's Syndrome Association	Information sources: for example calls, emails, webinars, collaboration with research organisations
Immunodeficiency UK	Survey (11-27 August 2022): 516 responses, 30% shielding, 43% had limited confidence in going out, 59% who tested positive had long term effects
Kidney Care UK	Patient support and advocacy officers, counselling services, social media, responses in newsletters, 3 past surveys during the pandemic
Long Covid Kids	Personal experiences shared in support groups and meetings with families
Long Covid SOS	Social media, direct messages and via Body Politic Slack support group
LUPUS UK	• Survey (16-23 August 2022): 96/204 respondents with COVID-19 and 8 hospitalised, 35% of 88 received community treatment, 30% within 1 day. • Data also supplemented by prior surveys
Multiple sclerosis (MS) Society	Past surveys, research, helpline queries, consultation with medical advisors

Patient perspectives (2/5)

Need for post-exposure treatment options to prevent progression to severe COVID-19 symptoms

- COVID-19 led to severe mental and physical health impacts for some groups
  - worsening of existing underlying condition (57% of 203 multiple sclerosis (MS) survey responders reported MS symptom exacerbation)
- COVID-19 hospitalisations had detrimental emotional/psychological impacts especially when reasonable adjustments were not available
- Some people at high-risk are still shielding, experiencing high levels of anxiety, often unable to work/lead a normal social and/or family life. Carers have made significant adjustments to their own lifestyle
- Positive COVID-19 test can lead to significant stress, anxiety, depression symptoms (72.1% of 568 blood cancer survey responders felt anxious)
- Post-exposure treatment options increase patient and carer confidence in safe access to healthcare, lower anxiety, relieve severe COVID-19 symptoms
  - Oral medications favoured over intravenous (IV) because of logistics, ease of access, preferences

‘Any therapeutic which prevents a hospital stay has a value that extends beyond just the patient, but impacts on their family, as a whole.’ Down's Syndrome Association

‘Having quick and safe access to treatments in the community has been a relief and gives people a bit more confidence to return to their previous routines and activities.’ MS Society

Patient perspectives (3/5)

Challenges to timely access of COVID-19 treatments following a positive test

- Commonly identified barrier to timely access was uncertainty amongst GPs, primary care providers, NHS111, Covid medicines delivery unit (CMDUs) and other referrers around eligibility criteria and the COVID-19 treatment pathway
    - patients and carers needed to persist in advocating for timely access to treatment despite feeling unwell
    - patients and carers reported treatment delays or no treatment
    - people with mild symptoms often not referred for COVID-19 treatment despite meeting the high-risk eligibility criteria. For some people (for example with blood cancer), mild COVID-19 symptoms may quickly progress to severe outcomes
- Unexplained differences in access to treatments for certain subgroups (people in care homes, people from Black or Asian family backgrounds)

‘COVID-19 medications are highly valued but there are problems with gaining access and availability’
Immunodeficiency UK

‘It is essential that treatments are made available in an equitable manner taking account of existing access issues’
Blood Cancer submissions

Patient perspectives (4/5)

Conflicting information on contraindications

- Lupus UK and Kidney Care UK raised concerns about contraindications with some COVID-19 treatments which limited the choice of treatments
- Blood cancer groups noted conflicting messages surrounding contraindications (for example with nirmatrelvir / ritonavir)

Delay and disruption in current care

- Most submissions reported disruptions to their current care
    - regularity of appointments, treatment pathways and routine testing adversely affected
    - Lupus UK survey (43% of responders said their Lupus specific treatment was affected)
    - Carers described disruption to services during the pandemic

‘Interactions should not be considered barriers to access. Clinicians should be able to judge the treatment best suited’
Blood Cancer submissions

‘I had to postpone some medical tests and treatments relating to lupus because I was taking a long time to recover. I was too unwell/fatigued and in pain to attend the appointments’
Lupus UK

Patient perspectives (5/5)

All submissions stated the substantial impact of the relapsing-remitting nature of Long-COVID

- A significant proportion who tested positive for COVID-19 reported long-term health problems lasting several months with severe impacts on physical / mental health and ability to work
- Physical symptoms may affect a single organ or present as a multisystemic cluster
    - examples include cardiovascular system, breathing difficulties, neurological conditions, dysautonomia presenting as postural orthostatic tachycardia syndrome (POTS), fatigue, pain, loss of taste and smell, muscle weakness, sexual dysfunction, disturbance to menstrual cycle, gastrointestinal issues
- Long-COVID should be treated as a high-risk population

'People are seeking out-of-pocket treatments to manage individual symptoms. Some people cannot afford to pay for these treatments giving rise to health inequalities'
Long Covid SOS

'Both children and adults with Long Covid are immunocompromised (maladaptive immune response and T cell exhaustion) and therefore should be treated as high risk, medically vulnerable and offered antivirals as soon as they test positive for repeat Covid infection'
Long Covid Kids

Clinical perspectives (1/3)

Hospital pathways are better defined than community care pathways, early treatment is preferred where possible

Submissions from UK Renal Pharmacy Group, UK Kidney Association, UK Clinical Pharmacy Association (Critical Care), Faculty of Pharmaceutical Medicine

- Current care for COVID-19
    - Key elements: 1) vaccination 2) early treatment for high-risk groups 3) symptomatic treatment if acutely unwell
    - Community care pathways are poorly defined: anecdotal reports of regional differences in community use of antiviral therapies. Surveys report challenges accessing antiviral therapies
    - Early intervention with effective antiviral treatment may reduce numbers who progress to severe illness, lower need for hospitalisation, and reduce mortality
    - Long action of tixagevimab/cilgavimab could be an effective preventative in addition to vaccination in people at highest risk
    - Hospital care pathways are more consistently defined: offerings include supportive care, oxygen therapy, anticoagulation, and anti-inflammatory treatments (for example dexamethasone, baricitinib or tocilizumab)

Clinical perspectives (2/3)

Considerations for triaging hospital treatments, Long-COVID poorly understood with limited treatment options

- Challenges with current care
    - Staffing largely unfunded for pre-hospital treatment in secondary care. The service provided (for example Covid medicines delivery unit (CMDU) triaging and drug delivery/administration) is in addition to routine workload and unlikely to be sustainable
    - Intravenous treatments can be challenging to administer logistically. Difficult for people testing positive for COVID-19 to attend health care facilities. Should be greater availability via more local hubs to administer the drugs with oversight from the centre
    - People with a highly weakened immune system—the risk benefit of adding baricitinib / tocilizumab is not clearcut. Likely some trusts are risk averse and do not use these treatments
    - People with COVID pneumonitis have a straightforward treatment pathway. The pathway is not clear for patients who incidentally test positive in hospital because of timely referral limitations
- Long-COVID
    - Defined inconsistently: it remains poorly understood with no approved treatment options

Clinical perspectives (3/3)

Treatment efficacy concerns with newer variants, people with renal impairment have treatment restrictions

- Unmet need
  - Increasing concern about reactivation of viral activity after initial treatment.
  - Novel treatments for new infections are needed
- Equality issues
  - People with poor kidney function (estimated Glomerular Filtration Rate (eGFR) <30ml/min) and who are not on dialysis have restricted treatment options reflecting limited drug dosing data in chronic kidney disease (CKD)
    - For example remdesivir, nirmatrelvir / ritonavir, baricitinib (eGFR <15ml/min), molnupiravir do not have clinical data for people on dialysis or with renal impairments
  - People from Black or Asian family backgrounds have greater rates of CKD, less likely to have transplants. Over-represented among worst outcomes from COVID-19.
  - People with renal impairments voluntarily shield: they have lost their jobs and social networks. They feel completely unprotected. The mental health toll is immense.
  - Pre hospital treatment has improved outcomes, there are disparities in uptake.

Section 1 General introduction

- COVID-19 and a constantly changing virus
- Patient and clinical perspectives
- Decision problem & modelling

Decision problem for whole population

Community and in-hospital population definitions updated in AG decision problem

Table: Population, intervention, comparators and outcomes from the scope

	Final scope	AG comments / rationale
Population	• People with mild COVID-19 at high-risk of progressing to severe COVID-19 • People with severe COVID-19	• People who are at high-risk of needing hospital care because of COVID-19 • People who have been hospitalised directly because of COVID-19 Definition of 'high-risk' was aligned with the PANORAMIC clinical study, except age 50+ was excluded as a risk factor Subgroup considered: Oxygen needs at hospital admission
Intervention (x8)	Baricitinib*, Casirivimab and imdevimab, Molnupiravir, Nirmatrelvir and ritonavir, Remdesivir, Sotrovimab, Tixagevimab and cilgavimab*, Tocilizumab	All included.

*Note: Baricitinib and tixagevimab and cilgavimab do not currently have UK marketing authorisation

Source: Final scope and Final AG report. AG, Assessment group

Decision problem for whole population

All model outcomes included, except virological outcomes

Table: Population, intervention, comparators and outcomes from the scope

	Final scope	AG comments / rationale
Comparators	• Established clinical management with or without corticosteroids and appropriate respiratory support • The interventions will be compared to each other	• All interventions • Standard of Care – Treatment widely accepted/routinely funded by NHS (includes supplemental oxygen, dexamethasone). Varies across randomised controlled trials.
Outcomes	Mortality, respiratory support needs, time to recovery, hospitalisation (requirement and duration), time to return to normal activities, virological outcomes (viral shedding and viral load), symptoms of post-COVID-19 syndrome, adverse effects of treatment, health-related quality of life	All model outcomes, except virological outcomes were not assessed.

Source: Final scope and Final AG report

AG, Assessment group

Treated in the community, high-risk of hospitalisation

	Molnupiravir (Lagevrio, MSD)	Nirmatrelvir and ritonavir (Paxlovid, Pfizer)	Sotrovimab (Xevudy, GSK)	Tixagevimab and cilgavimab (Evusheld, AstraZeneca)
Marketing authorisation	Adults with at least one risk factor for developing severe illness	Adults who do not need supplemental oxygen and with COVID-19 increased risk for progression to severe	Adults with acute COVID-19 infection no supplemental oxygen, with COVID-19 increased risk for progression to severe	Anticipated MA: adults with COVID-19, who do not need supplemental oxygen and with COVID-19 increased risk for progression to severe*
Mechanism of action	Causes errors in viral genetic code	Viral protease inhibitor (ritonavir 'booster')	Neutralising mAb	Neutralising mAb
Administration	Oral (800mg every 12 hours for 5 days)	Oral (300mg (nirmatrelvir) and 100mg (ritonavir) twice daily for 5 days)	IV (500mg over 30 minutes)	IM (300mg tixagevimab and 300mg cilgavimab)
Price	[redacted] per pack	Pack cost £829	£2209	150mg vial 2 x1.5ml: [redacted] 150mg vial 4 x1.5ml: [redacted]
NHS policy (May 2022) / high-risk	Yes (Third line) / Yes	Yes (First line) / Yes	Yes (First line) / Yes	No / Yes *CHMP adopted an extension to the existing indication for Evusheld to include the treatment of COVID-19

GSK, GlaxoSmithKline; IM, Intramuscular injection; IV, Intravenous injection; mAb, monoclonal antibodies; MSD, Merck Sharp & Dohme

Treated in hospital

Technologies:	**Baricitinib*** (Olumiant, Eli and Lilly)	**Casirivimab / imdevimab** (also for high-risk in community) (Ronapreve, Roche Products)	**Remdesivir*** (also for high-risk in community) (Veklury, Gilead Sciences)	**Tocilizumab** (RoActemra, Roche Products)
Marketing authorisation	Anticipated MA for COVID-19	Prophylaxis and acute COVID-19 infection	Adults and children (at least 4 weeks and 3kg) with: 1. pneumonia who need oxygen (2. Adults and children (at least 40kg) Mild/moderate COVID-19 with at least 1 risk factor for severe illness)	Adults receiving systemic corticosteroids supplemental oxygen/ mechanical ventilation.
Mechanism of action	JAK inhibitor	Neutralising mAb	Inhibits RNA polymerase	Immunomodulator
Administration	Oral (4mg) Optimal duration unclear	IV/SC: 600mg+600mg (Treatment dose)	IV: Day 1-200mg, Oxy: Day2+: 100mg daily (Oxy: min 5, max 10 days; No Oxy: 3 days)	SC/IV: 8mg/kg for 1 hour
Price	£805.56 per pack (28 pack of 2mg or 4mg) (PAS applies)	[redacted]	£340.00 one vial 100mg powder for concentrate for solution for infusion	80mg/4ml vial x 1 = £102.40, 200mg/10ml vial x 1 = £256.00, 400mg/20ml vial x 1 = £512.00 (PAS applies)
NHS policy (May 2022) / high-risk	Yes / NA	No / Yes	Yes / Yes (second line)	Yes / NA

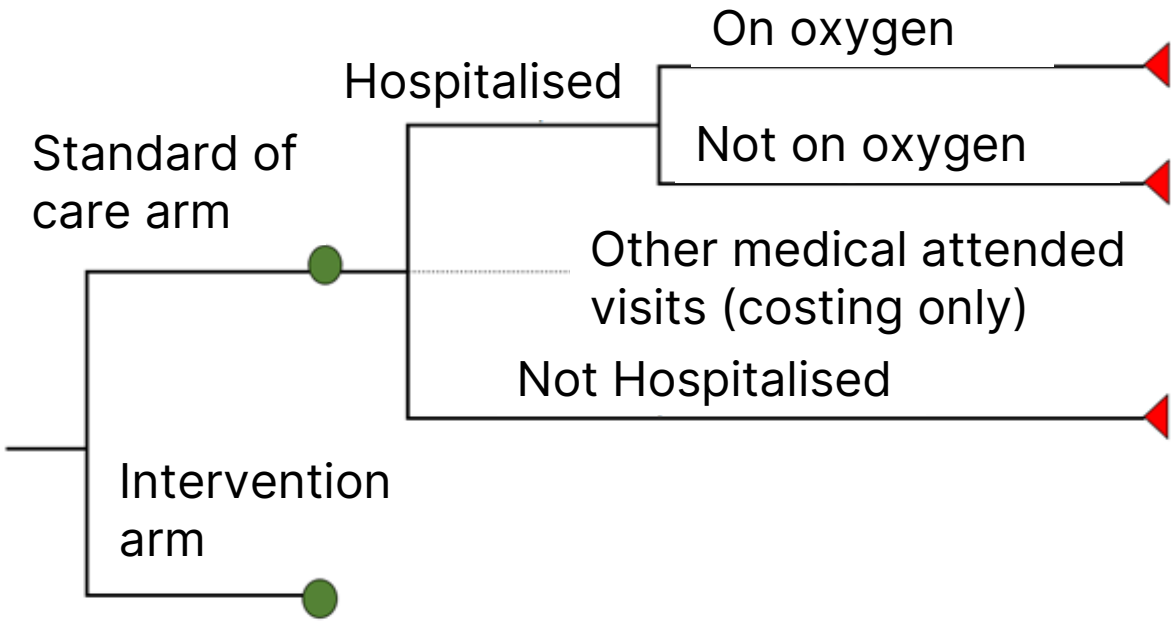
*Baricitinib with remdesivir is also assessed within the AG report

AG, Assessment group; JAK, Janus Kinase; PAS, Patient access scheme; SC, Subcutaneous

