Nirmatrelvir plus ritonavir for treating COVID-19

Partial review of TA878 (ID6262)

Technology appraisal committee C

Chair: Stephen O'Brien

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

Technical team: Anna Brett, Anuja Chatterjee, Adam Brooke, Ross Dent

Company: Pfizer

Background and context to decision problem

Background

ID6262 is a partial review of recommendations for nirmatrelvir plus ritonavir

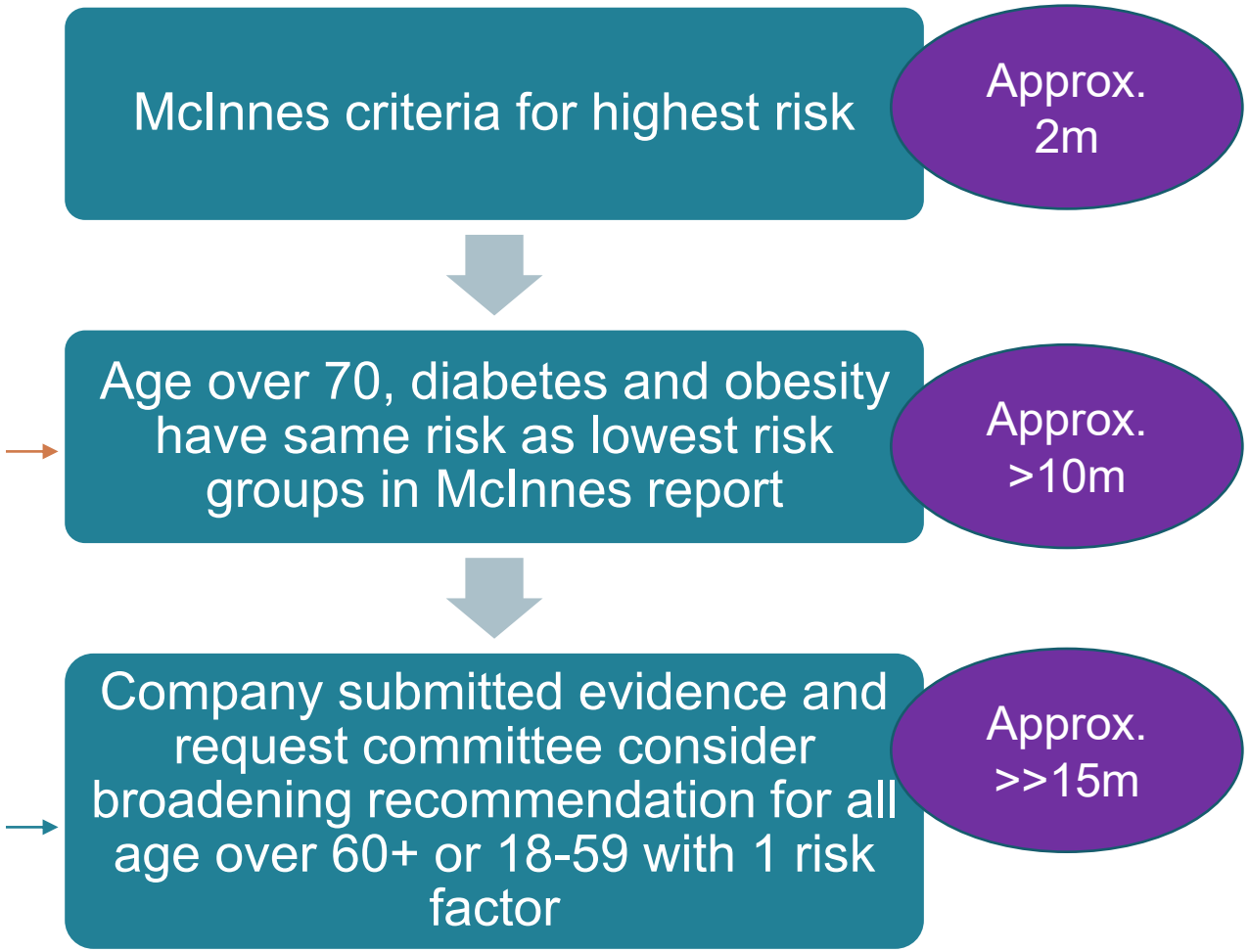
- TA878 recommends nirmatrelvir plus ritonavir for treating COVID-19 in adults, only if they do not need supplemental oxygen for COVID-19 and have an increased risk for progression to severe COVID-19, as defined in the independent advisory group report commissioned by the DHSC (**McInnes report**)
- The Therapeutics Clinical Review Panel modelling group findings on risk of severe COVID-19 outcomes (**Edmunds report**) identified additional groups of people with an increased risk of severe COVID-19 and the company requested to submit evidence supporting the cost effectiveness of nirmatrelvir plus ritonavir in a broader population than McInnes high-risk
- DHSC considered that based on the Edmunds report, age 70 and over, diabetes and obesity were important risk factors but cost-effectiveness should be examined, given MTA guidance
- At its first meeting, committee considered the cost-effectiveness estimates for nirmatrelvir plus ritonavir in a broader population above what NICE considers an acceptable use of NHS resources