Model overview

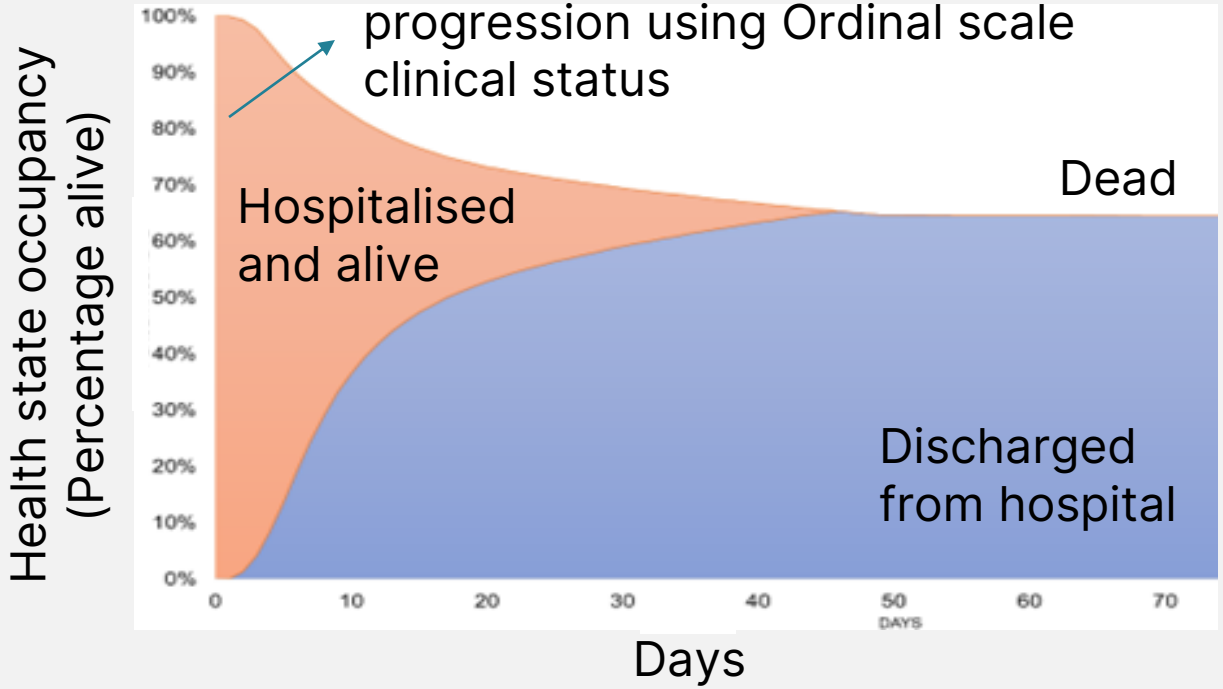
Approaches used by AG to model the community and hospital settings

Figure: Community Model structure



Decision tree model added before the hospital model. People who need hospitalisation enter the hospital partitioned survival model.

Figure: Hospital Model structure



Partitioned survival model with three mutually exclusive health states: discharged from hospital and alive, hospitalised with or without COVID-19, all cause death

NICE Source: Final AG report (Figure 10,12)

Ordinal scale of clinical status

Used to define baseline oxygen needs and estimate changes in hospital oxygen needs

Table: Eight-points ordinal scale of clinical status used in Adaptive COVID-19 Treatment Trial

		Clinical status
Community	1	not hospitalised and no limitations of activities
	2	not hospitalised, with limitation of activities, home oxygen requirement, or both
Hospital	3	hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalisation was extended for infection-control or other nonmedical reasons)
	4	hospitalised, not requiring supplemental oxygen but requiring ongoing medical care (related to Covid-19 or to other medical conditions)
	5	hospitalised, requiring any supplemental oxygen
	6	hospitalised, requiring non-invasive ventilation or use of high-flow oxygen devices
	7	hospitalised, receiving invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO)
	8	Dead

Source: Final AG report (Table 6): Inverted version of scale used for severe influenza requiring hospitalisation recommended by the WHO. Used in the Adaptive COVID-19 Treatment Trial (ACTT-1) and Remdesivir Effectiveness Evaluation Study (REES)

Positioning of treatments based on 8 point scale

Table: Ordinal scale points at which treatments can be given based on marketing/conditional authorisation

	Ordinal Scale						
Intervention	1	2	3	4	5	6	7
Cas and imd							
Molnupiravir	A	A	A				
Tocilizumab					B	B	B
Nirm and rit	A	A	A				
Remdesivir (Rem)	C	C	C	C	C	C	
Sotrovimab	A	A	A				
Tix and Cil	A	A	A				
Baricitinib (Bari)							
Bari and rem							

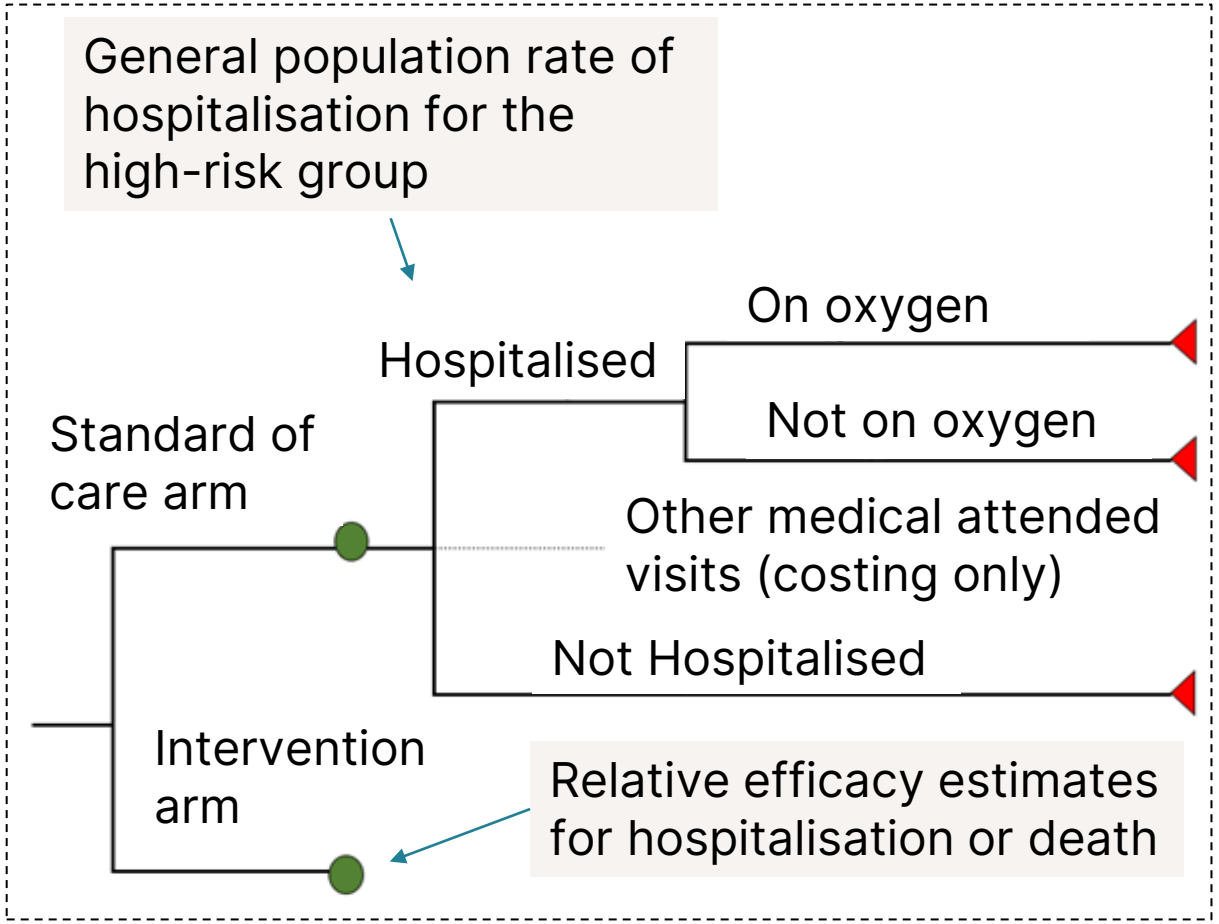
A – with one risk factor of illness to become severe, B - when receiving corticosteroids,
C - in people with pneumonia
Interventions are permitted in cells shaded darker green and not permitted in cells shaded lighter green
Source: Final AG report (Table 7)

Key model inputs and drivers - Community

Key model drivers:

- ✓ Rate of hospitalisation for the high-risk general population
- ✓ Relative risk of all cause mortality at 28 days
- ✓ Outcomes once hospitalised (this is a secondary driver, discussed further on the next slide)

Figure: Community Model structure



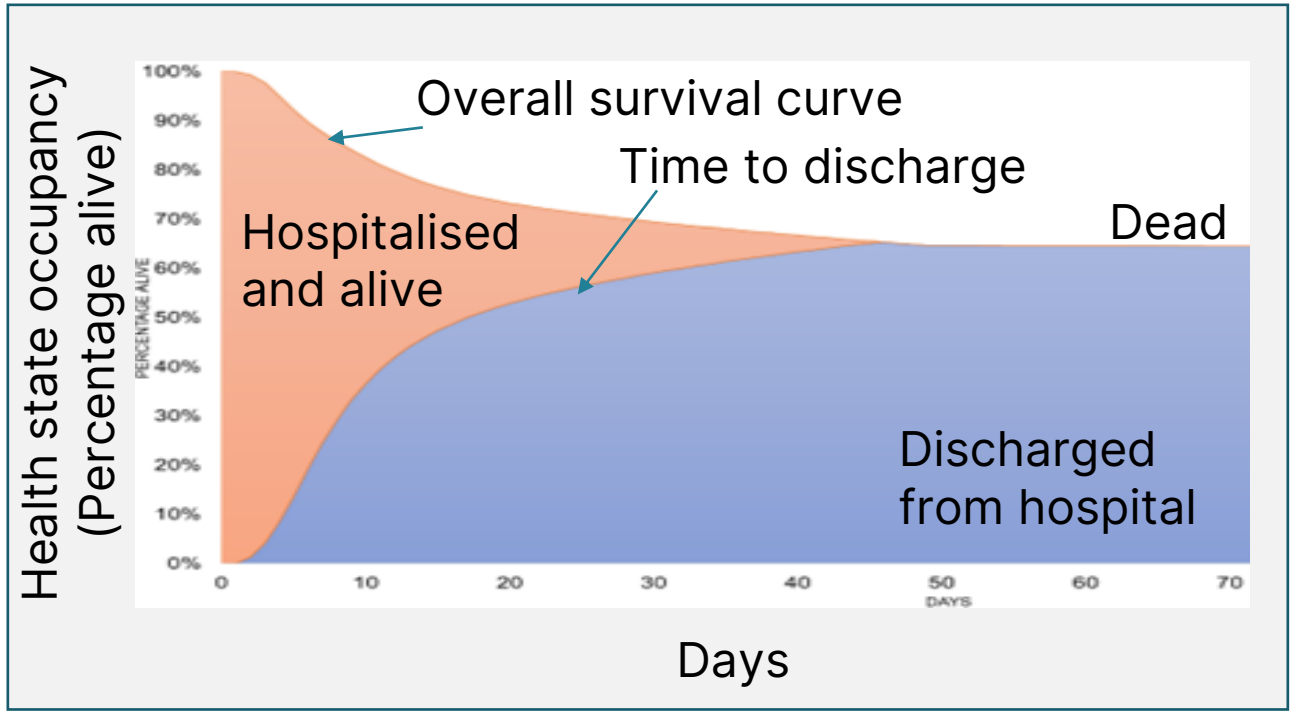
Source: Final AG report (Figure 12)

Key model inputs and drivers – Hospital

Key model drivers for the hospital setting:

- ✓ Clinical outcomes for the standard of care (SoC) arm
  - Overall survival
  - Time to discharge
- ✓ Treatment effect applied to the SoC arm:
  - Hazard ratio of time to all cause death
  - Relative risk of clinical improvement at day 28
  - Hazard ratio of time to discharge

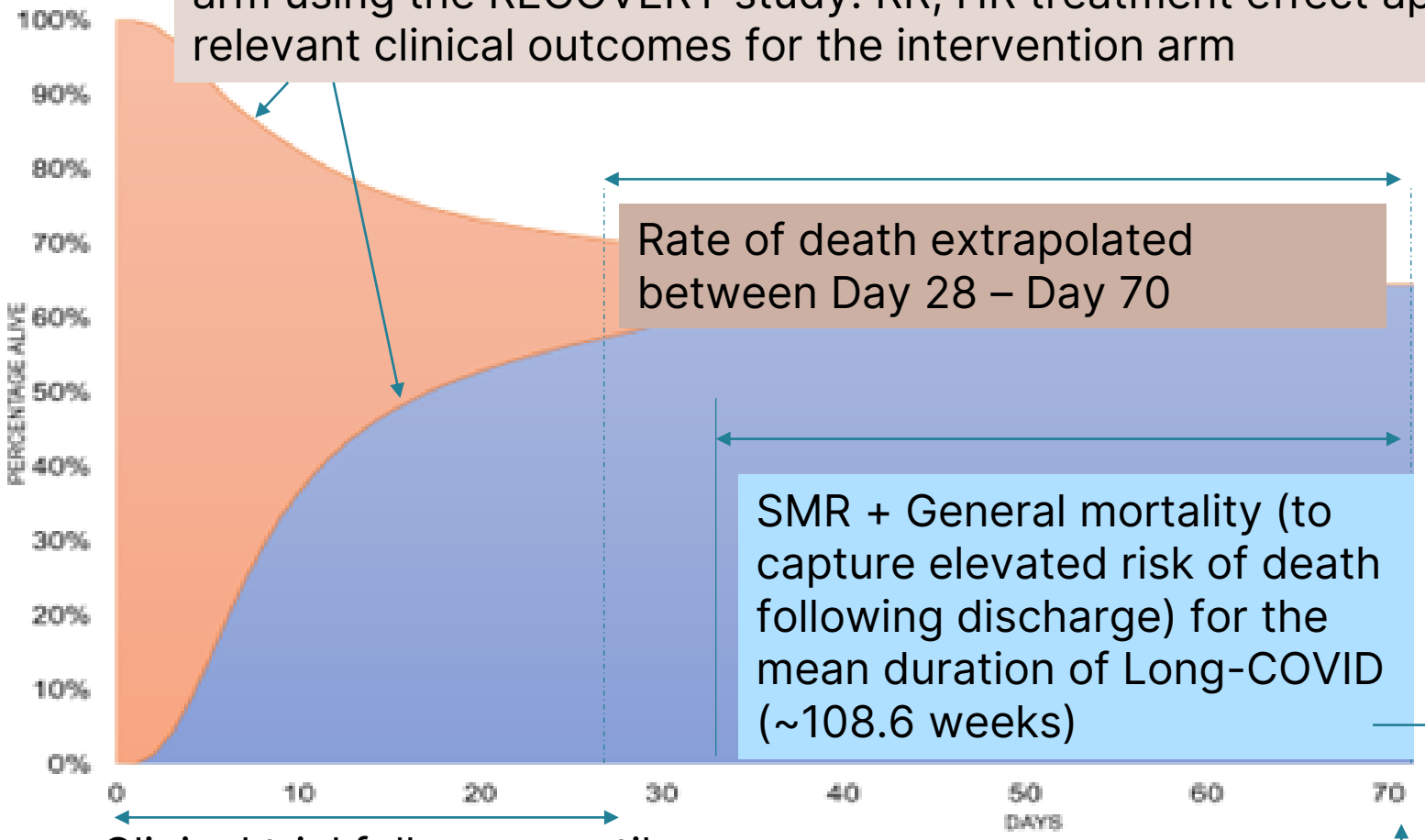
Figure: Hospital Model structure



Source: Final AG report (Figure 10)