Aim of review

Is nirmatrelvir plus ritonavir clinically and cost-effective in a population broader than those identified in McInnes report?

DHSC Antiviral and Therapeutics Task force commissioned a report by John Edmunds (Edmunds report) to assess whether there are any groups that have a risk that is at least as high as McInnes groups (published 29 March 2023)

Company submitted additional evidence for nirmatrelvir plus ritonavir after final draft guidance issued to support expansion of the high-risk group definition

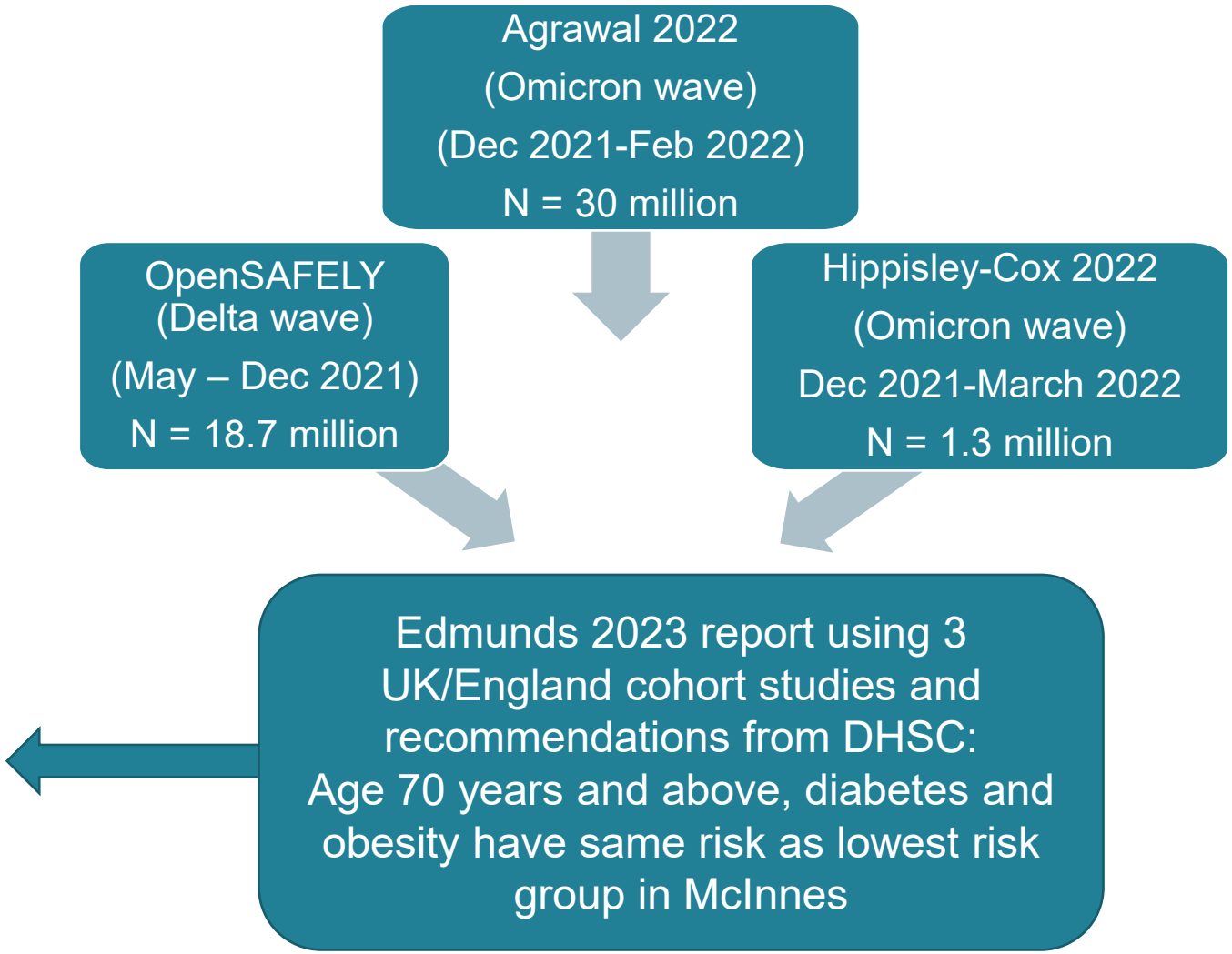


McInnes definition and Edmunds report

McInnes: People more likely to develop severe COVID-19

Some people have a health condition that may increase their risk of getting seriously ill from COVID-19, such as:

- Down's syndrome
- certain types of cancer including leukaemia
- certain conditions affecting the blood, such as sickle cell disease
- people who have had a stem cell transplant
- kidney disease
- liver disease
- people who have had an organ transplant
- conditions affecting the immune system, such as HIV or AIDS, inflammatory conditions or immunodeficiency
- conditions affecting the brain or nerves (MS, motor neurone disease, Huntington's disease etc).