Figure of the hospital model structure and key assumptions

Overall survival and time to discharge clinical outcomes: 3 knot hazard spline model fit to SoC arm using the RECOVERY study. RR, HR treatment effect applied to SoC arm to generate relevant clinical outcomes for the intervention arm



Rate of death extrapolated between Day 28 – Day 70

SMR + General mortality (to capture elevated risk of death following discharge) for the mean duration of Long-COVID (~108.6 weeks)

The models were adjusted so that by day 28, 73.5% were alive in cohort that needed oxygen and 86% were alive in cohort that did not need oxygen to reflect the rates from NICE COVID-19 rapid guidelines 2022

Unadjusted general population mortality rate applied after the mean Long-COVID duration

Clinical trial follow-up until Day 28

Everyone is assumed to be discharged from hospital by Day 70

Source: Final AG report (Section 3.2.2). HR, Hazard ratio; RECOVERY platform trial, Randomised Evaluation of COVid-19 thERapY; RR, Relative risk; SMR, Standardised mortality ratio; SoC, Standard of Care

Method adopted for evidence generation

- A systematic review of clinical evidence was not done because of time constraints
- In line with best practice recommendations for the assessment of diagnostics and therapeutics for COVID-19 published by HORIZON 2020, 'living' systematic reviews were used
    - A 'living' systematic review regularly update and incorporate relevant new evidence when it becomes available

COVID-NMA (Primary source)	• Supported by WHO and Cochrane living systematic review • Living systematic review of registered randomised trials. • Evidence collected, appraised, synthesised using pairwise comparisons and NMA methods Analyses update every two weeks
metaEvidence (Secondary source)	• Supported by University Hospital of Lyon and University of Lyon • Living meta-analysis, evidence synthesis and risk of bias of the evidence on COVID-19 therapies. Analysis updated within 24 hours
Excluded sources	• WHO living guideline and NICE COVID-19 rapid guideline • Data not available in format needed for the model

Source: Final AG report (Section 2.1), HORIZON 2020 (Elvidge 2021), NMA, Network meta-analysis; WHO, World health organisation

Data extracted from living reviews and meta-analysis

- Data extracted from COVID-NMA (March-September 2022):
  - time to death, clinical improvement at day 28 or day 60
  - incidence of serious adverse events (SAEs)
- Missing data from COVID-NMA supplemented by meta-evidence
- Where data were not available for clinical improvement or time to discharge a value of 1.0 was used. Sensitivity analysis showed that assuming a hazard ratio of 1 for these two outcomes did not substantially change the ICERs.
- SAEs were excluded because data extracted not suitable for the model

Key limitations:

- Relative treatment effects across different settings assumed comparable to COVID-19 treatment in Summer of 2022
- There were differences in trial cohort age, COVID-19 severity, vaccination status, history of SARS-CoV-2 infection, the SoC at that time, the geographical location and the dosage of the interventions
- Impact of the potential treatment effect modifiers were not assessed
- To overcome the limitations, scenarios with 'mean', 'low' and 'high' efficacy were presented

NICE

Source: Final AG report (Section 2.1 and 2.2). ICER, Incremental cost-effectiveness ratio; SoC, Standard of care

How AG incorporated evidence into model

Multiple evidence sources used including stakeholder submissions

Table: Overview of key Inputs and evidence sources used across both community and hospital models

Input	Assumption and evidence source
Baseline characteristics	Age and sex distribution, absolute number of admissions, death, discharged by age band: ONS May 2022, Intensive Care National Audit & Research Centre COVID-19 report, baseline age, sex, hospitalisation rate from PANORAMIC trial
Dosage	Marketing authorisations, NICE guideline, TACKLE trial, COVID-NMA
Intervention efficacy	COVID-NMA and metaEvidence
Comparator efficacy	COVID-NMA and metaEvidence, RECOVERY study control arm, NICE COVID-19 rapid guideline, Placebo arm ACTT-1
Utilities	Rafia 2022, Wilcox 2017, Hollmann 2013, Age adjustment using Ara 2010, Long-COVID - Evans 2022
Costs and resource use	eMIT, NHS Reference costs, Long-Covid (Vos-Vromans D 2016) costs assumed close to chronic fatigue
Other clinical inputs	Mortality rate post-hospital: Lifetables, Ayoubkhani 2021, Long-COVID prevalence – ONS May 2022, duration – ONS report June 2022, Evans 2022

ACTT-1, Adaptive COVID-19 treatment trial ; eMIT, Electronic market information tool ; ONS, Office for National Statistics; PANORAMIC, Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community clinical study; RECOVERY, Randomised Evaluation of COVid-19 thERapY

Overview of the day

	Chair overview	
Section	Morning	
1	General introduction	Public
2.1	Community setting – Part 1	Public
2.2	Community setting – Part 2	Private
	Afternoon – 2PM	
3.1	Hospital setting – Part 1	Public
3.2	Hospital setting – Part 2	Private

Section 2.1 (public) Community setting

- Recap of key model drivers, technologies and clinical trials
- Clinical effectiveness data
- Key issues:
    - uncertainty around clinical efficacy
    - uncaptured benefits
    - modelling inputs
- Snapshot of results that will be discussed in Part 2

Section 2.1 (public) Community setting

- Recap of key model drivers, technologies and clinical trials
- Clinical effectiveness data
- Key issues:
    - uncertainty around clinical efficacy
    - uncaptured benefits
    - modelling inputs
- Snapshot of results that will be discussed in Part 2

Model overview and key input drivers recap

Figure: Community Model structure

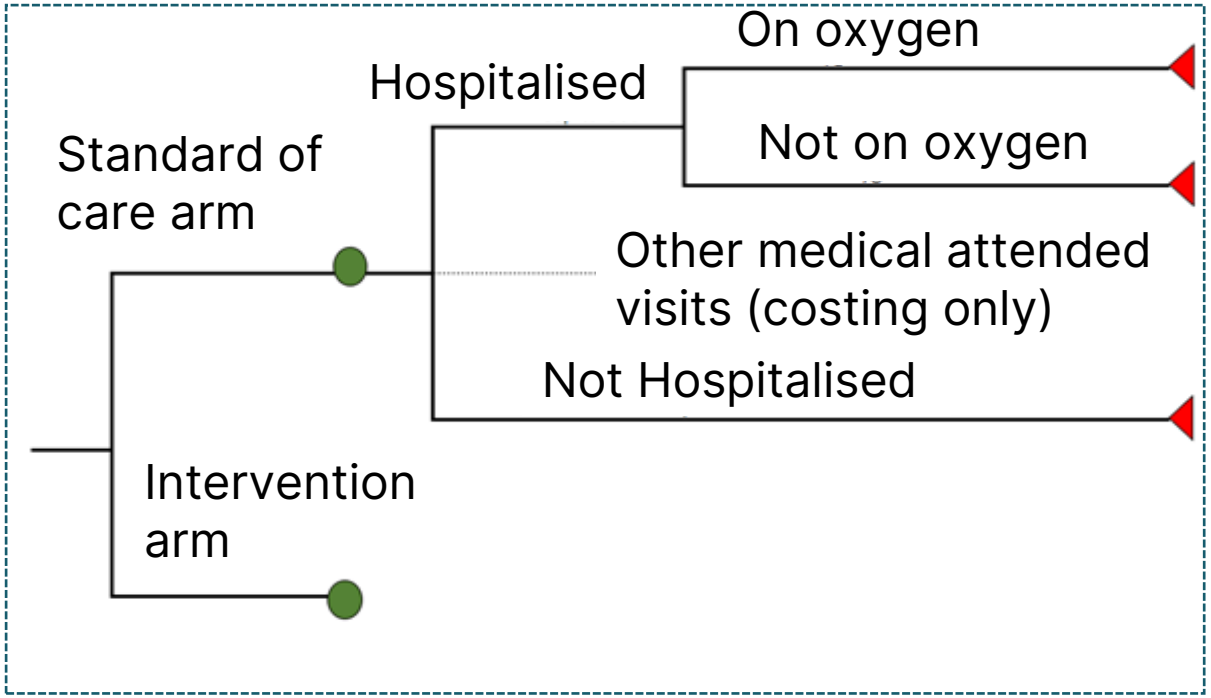
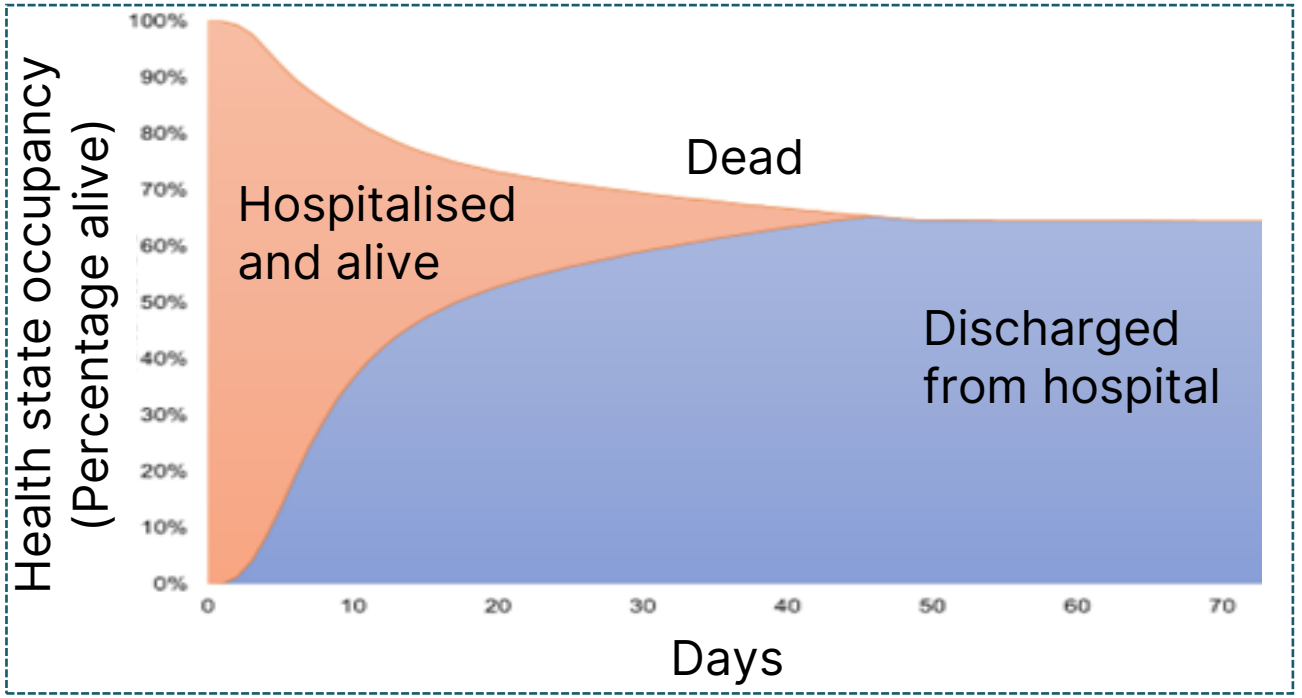


Figure: Hospital Model structure



Key drivers of the community model:

- ✓ Rate of hospitalisation for the high-risk general population
- ✓ Relative risk estimates for hospitalisation or death for the technologies under evaluation
- ✓ Relative risk of all cause mortality at 28 days
- ✓ Outcomes once hospitalised

Key drivers of the hospital model:

- ✓ Hazard ratio of time to all cause death
- ✓ Relative risk of clinical improvement at day 28
- ✓ Hazard ratio of time to discharge

Technologies under evaluation

Table: Technologies overview and key sources of clinical evidence used

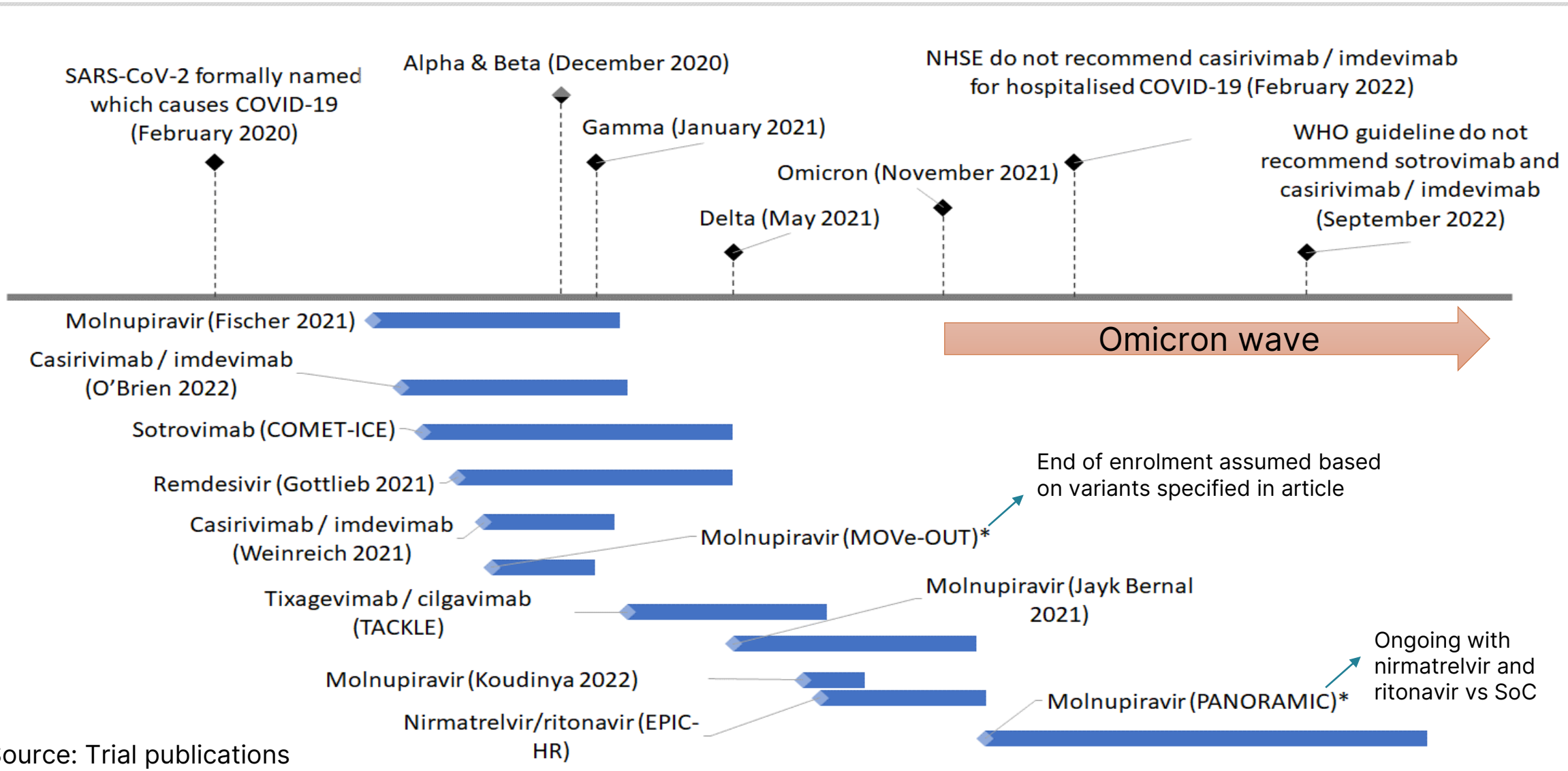
Technology	Mechanism of action	Administration route	Source of clinical evidence (Official name of trial if applicable)
Casirivimab / imdevimab	Neutralising mAb	IV/SC	O'Brien 2022, Weinreich 2021
Molnupiravir	Antiviral	Oral	Caraco 2021 (MOVe-OUT), Fischer 2021, Jayk Bernal 2021, Koudinya Tippabhotla 2022, PANORAMIC 2022
Nirmatrelvir / ritonavir	Antiviral	Oral	Hammond 2022 (EPIC-HR)
Remdesivir	Antiviral	IV	Gottlieb 2021 (PINETREE)
Sotrovimab	Neutralising mAb	IV	Gupta 2022 (COMET-ICE)
Tixagevimab / cilgavimab	Neutralising mAb	IM	Montgomery 2022 (TACKLE)

All clinical data were from Phase 2 or 3 randomised controlled trials with a placebo/standard of care arm. Apart from the PANORAMIC trial, most trial enrolment periods were prior to the Omicron wave.

IM, Intramuscular injection; IV, Intravenous injection; mAb, monoclonal antibodies; SC, Subcutaneous

Global VOC and clinical trial enrolment dates - Community

Most of the community trials pre-date the declaration of Omicron as a VOC



Source: Trial publications

PANORAMIC trial

The study population and outcomes are UK specific, includes the Omicron wave and highly relevant

- Over 25,000 participants randomised to either molnupiravir plus SoC (12,821) or SoC alone (12,963)
- Randomisation period 8th of December 2021 - 27th of April 2022
- 98.9% had at least one dose of vaccine, with 92.6% having three doses
- For SoC group 96 out of 12,484 people (0.77%) were hospitalised or died
- No data were reported relating to the average weight of people or the proportions that needed supplemental oxygen, or invasive mechanical ventilation, on admission to hospital

Source: Butler 2022 (pre-print)

SoC, Standard of Care

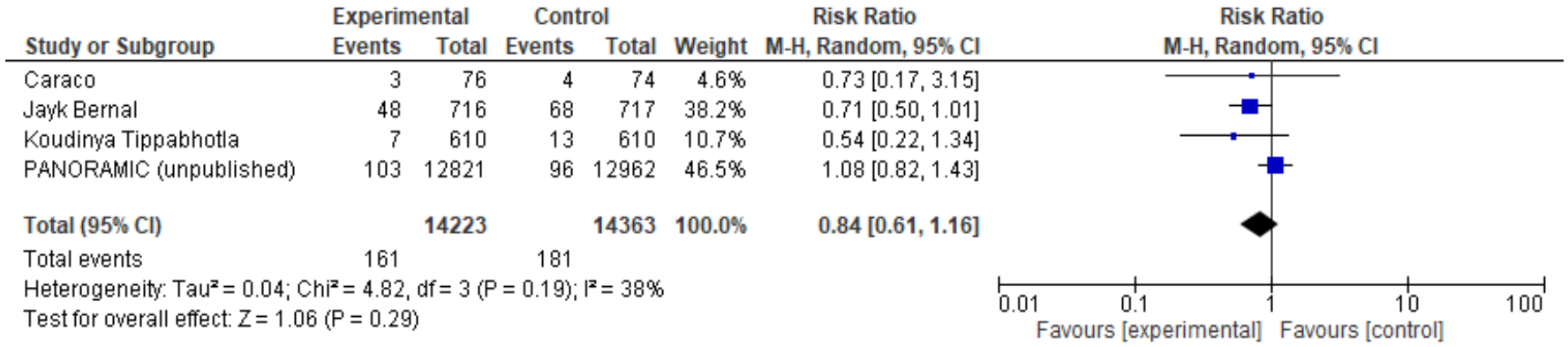
Section 2.1 (public) Community setting

- Recap of key model drivers, technologies and clinical trials
- Clinical effectiveness data
- Key issues:
    - uncertainty around clinical efficacy
    - uncaptured benefits
    - modelling inputs
- Snapshot of results that will be discussed in Part 2

Clinical effectiveness evidence from PANORAMIC

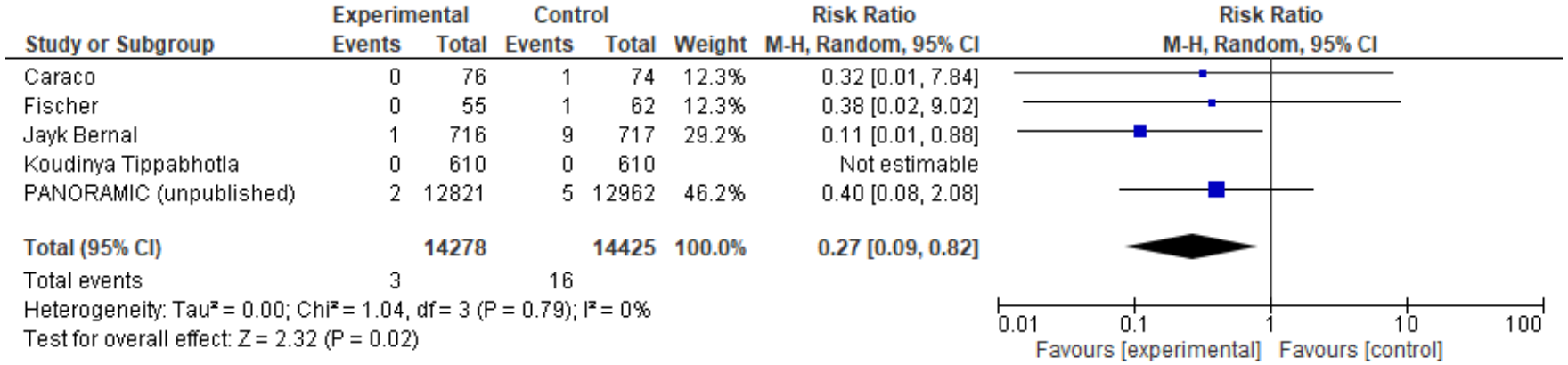
PANORAMIC outcomes were meta-analysed with existing literature for molnupiravir

Figure: Meta-analysis of molnupiravir efficacy in preventing hospitalisation or death



0.82% receiving molnupiravir and SoC were hospitalised or died - risk ratio of 1.08 (95% CI 0.82 to 1.43)
The meta-analysed risk ratio - 0.84 and not statistically significant

Figure: Meta-analysis of molnupiravir efficacy in preventing death



Two deaths events in molnupiravir and SoC and 5 in SoC arm, risk ratio of 0.40 (95% CI 0.08 to 2.08).
Meta-analysed outcome is 0.27 and is statistically significant

Source: AG report (confidential appendix - data no longer confidential Butler 2022 pre-print now public), CI, Confidence interval; SoC, Standard of Care

Summary of data used from PANORAMIC

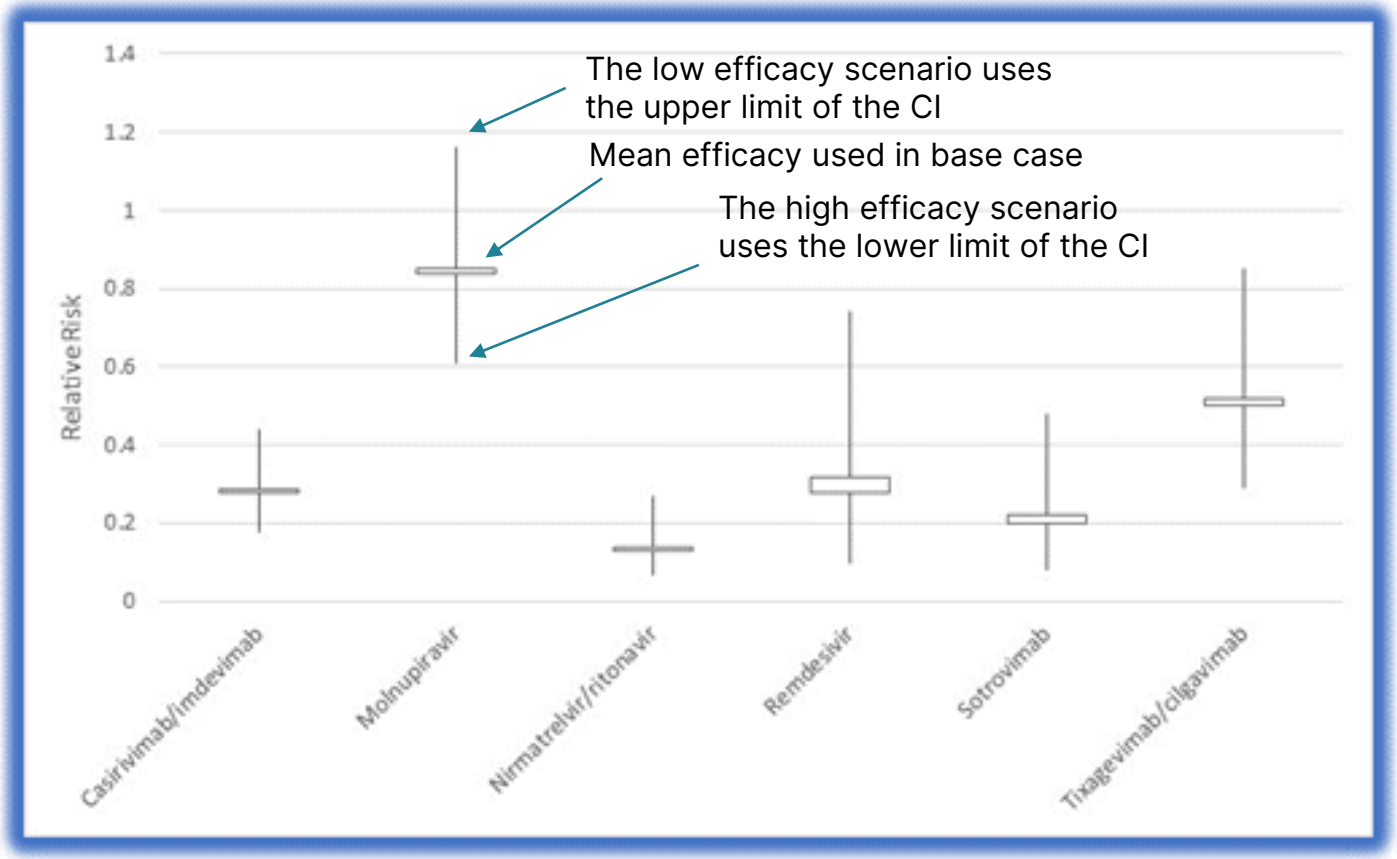
- Updates from the PANORAMIC trial:
  - High-risk hospitalisation rates: 0.77%
  - Baseline characteristics:
    - Age (years) = 56.6
    - Female % = 58.6%
  - Updated molnupiravir clinical effectiveness evidence, meta-analysed with existing evidence base:
    - Risk of hospitalisation or death = 0.84 (95% CI 0.61 to 1.16) (not statistically significant)
    - Risk of death = 0.27 (95% CI 0.09 to 0.82)

Source: Butler 2022 (pre-print). CI, Confidence interval

Relative risk of hospitalisation or death

Despite assuming generalisable efficacy, uncertainty remains in the clinical effectiveness of the interventions

Figure: The relative risk of hospitalisation or death at 28 days



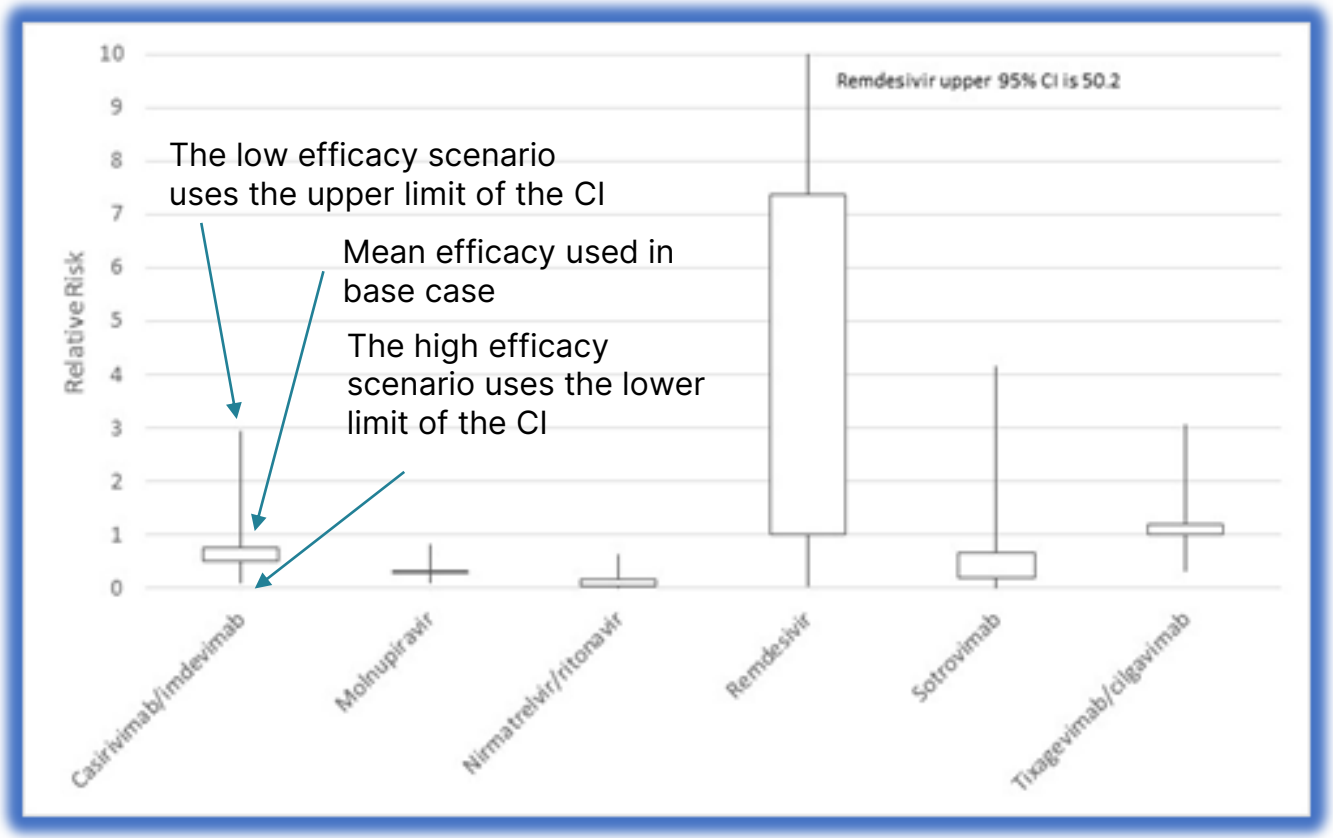
- Only molnupiravir's confidence interval (CI) crosses unity, the width of all CIs differ
- Nirmatrelvir/ritonavir has narrowest CI showing most precision, although the CI associated with this intervention overlaps with that of casirivimab/imdevimab, remdesivir, and sotrovimab indicating considerable uncertainty in the most clinically effective intervention

Source: AG report (confidential appendix - data no longer confidential Butler 2022 pre-print now public)

All-cause mortality relative risk at 28 days

Considerable probability that all interventions except molnupiravir and nirmatrelvir/ritonavir could increase the risk of death

Figure: The relative risk of all-cause mortality at 28 days



- Wide confidence intervals for all treatments observed except molnupiravir and nirmatrelvir/ritonavir
  - For these treatments the upper confidence limits do not exceed 1.0

Wide confidence intervals are because of sample size and limited events observed in each treatment arm

After adding outcomes of PANORAMIC trial, the estimated probability that molnupiravir increases death was approximately 1%.