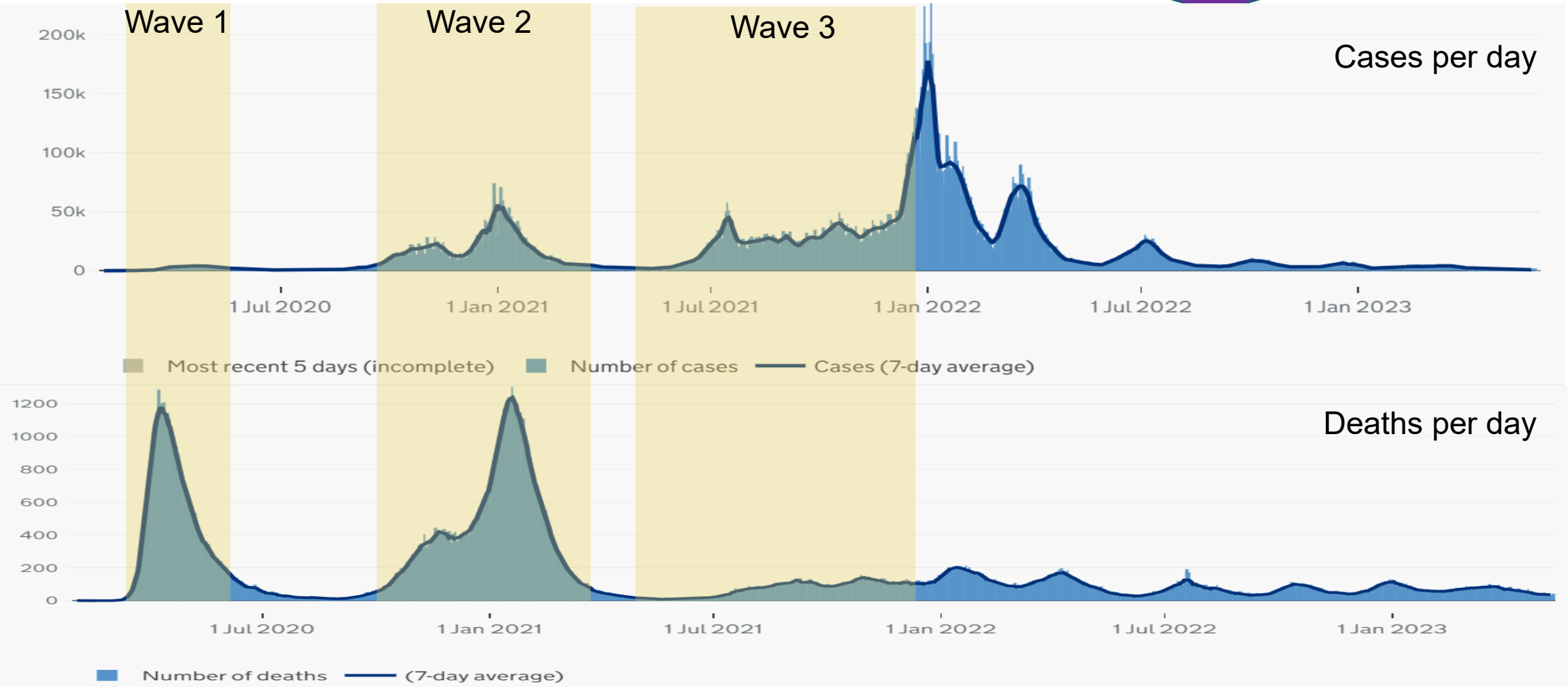


The full list of conditions is available in the independent advisory group report commissioned by the Department of Health and Social Care.