Source: AG report (confidential appendix - data no longer confidential Butler 2022 pre-print now public)

Section 2.1 (public) Community setting

- Recap of key model drivers, technologies and clinical trials
- Clinical effectiveness data
- Key issues:
  - uncertainty around clinical efficacy
  - uncaptured benefits
  - modelling inputs
- Snapshot of results that will be discussed in Part 2

Key issue: How is 'high-risk' defined and what impact does that have on clinical and cost effectiveness?

High-risk group definition and age

- The definition of 'high-risk' is variable (see next slide) and not defined in marketing authorisations.
- The AG used the PANORAMIC trial to define the 'high-risk' group in the model.
- The key difference in the high-risk definition between the PANORAMIC trial and the AG model was that age was excluded as a risk factor from the AG model:
  - There was no evidence based biological rationale for age greater than or equal to 50 **alone** to be a risk factor and
  - It was considered more equitable to not include age alone as a risk factor

Hospitalisation rate for the high-risk group

- Baseline hospitalisation rate for the SoC used in the model was 0.9%.
  - The rate was taken from Nyberg 2022 which reported on Omicron (B.1.1.529) and delta (B.1.617.2) variants in England
- For the high-risk group, the rate needed to be inflated.
  - Based on Hippsley-Cox 2021 (QCOVID3 model reporting on cause specific hospitalisation rates) and clinical advice, a multiplier of 2 was applied to data from Nyberg 2022
- High-risk group hospitalisation rate for SoC used in the model was 1.8% (equals to 0.9% multiplied by 2).

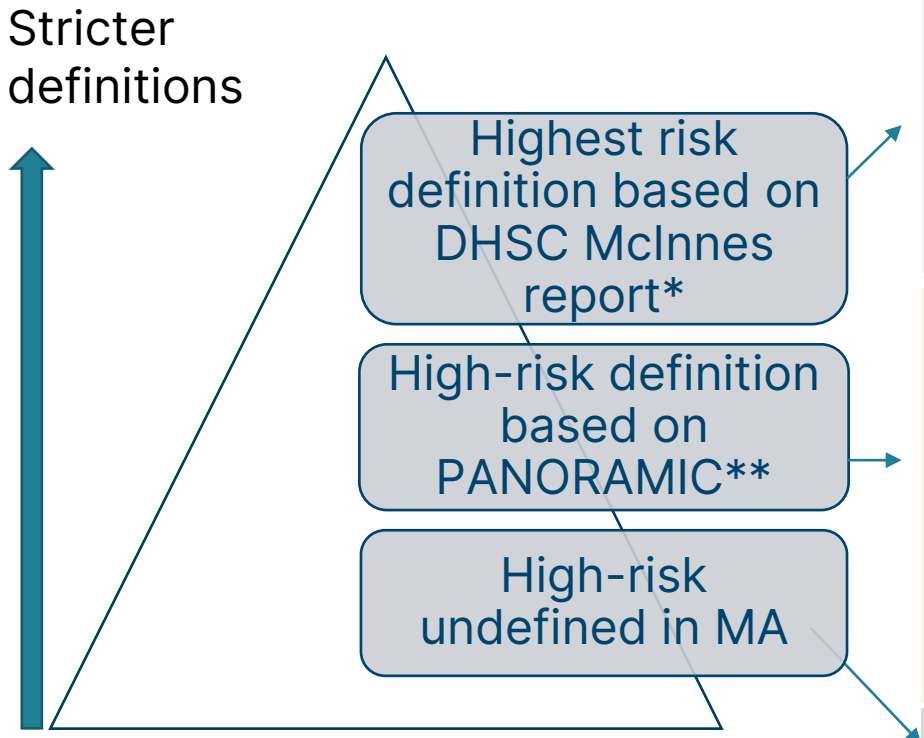
NICE

Source: Draft and Final AG report
SoC, Standard of care

Should age 50 and above be considered an independent risk factor?

Key issue: High-risk definition
Variable definition of 'high-risk of progression'

Figure: Hierarchy of high-risk definition



Advisory group commissioned by DHSC, supported by NHS England RAPID-COVID-19 team

To identify conditions resulting in highest risk of hospitalisation or death. Results would support deployment of approved treatment or prophylaxis.

Poor risk outcomes were assessed using data from population based studies (QCOVID - risk prediction tool and ISARIC), extensive literature searches and expert opinion.

UK wide clinical study sponsored by University of Oxford and funded by NICE to assess clinical effectiveness of new antivirals versus NHS standard of care for COVID-19

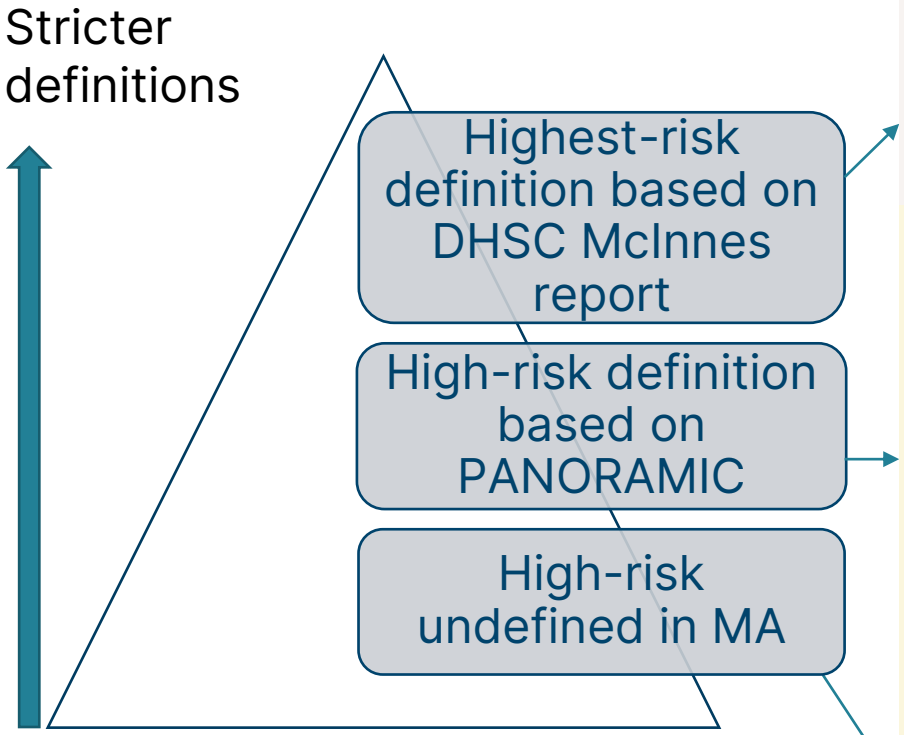
Study is open to people with ongoing symptoms of COVID-19 and a positive COVID-19 test, regardless of vaccination status, aged 50+ or 18+ with pre-existing conditions

26,348 participants recruited across 65 sites

Trials per technology have varied definitions of 'high-risk'

Source: *Defining the highest-risk clinical subgroups upon community infection with SARS-CoV-2 when considering the use of neutralising monoclonal antibodies (nMABs) and antiviral drugs: independent advisory group report **www.panoramictrial.org
DHSC, Department of Health & Social Care; ISARIC, International Severe Acute Respiratory and emerging Infection Consortium; MA, Marketing authorisation

Variable definition of ‘high-risk of progression’



Highest risk of severe COVID-19 (that is, the ultimate risk) despite full adherence with community-wide public health measures including vaccination:

Down’s syndrome and other genetic disorders, Solid cancer, Haematological diseases and recipients of haematological stem cell transplant (HSCT), Renal disease, Liver diseases, Solid organ transplant recipients, Immune-mediated inflammatory disorders, Immune deficiencies, HIV/AIDS, Rare neurological and severe complex life-limiting neurodisability conditions

Aged ≥50 years OR Aged 18-49 with any of the following underlying health condition: Long term lung disease (including chronic obstructive pulmonary disease (COPD), cystic fibrosis and asthma needing at least daily use of inhalers), long term issues (heart or vascular disease, kidney disease, liver disease, neurological disease (including dementia, stroke, epilepsy)), Severe and profound learning disability, Down’s syndrome, Diabetes, Weakened immune system because of disease or treatment (for example sickle cell, HIV, cancer, chemotherapy), having a transplant (for example kidney, liver, heart, lung, bone marrow or stem cells) *A proportion of highest risk group from McInnes report could be excluded in the PANORAMIC trial

TACKLE trial example: at least one risk factor, **including age (≥65 years)** or having at least one comorbidity (cancer, chronic lung disease, obesity, hypertension, cardiovascular disease, diabetes, chronic kidney disease, chronic liver disease, immunocompromised state, sickle cell disease, or smoking)

Source: *Defining the highest-risk clinical subgroups upon community infection with SARS-CoV-2 when considering the use of neutralising monoclonal antibodies (nMABs) and antiviral drugs: independent advisory group report **www.panoramictrial.org Final AG report - TACKLE: Montgomery 2022

Key issue: How is 'high-risk' defined and what impact does that have on clinical and cost effectiveness?

Consultation comments

- There was a need for an optimised high-risk population. The key concerns raised included:
  - Age >50 not included within the high-risk definition
  - Risk of hospitalisation too low
  - The population for the nirmatrelvir / ritonavir trial were less medically complex and therefore the group could not be considered the 'highest risk'

Changes made by AG to address consultee comments

- The latest preprint results from the PANORAMIC trial were used to address some comments. Note Omicron BA.5 not captured in the study results.
- The final AG report included baseline characteristics (age = 56.6) and hospitalisation rates (0.77%) from the PANORAMIC trial.
  - Sensitivity analysis was run with age 54 and 60
  - The AG also ran sensitivity analyses using ranges from the hospitalisation rates provided during consultation: 0.5%, 2.8%, 1.5%, 5% and 10%

Is the high-risk community setting appropriately captured in the AG model? Is there a need for a separate 'highest risk' group?

Source: AG report (confidential appendix - data no longer confidential Butler 2022 pre-print now public)

Key issue: How valid are the clinical trial data given the changing nature of SARS-CoV-2?

Background

- Clinical evidence was collected from 'living' systematic reviews and NMA. Relative treatment effects across different settings were assumed comparable.

Consultation comments

- Lack of systematic approaches to inform the model inputs. For example the full SOLIDARITY study is excluded, nirmatrelvir/ritonavir is based on only one study (EPIC-HR), additional sources like EPIC-SR have not been included
- Inappropriate to assume transferable effectiveness. Treatment effect modifiers such as SoC, SARS-CoV-2 variant, vaccination status, case mix and prior infection not adjusted
  - Differences in variants are not considered, for example treatments like casirivimab/imdevimab do not work against the Omicron variant
- Therefore naive comparisons are done to assess treatment efficacy which introduces significant uncertainty in the clinical efficacy estimates informing the model outcomes
  - It is inappropriate to rank interventions given the underlying heterogeneity in the data
    - Having one incremental analysis for all treatments per setting may not be a valid approach
    - Incremental approach commonly used to assess comparators that displace each other, some treatments may not be mutually exclusive

NICE

Source: Stakeholder consultation comments, Final AG report, NMA, Network meta-analysis; SoC, Standard of Care

Key issue: How valid are the clinical trial data given the changing nature of SARS-CoV-2?

Changes made by AG to address consultee comments

- **Clinical effectiveness data selection**:
  - Best practice recommendations for using living systematic reviews for COVID-19 were followed
  - Results from some clinical evidence sources not used because the outcomes were not reported in a usable format for the model
- **Clinical effectiveness data use**:
  - Points raised by the consultees reported within AG report limitations. Limited evidence available to appropriately adjust treatment effect modifiers. Given the nature of the pandemic and time pressures the most recent and relevant high quality evidence have been incorporated in the model from the PANORAMIC trial.
  - Mean, low and efficacy scenarios were run to account for the heterogeneity in the clinical data.
  - Regarding the full incremental analysis, the net monetary benefit outcomes have been presented alongside the incremental cost-effectiveness results. If a stakeholder does not consider a treatment suitable for the specific population (for example because of susceptible to recent SARS-CoV2 subvariants) they can choose to exclude the intervention from the analysis.

Does the committee agree with the method of clinical effectiveness data selection and use?

NICE

Source: Final AG report

Section 2.1 (public) Community setting

- Recap of key model drivers, technologies and clinical trials
- Clinical effectiveness data
- Key issues:
    - uncertainty around clinical efficacy
    - uncaptured benefits
    - modelling inputs
- Snapshot of results that will be discussed in Part 2

Key issue: Are there broader benefits offered by these new treatments other that immediate clinical benefit?

Table: Additional attributes not taken into account

The following attributes included in the antimicrobial evaluation framework should be considered for the COVID-19 MTA:	AG's response per value
Transmission value (stopping people getting infected)	Transmission value should be low because people with COVID-19 should stay at home (unless intravenous treatment needed).
Enablement (allowing other operations / care to proceed when they wouldn't otherwise)	Enablement should be considered in the discussion and also by the committee. The model is unable to account for this.
Insurance value (the value of having effective treatments)	Insurance value unlikely to be relevant for COVID-19 treatments because mechanism of developing resistance to key antimicrobials is different.

Does the committee agree with AG's responses? Are there additional attributes that should be considered?

Key issue: Are there broader benefits offered by these new treatments other that immediate clinical benefit?

Concerns raised during consultation	AG's responses
Residual impact of some community treatments (for example nirmatrelvir / ritonavir) in terms of improved hospital outcomes and reduced health care resource usage not considered. Instead the model only accounts for the impact of community treatment on hospitalisation rates.	New sensitivity analysis has been run where more people from the community enter a lower ordinal state (less a severe cohort where lower proportion need oxygen in hospital)
The model cannot account for treatment sequencing when antivirals may need to be followed up with monoclonal antibodies.	Modelling this led to counterintuitive results where risk of death was higher if people were receiving treatments other than SoC in hospital
Community treatments may help reduce duration of staff absence (including unpaid carers) to ensure sufficient resourcing of the health and care system and reduced need for emergency care	The AG has acknowledged this limitation within their updated report
The costs avoided (pharmacy costs/reduced risk of hospitalisation) and the QALYs gained are larger with some treatments than others that may have drug-drug interactions	The net monetary benefit approach allows the model to help calculate costs avoided if needed
Societal impact in terms of (productivity, absenteeism, other indirect costs (travel expenses, carer burden), utilities (carer burden), Long-COVID) should be captured to account for the full benefit COVID-19 treatments, in particular oral community based treatments	The evaluation assumes endemic settings and standard NICE methods apply for this case (which exclude broader societal perspective)

Other considerations

Equality considerations

- Immunosuppression, or being immunocompromised, are considered risk factors for more severe COVID-19. People with a weakened immune system may be at a greater risk of severe illness from COVID-19 because of impaired immune defences.
- Vaccination status uptake rates are known to vary based on socioeconomic status and/or ethnicity. This could further heighten risk of infection and/or disease progression in these groups compared with the general population. Subgroups related to these groups should be considered to address equality issues
- Absence of monoclonal antibodies could give rise to an unmet need because some antivirals (for example nirmatrelvir / ritonavir, molnupiravir and remdesivir) are contraindicated. Some people who are at high-risk may not be offered antivirals because of these contraindications.

Are there any equality considerations relevant to the recommendations?

Source: Gilead and GSK submission, Patient organisation submissions

Section 2.1 (public) Community setting

- Recap of key model drivers, technologies and clinical trials
- Clinical effectiveness data
- Key issues:
    - uncertainty around clinical efficacy
    - uncaptured benefits
    - modelling inputs
- Snapshot of results that will be discussed in Part 2

Key issue: Long-COVID
Clinical assumptions

Background

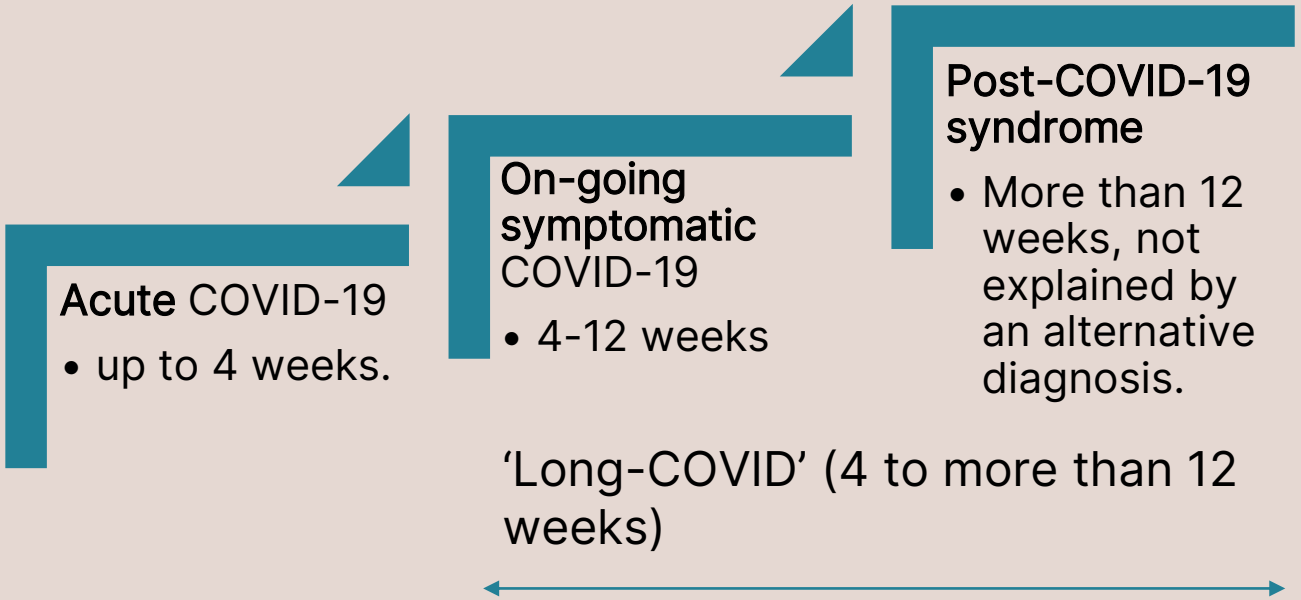
AG definition:

Duration estimated from ONS publication June 2022. This included people with self-reported Long-COVID, defined as "symptoms continuing for more than four weeks after the first suspected COVID-19 infection that were not explained by something else"

The final analysis does not assume that everyone must have Long-COVID for at least 4 weeks.

Base case: Mean duration of Long-COVID is 108.6 weeks (Lognormal distribution)

Figure: NICE COVID-19 rapid guideline definition of Long-COVID split by duration of signs and symptoms



Source: Final AG report (Section 3.2.9), COVID-19 rapid guideline: managing the long-term effects of COVID-19 - NICE, RCGP, and SIGN. ONS, Office of national statistics

Key issue: Long-COVID

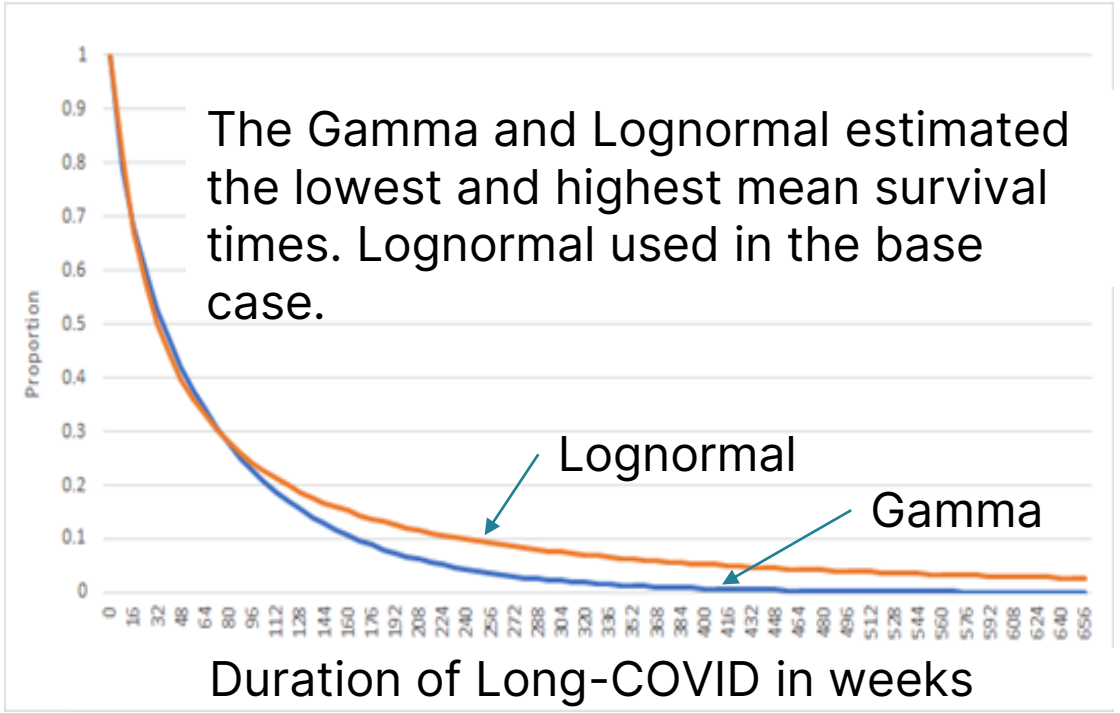
Analysis background

- Rates of Long-COVID assumed to be 10% among high-risk community setting and 100% amongst hospitalised setting (ONS report May 2022)
- 6 month recovery rates validated with literature (Evans 2022)
- Based on available evidence, same rates are assumed same regardless of treatment type

Consultation comments

- Long-COVID analysis does not differentiate between severity and vaccination status. Long-COVID may be more prevalent in SoC arm. It may be useful to test residual effect community treatments can have on Long-COVID.
- Error in Long-COVID QALY calculation was identified in the model (addressed now)

Figure: Parametric distributions fitted to 12 week, 1 year and 2 year estimates from ONS



Source: Stakeholder consultation comments, Final AG report (Section 3.2.9)

ONS, Office of National Statistics; QALY, Quality adjusted life years; SoC, Standard of care

AG response: Duration of Long-COVID assessed in sensitivity analysis and outcomes are considered informative despite limitations with the approach
No evidence identified for hospital treatment effectiveness for Long-COVID

Key issue: Long-COVID

Cost and utility (health-related quality of life) assumptions

Background

- Management costs of Long-Covid were assumed to be comparable to chronic fatigue syndrome (CFS). Annual cost per person with Long-COVID of £1,013 was assumed based on resource use collected from a Netherlands CFS study and NHS cost inflation pay and price indices

- Utility loss (0.13) was informed by Evans 2022 (PHOSP COVID) study for people with Long-COVID. The value was comparable for people following severe sepsis. The utility loss was applied for the full duration of Long-COVID.

Consultation comments

- Costs: No considerations were made for serious implications of Long-COVID. Therefore cost of Long-COVID may be underestimated. Relevant unit costs for Long-COVID clinics and rehabilitation centres in the UK may be available and more appropriate to use

- Utility: There are known differences in the variable severity levels of Long-COVID, assuming the same utility loss may underestimate the cumulative utility loss for Long-COVID.

Changes made by AG to address consultee comments

- In a sensitivity analysis, a higher cost of £2,500 per year per person was assumed to account for organ damage and additional consequences not associated with chronic fatigue
- The utility source was recommended by multiple professional organisations within their submission statements to NICE. No changes were made to the utility loss value.

Source: Stakeholder consultation comments, Final AG report

Key issue: Utilities used in the community model

Current utility assumptions may disadvantage community treatments

Background

- Because of time constraints a formal systematic review for utility estimates was not done. The AG used utility decrement from Rafia 2022 which was used for a cost-effectiveness analysis for remdesivir
- People at high-risk in community without Long-COVID have same age-sex adjusted general population utility

Consultation comments

- Consultees commented that the utility estimates were a proxy from recurrent Clostridium difficile infection and influenza rather than COVID-19.
- Utility is assumed the same for everyone in the community irrespective of limitations or oxygen needs (health state 1 and 2). No disutility applied post hospital discharge. This may disadvantage some community treatments

- No changes to utility values were made by the AG, intravenous treatment utility decrement scenario was run
- The systematic reviews suggested during consultation did not have relevant usable outcomes for the model (Nobari 2021, Hay 2021, Walle-Hansen 2021)

Does the committee agree with the utility estimates and assumptions?

Source: Stakeholder consultation comments, Final AG report

Key issue: Administration costs

Background

- Administration costs not assumed for oral or subcutaneous treatments
- £221 used for intravenous administration (NHS reference code SB12Z)
- Administration costs associated with hospital treatment assumed incorporated in the unit costs associated with hospitalisation

Consultation comments

- Alternative references were suggested during consultation (for example: £173 (2019 prices) was preferred to the £221 used for IV)
- Courier costs for oral treatments were not considered in the community
- Time for full medication reviews to assess drug-drug interactions not considered

Other considerations

- NICE consulted with NHSE, who provided a breakdown of CMDU deployment costs for the community setting
- The next slide provides a short overview
- The AG have updated their analysis with the NHSE costs, noting the limitation that medication review and permanent staffing structures are not accounted for

CMDU, Covid medicines delivery unit

Key issue: Administration costs

CMDU deployment costs provided by NHSE used in the updated AG model

- The average unit cost per person offered treatment with oral antivirals was £410
- The average unit cost per person offered treatment with nMABs (IV infusion) was £820

CMDU costs include

- Perspective of different CMDU delivery models were considered (renal units/ triage/GP hub/nursing team)
- Pay costs: Staff (medical/other clinical), Admin support, dispensing costs
- Non-pay costs: Clinical consumables, medical courier costs, travel costs, stationery, transport hire, room hire, patient travel expenses

Does not include:

- assessment of contraindication costs (costing done prior to nirmatrelvir / ritonavir
- Costs based on permanent staffing structure

Are the NHS England CMDU deployment costs appropriate to use?

CMDU, Covid medicines delivery unit

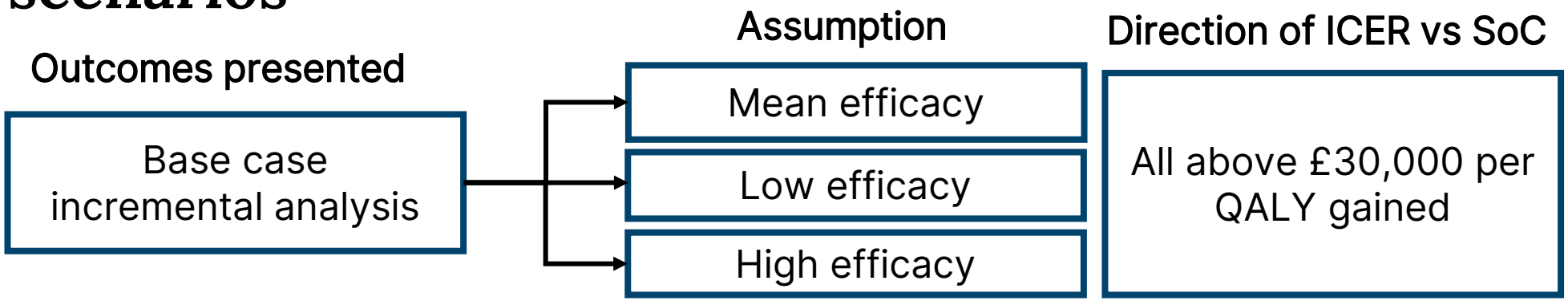
Section 2.1 (public) Community setting

- Recap of key model drivers, technologies and clinical trials
- Clinical effectiveness data
- Key issues:
    - uncertainty around clinical efficacy
    - uncaptured benefits
    - modelling inputs
- Snapshot of results that will be discussed in Part 2

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential list prices for casirivimab/imdevimab, molnupiravir, and tixagevimab/cilgavimab

Community setting: Cost-effectiveness base case outcomes and scenarios



Note - Age can be confounded

Scenarios applied to mean base case efficacy	Base case value	Direction of ICER vs SoC
0.5% hospitalisation rate	0.77%	Large ++ increase for all
1.5%, 2.8%, 5%, 10% hospitalisation rate	0.77%	Large ++ decrease for all
Average age in community 54years	56.6 years	Small decrease for all
Average age in community 60 years	56.6 year	Small-medium increase for most
Duration of Long-COVID halved	108.6 weeks	Small increase for most
Duration of Long-COVID doubled	108.6 weeks	Small-medium decrease for most
Cost of Long-COVID £2,500 annually pp	£1013 annual pp	Minor (~0.2%) reduction for all
Utility decrement for IV administration	No decrement	Minor (~0.2%) increase for two interventions

ICER, Incremental cost-effectiveness ratio; IV, Intravenous; PP, per person; QALY, Quality adjusted life year; SoC, Standard of care, ++ indicates substantial change

Overview of the day

	Chair overview	
Section	Morning	
1	General introduction	Public
2.1	Community setting – Part 1	Public
2.2	Community setting – Part 2	Private
	Afternoon – 2PM	
3.1	Hospital setting – Part 1	Public
3.2	Hospital setting – Part 2	Private

Section 3.1 (public) Hospital setting

- Recap of key issues
- Hospital model structure
- Technologies under evaluation and clinical data
- Key issues: uncertainty around clinical efficacy and modelling inputs
- Snapshot of results that will be discussed in Part 2

Section 3.1 (public) Hospital setting

- Recap of key issues
- Hospital model structure
- Technologies under evaluation and clinical data
- Key issues: uncertainty around clinical efficacy and modelling inputs
- Snapshot of results that will be discussed in Part 2