Current endemic context

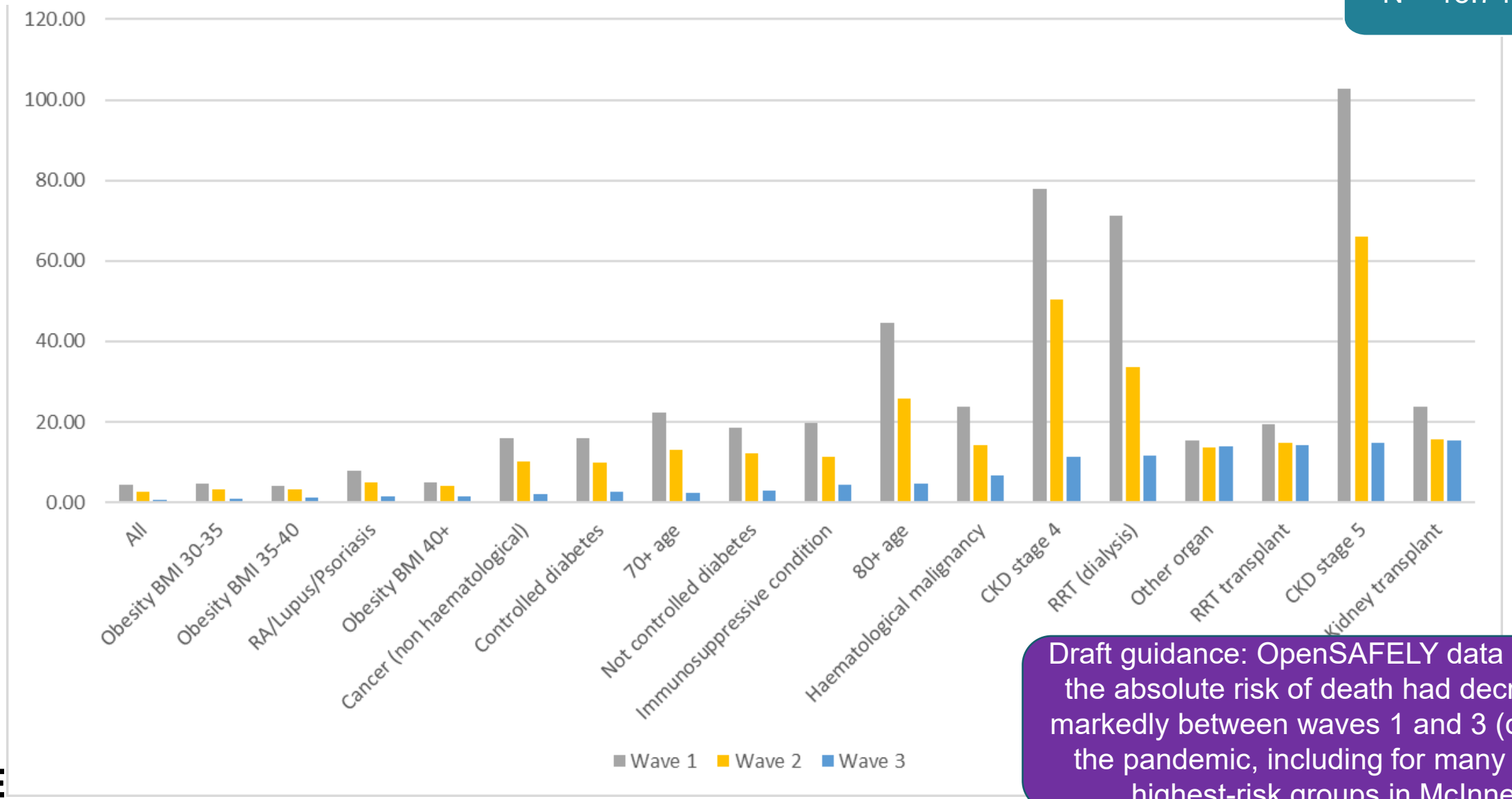
Government coronavirus dashboard

Draft guidance: committee mindful of current endemic setting with high background vaccination, less severe disease and much lower risk of hospitalisation and mortality



Death rate per 1000 person years across waves

OpenSAFELY
(All waves)