Key issues relevant for the hospital setting

	Issue	Applies to community / hospital / both?	Discussed?	ICER impact
	Uncertainty around clinical efficacy			
★ 2	How valid are the clinical trial data given the changing nature of SARS-CoV-2?	Both	Partially discussed	Unknown 
	Uncaptured benefits?			
3	Are there broader benefits offered by these new treatments other that immediate clinical benefit?	Both	Discussed	Unknown 
	Modelling inputs			
4	Long-COVID assumptions	Both	Discussed	Unknown 
★ 5	Utility values	Mainly hospital setting / both	Partially discussed	Small 
6	Administration costs	Mainly community setting / both	Discussed	Small 
★ 7	Hospitalisation costs	Mainly hospital setting / both	Partially discussed	Small 

★ Will be discussed in Part 1

Section 3.1 (public) Hospital setting

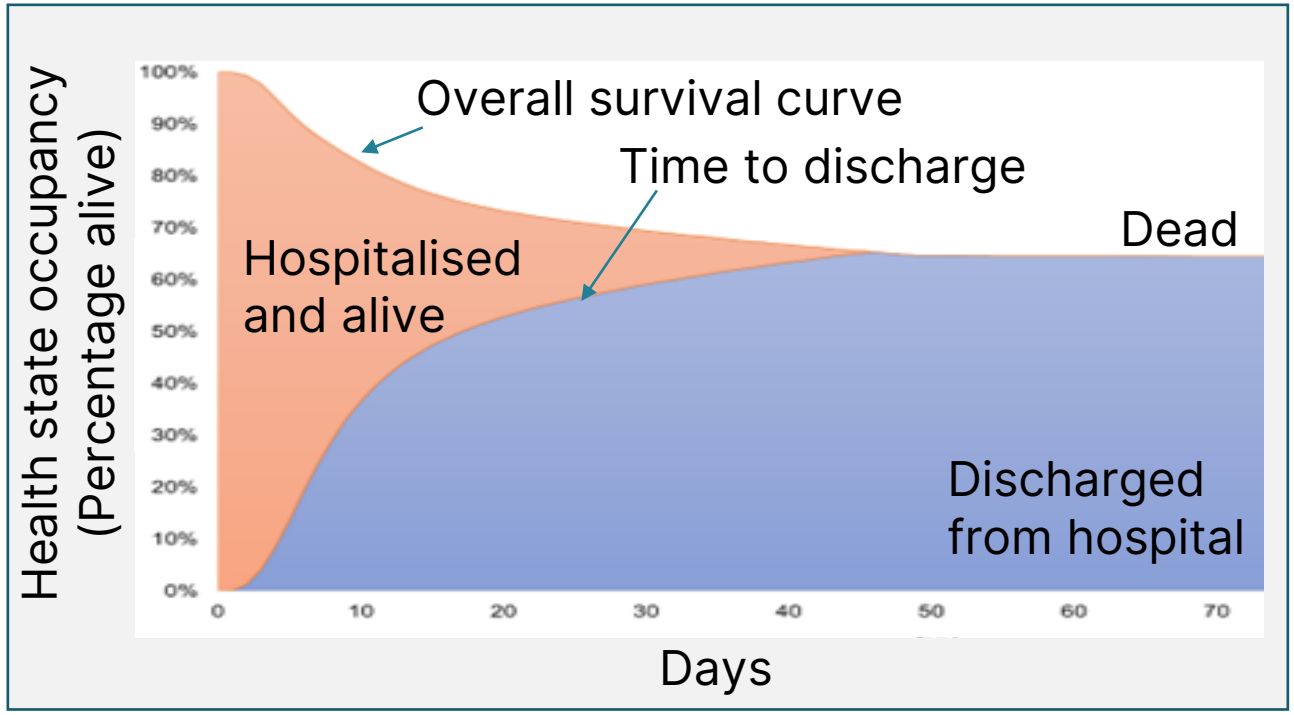
- Recap of key issues
- Hospital model structure
- Technologies under evaluation and clinical data
- Key issues: uncertainty around clinical efficacy and modelling inputs
- Snapshot of results that will be discussed in Part 2

Key model inputs and drivers – Hospital

Key model drivers for the hospital setting:

- ✓ Clinical outcomes for the standard of care (SoC) arm
  - Overall survival
  - Time to discharge
- ✓ Treatment effect applied to the SoC arm:
  - Hazard ratio of time to all cause death
  - Relative risk of clinical improvement at day 28
  - Hazard ratio of time to discharge

Figure: Hospital Model structure

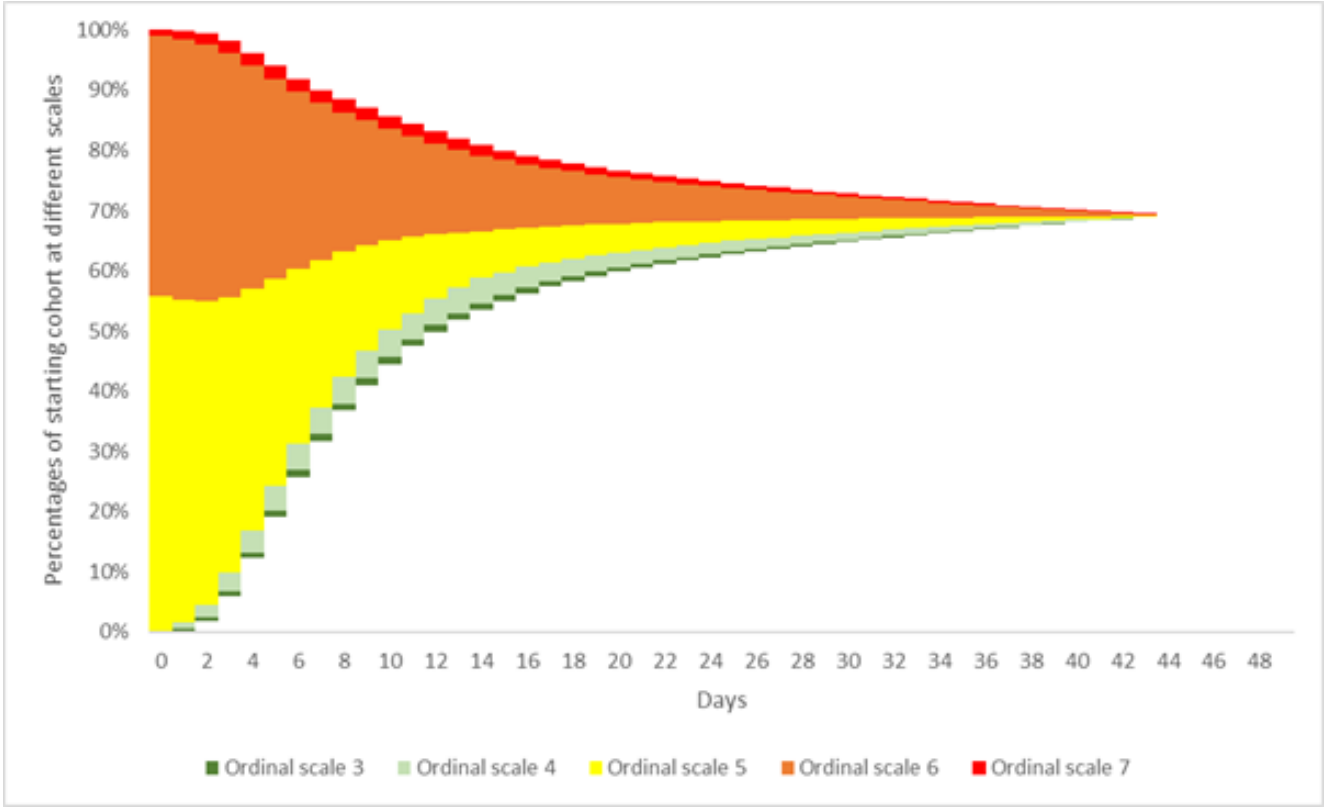


Source: Final AG report

Distribution of ordinal scale

- During hospital stay, the distribution of hospital/oxygen needs are according to Placebo arm of ACTT-1 study
    - The clinical status distribution of people offered SoC in the first 14 days of hospitalisation (baseline and day 15 transitions across the WHO ordinal scales 3-7) were extracted from the ACTT-1 trial

Figure: Example cohort admitted to hospital who need supplemental oxygen and receiving SoC



Source: Final AG report (Section 3.1.1, Figure 11)
ACTT-1, Adaptive COVID-19 Treatment Trial; SoC, Standard of care

Section 3.1 (public) Hospital setting

- Recap of key issues
- Hospital model structure
- Technologies under evaluation and clinical data
- Key issues: uncertainty around clinical efficacy and modelling inputs
- Snapshot of results that will be discussed in Part 2

Technologies under evaluation

Table: Technologies overview and key sources of clinical evidence used

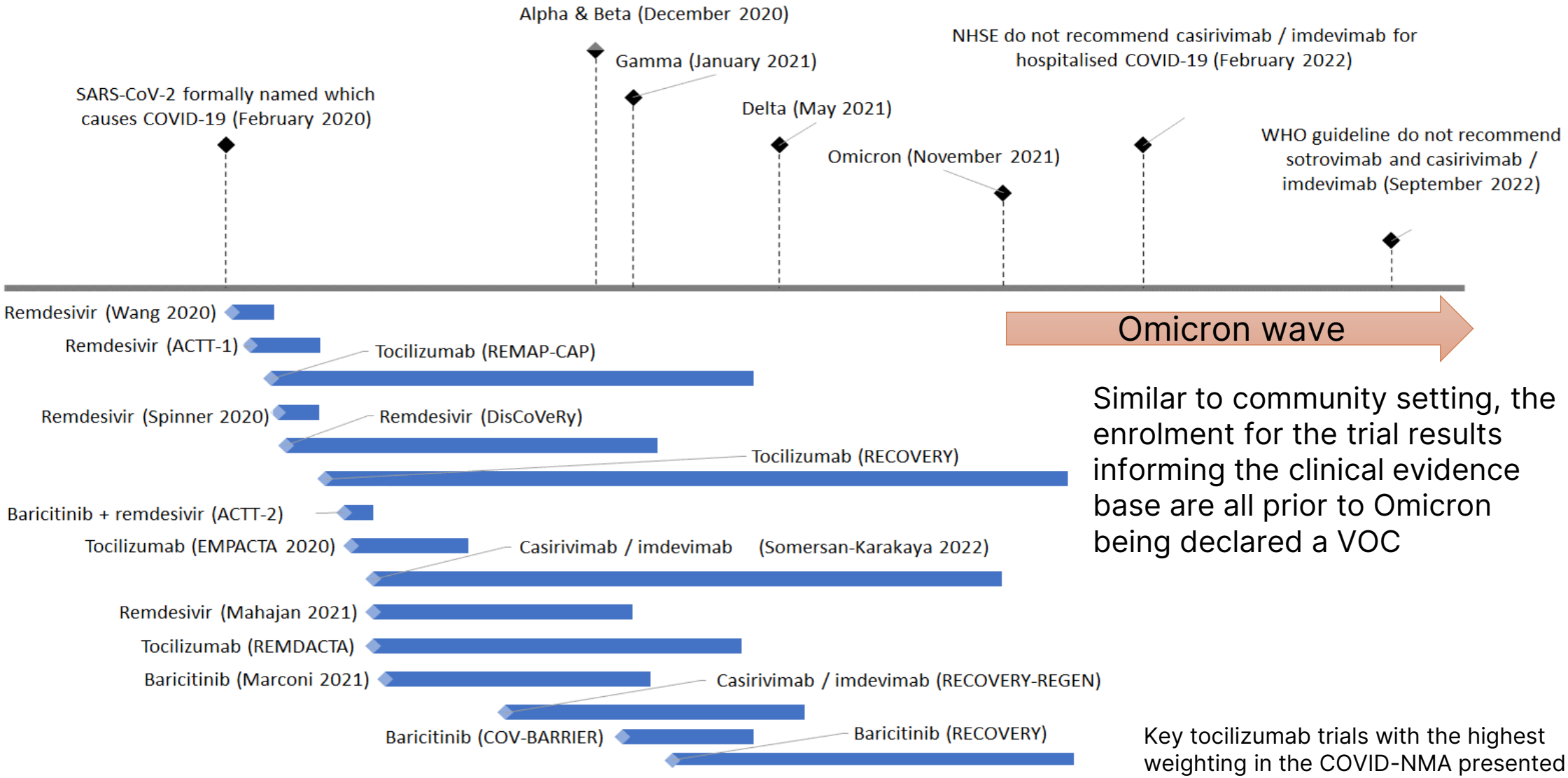
Technology	Mechanism of action	Administration route	Source of clinical evidence (Official name of trial if applicable)
Casirivimab / imdevimab	Neutralising mAb	IV/SC	Somersan-Karakaya 2022, Horby 2022 (RECOVERY-REGEN), RECOVERY 2021
Baricitinib	Immunomodulator	Oral	Marconi 2021, Ely 2022 (COV-BARRIER), Horby 2022 (RECOVERY)
Baricitinib + Remdesivir	Immunomodulator + Inhibit viral RNA synthesis	Oral+IV	Kalil 2020 (ACTT-2)
Remdesivir	Inhibit viral RNA synthesis	IV	Spinner 2020, Beigel 2020, Wang 2020, Mahajan 2021, Ader 2022
Tocilizumab	Immunomodulator	SC/IV	Derde 2021 and Horby 2021 with highest weighting, EMPACTA 2020, Rosas 2021 (REMDACTA)

All clinical data were from Phase 2 or 3 randomised controlled trials with either a placebo or standard or care arm. Most of the trial enrolment periods started earlier than the community trials and prior to the Omicron wave.