N = 18.7 million



Draft guidance: OpenSAFELY data showed the absolute risk of death had decreased markedly between waves 1 and 3 (delta) of the pandemic, including for many of the highest-risk groups in McInnes

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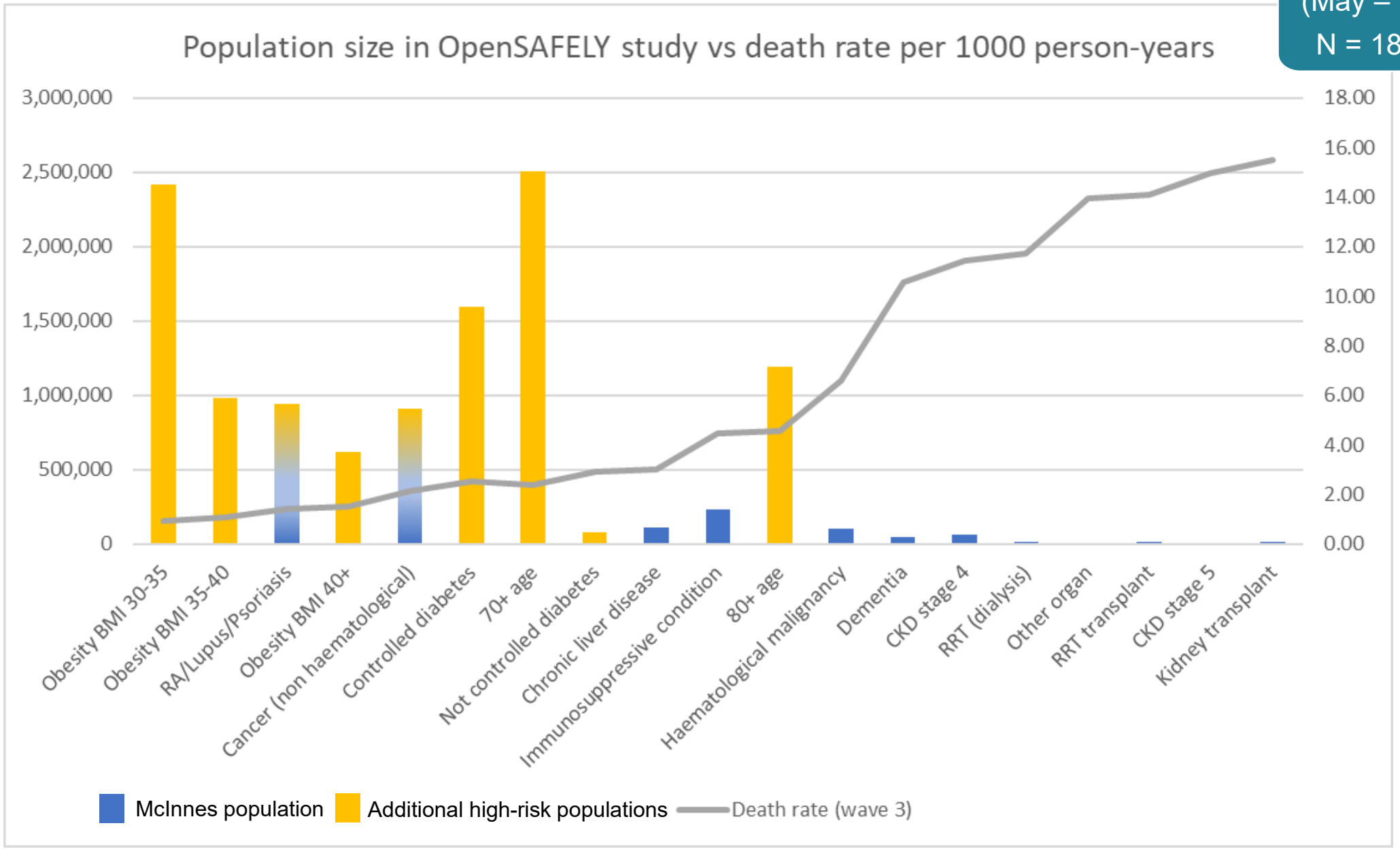
Death rate during Delta wave from OpenSAFELY