IV, Intravenous injection; mAb, monoclonal antibodies; SC, Subcutaneous

Global VOC and key clinical trial enrolment dates - Hospital

Most of the hospital setting trials started earlier than the community setting

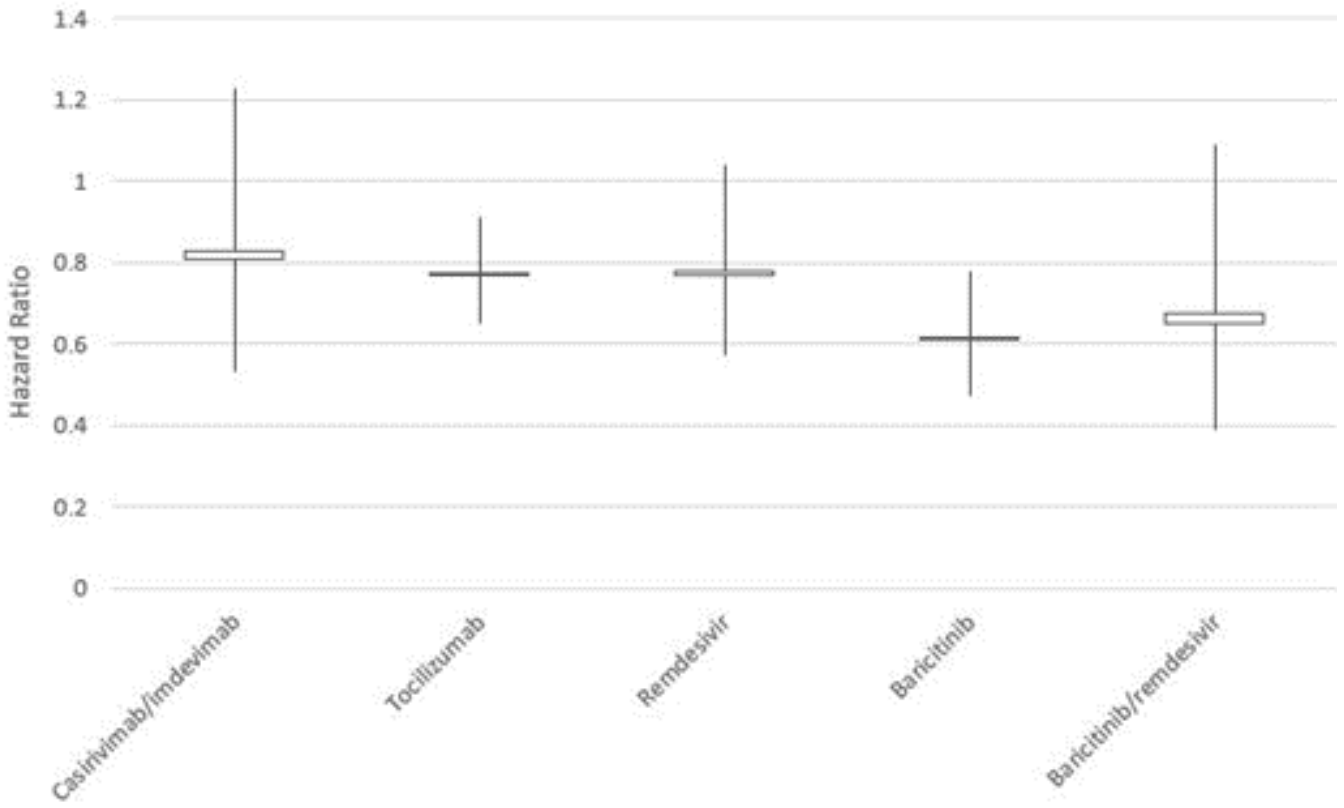


Similar to community setting, the enrolment for the trial results informing the clinical evidence base are all prior to Omicron being declared a VOC

Key tocilizumab trials with the highest weighting in the COVID-NMA presented

Figure showing the hazard ratio of all cause death for hospital interventions

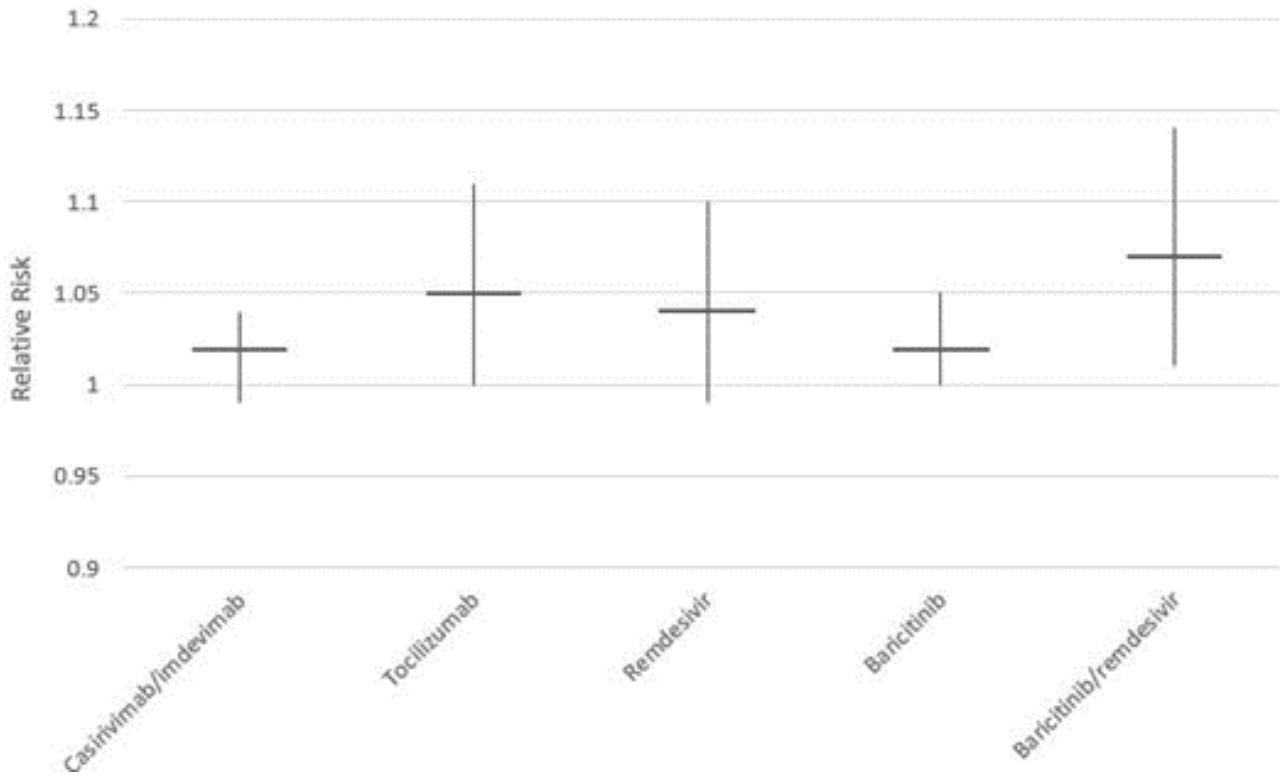
Considerable uncertainty observed across the treatments



- All treatments have a beneficial mean estimate for the HR associated with death.
- The confidence interval of each treatment overlap suggesting considerable uncertainty in the ranked order of clinical effectiveness

HR, Hazard ratio

Figure showing the relative risk of clinical improvement at 28 days for hospital interventions

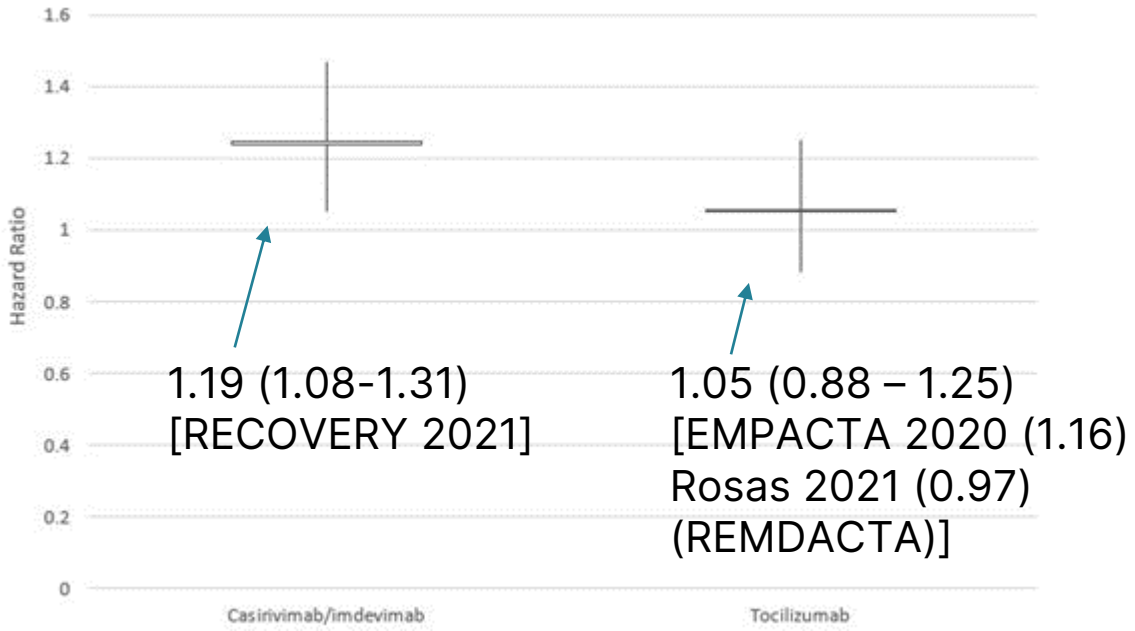


- All treatments have a beneficial mean estimate for the RR associated with clinical improvement
- The confidence interval of each treatment overlap suggesting considerable uncertainty in the ranked order of clinical effectiveness

RR, Relative risk

Figure showing the hazard ratio of time to discharge

Overall clinical evidence from living systematic reviews and final mean values used in the model



- Time to discharge outcomes were reported for only two treatments
- For these treatments beneficial mean estimates for HR associated with time to discharge was reported
- Similar to outcome measures for avoiding death and clinical improvement, the confidence intervals overlaps showing uncertainty in the ranked order of the treatments

HR, Hazard ratio

Section 3.1 (public) Hospital setting

- Recap of key issues
- Hospital model structure
- Technologies under evaluation and clinical data
- **Key issues: uncertainty around clinical efficacy and modelling inputs**
- Snapshot of results that will be discussed in Part 2

Key issue: How valid are the clinical trial data given the changing nature of SARS-CoV-2?

Consultation comments

- Lack of systematic approaches to inform the model inputs. Inappropriate to assume transferable effectiveness.
- Treatment effect modifiers for example SoC, SARS-CoV-2 variant, vaccination status, case mix and prior infection not adjusted
  - Differences in variants are not considered
  - The baseline SoC outcomes may vary based on current SARS-CoV-2 variants (for example ACTT-1 was an early study and the outcomes may not be relevant)
- Therefore naive comparisons are being done to assess treatment efficacy which introduces significant uncertainty in the clinical efficacy estimates informing the model outcomes
  - It is inappropriate to rank interventions given the underlying heterogeneity in the data
    - Having one incremental analysis for all treatments per setting may not be a valid approach
    - Incremental approach commonly used to assess comparators that displace each other, some treatments may not be mutually exclusive

Does the committee have any additional concerns specific to the hospital setting that were not previously addressed?

Source: Stakeholder consultation comments, Final AG report

Key issue: Hospitalisation costs

- AG used National schedule of NHS costs 2019-2020 The consultees have suggested alternative hospitalisation costs which have been used by the AG
    - More appropriate costs based on Sandmann 2021 for ordinal scales should be considered. Suggestion includes using ICD codes for viral pneumonia

Ordinal scale	Previous AG costs using in draft report	Updated AG cost codes and weighted average costs following consultation
3	£378 (non-elective excess bed days)	£248 (DZ11R-V) (Lobar, Atypical or Viral Pneumonia, without Interventions) for a regular day or night admission
4	£390 (Rehabilitation for respiratory disorders (VC40Z) – weighted average)	£563 (DZ19H-DZ19N) (Other Respiratory Disorders) for non-elective short stay
5	£663 (Regular day or Night admission; Other respiratory disorders, single intervention, CC score 0-4 (DZ19K))	£828 (DZ19H-DZ19N) (Other Respiratory Disorders) for non-elective long stay and average length of stay for each currency code
6	£1096 (Adult Critical Care, 0 Organs Supported (XC07Z))	£1977* Same codes and updated 2020-2021 NHS reference costs
7	£1703 (Adult Critical care one or more 1 organs supported (XC01Z-XC06Z) – weighted average)	£2393* Same codes and updated 2020-2021 NHS reference costs

Does the committee agree with the updated costs, are there any limitations to the current approach?

Key issue: Utilities used in the hospital model

Background

- Because of time constraints a formal systematic review for utility estimates was not done. For in hospital - the AG used utility decrement from Rafia 2022 which was used for the cost-effectiveness analysis for remdesivir. For post-discharge, an average utility decrement was applied from Evans 2022 for the duration of Long-COVID.

Consultation comments

- Consultees commented that the in-hospital utility decrements were a proxy from recurrent Clostridium difficile infection and influenza rather than COVID-19.
- Alternative systematic reviews and ordinal scale specific post-discharge utility decrements were proposed during consultation

- No changes to utility values were made by the AG because of the model structure. IV utility decrement scenario was run
- The systematic reviews (Nobari 2021, Hay 2021, Walle-Hansen 2021) suggested did not have relevant usable outcomes for the model

Does the committee agree with the current utility estimates and assumptions?

Table: In-hospital and post-discharge utility decrements

Ordinal score	In-hospital utility decrement applied to general population utility values	Post discharge utility decrement applied Evans 2022 (AG)	Alternative post discharge utility decrement (Haplin 2021)
3	0.36	0.13	0.061
4	0.36	0.13	0.016
5	0.58	0.13	0.155
6	0.58	0.13	0.155

Source: Stakeholder consultation comments (MSD), Final AG report (Table 14)

Section 3.1 (public) Hospital setting

- Recap of key issues
- Hospital model structure
- Technologies under evaluation and clinical data
- Key issues: uncertainty around clinical efficacy and modelling inputs
- Snapshot of results that will be discussed in Part 2

Cost-effectiveness results

All ICERs are reported in PART 2 slides

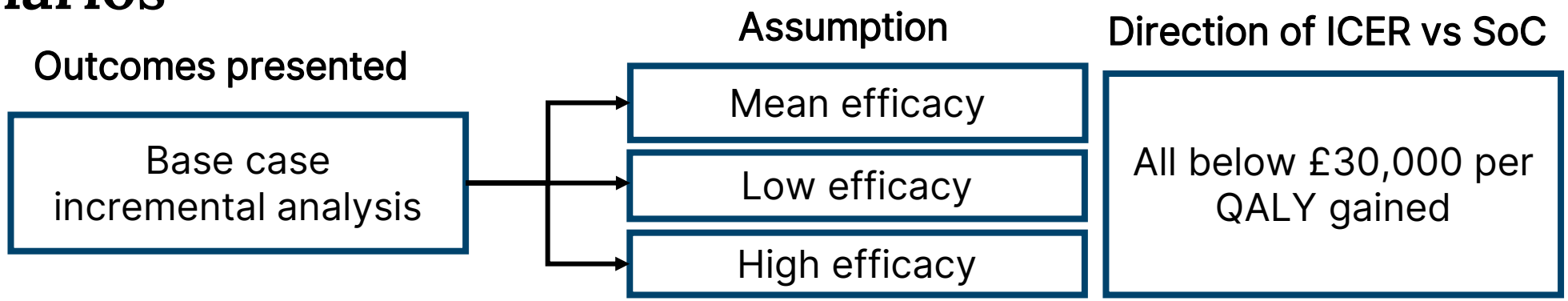
because they include the confidential list prices of:

casirivimab/imdevimab

The Patient Access Scheme prices of:

Baricitinib and tocilizumab.

Hospital setting: Cost-effectiveness base case outcomes and scenarios



Scenarios applied to mean base case efficacy	Base case values	Direction of ICER vs SoC
HR = 1 for time to discharge and clinical improvement for tocilizumab and casirivimab/imdevimab	See AG report	No change for some interventions to large increase for some
Long-COVID duration (doubled)	108.6 weeks	Small to medium increase
Long-COVID duration (halved)	108.6 weeks	Small to medium decrease
Long-COVID annual cost increased to £2,500 annually pp	£1,013 annually pp	Small to medium increase
Changing SMR for people with Long-COVID to 5	7.7	Small decrease
Changing SMR for people with Long-COVID to 10	7.7	Small increase

HR, Hazard ratio; ICER, Incremental cost-effectiveness ratio; PP, per person; QALY, Quality adjusted life year; SMR, Standardised mortality ratio; SoC, Standard of care,

NICE National Institute for Health and Care Excellence