OpenSAFELY (Delta wave)
(May – Dec 2021)
N = 18.7 million



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Recap of committee's conclusions

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Key decisions at ACM1

1 Does committee agree that people over 70 and people with diabetes or obesity are at equivalent levels of risk to the McInnes cohort?

Edmunds report comments: “Analysis requires closer scrutiny to understand to what extent risk may be modified by improved access to therapeutics.”

2 Is nirm/rit cost-effective in this wider cohort?

Population
70+ or 70+ & McInnes? Can 70+ data be extrapolated to people with diabetes or obesity?
Baseline risk
PANORAMIC 70+ or McInnes? Can 70+ data be extrapolated to people with diabetes or obesity?
Relative efficacy
Covid NMA or EPIC-SR? Low, mean or high estimate?

Original **uncertainty** about generalisability of evidence, and increased uncertainty in considering subgroups

Decision risk – population numbers

Update recommendation

Consider implications relating to unmet need for people in this cohort who cannot have nirm/rit?

Re-cap of committee's conclusions: Edmunds report

Evidence not sufficiently robust to suggest that the broader population in the Edmunds report has equivalent high-risk to the group in the McInnes report

- Methodological limitations:
  - 'Any groups identified . . . would require closer scrutiny to better understand their risk **and to what extent this might be modified by improved access to antivirals and therapeutics**'
  - The 3 sources of evidence used different definitions of risk groups and outcomes, adjusted for different variables, and collected evidence during different waves of the pandemic
- The aims and methods of the McInnes and Edmunds reports were different:
  - McInnes considered which groups were most likely to benefit from treatment; Edmunds considered whether additional groups had a risk level at least as high as those already eligible for treatment
  - McInnes specified whether certain autoimmune or inflammatory conditions are active or uncontrolled, and specific medicines likely to affect immune response to vaccination; Edmunds used diagnosis codes to identify people with certain conditions
- The groups in the Edmunds report were therefore considered likely to be heterogenous, and include a significant proportion of people with much lower risk who were less likely to benefit from treatment

Re-cap of committee's conclusions: Cost-effectiveness

ICERs were above the threshold considered a cost-effective use of NHS resources when committee's preferred assumptions were applied

Population: aged 70+ (rather than aged 70+ combined with McInnes, where overall risk estimate would mask a significant proportion of people with lower risk)

Baseline risk: derived from PANORAMIC subgroup of people aged 70+ (reflects endemic context)

Relative efficacy

- Estimates from EPIC-SR preferred to the COVID NMA (EPIC-HR data only)
- TA878 concluded EPIC-HR estimates could only be extrapolated (and with caution) to groups with conditions/medications that put them at similar risk to unvaccinated (McInnes group)
- Broader population (Edmunds group) not considered at equivalent levels of risk to McInnes
- EPIC-SR better reflected endemic setting and lower risk population with lower absolute risks and a more heterogeneous population (mean and low efficacy estimates considered)

Note: no specific analysis presented for people with diabetes or obesity – committee concluded reasonable to extrapolate risk from aged 70+ but subject to significant uncertainty

Draft guidance consultation comments

Responses from:

- The company (Pfizer)
- 3 patient and professional groups (British Society for Heart Failure, Cardiothoracic Transplant Patient Group at NHS Blood and Transplant, Long Covid SOS)
- Comment from UKHSA
- 1 web comment

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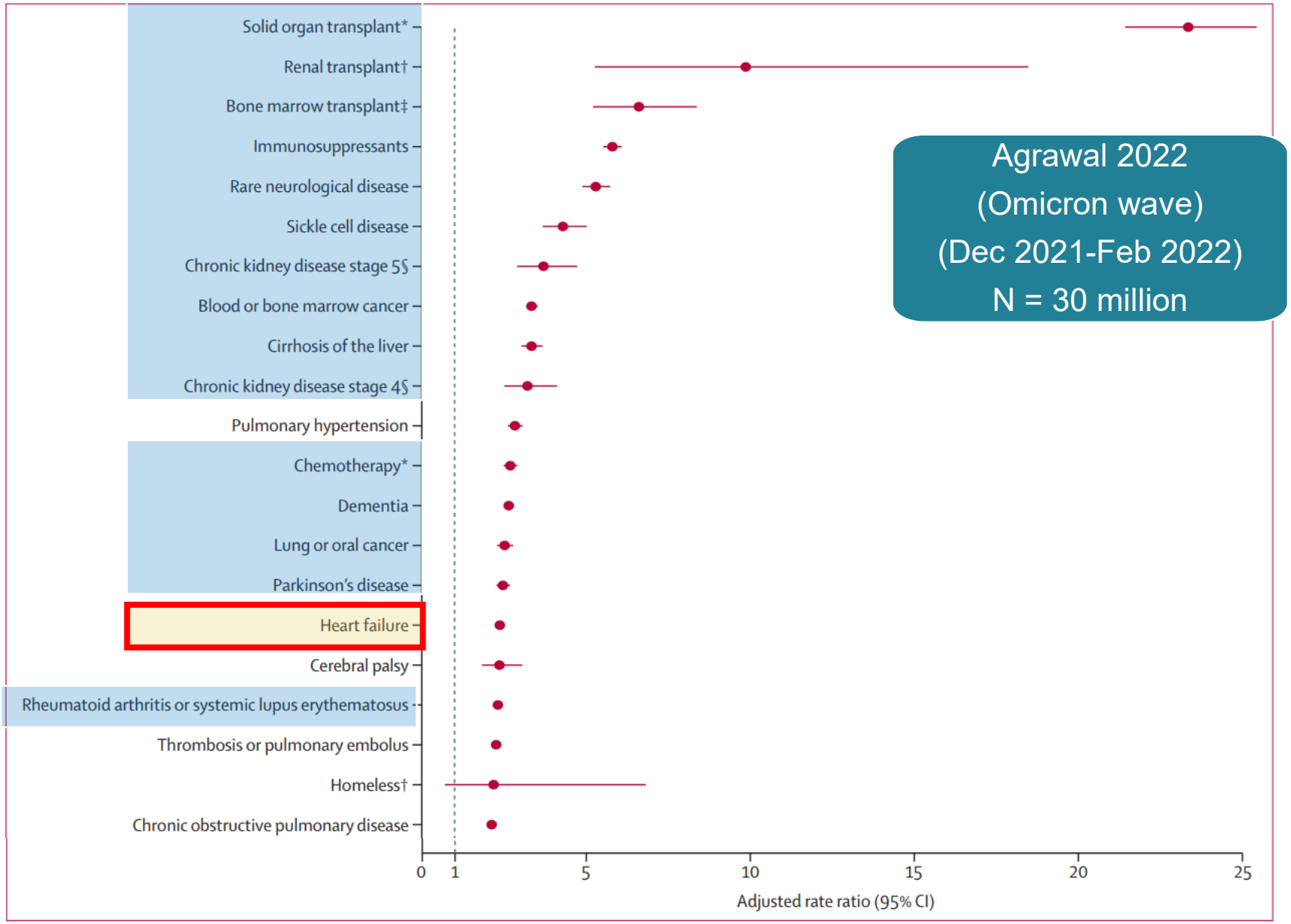
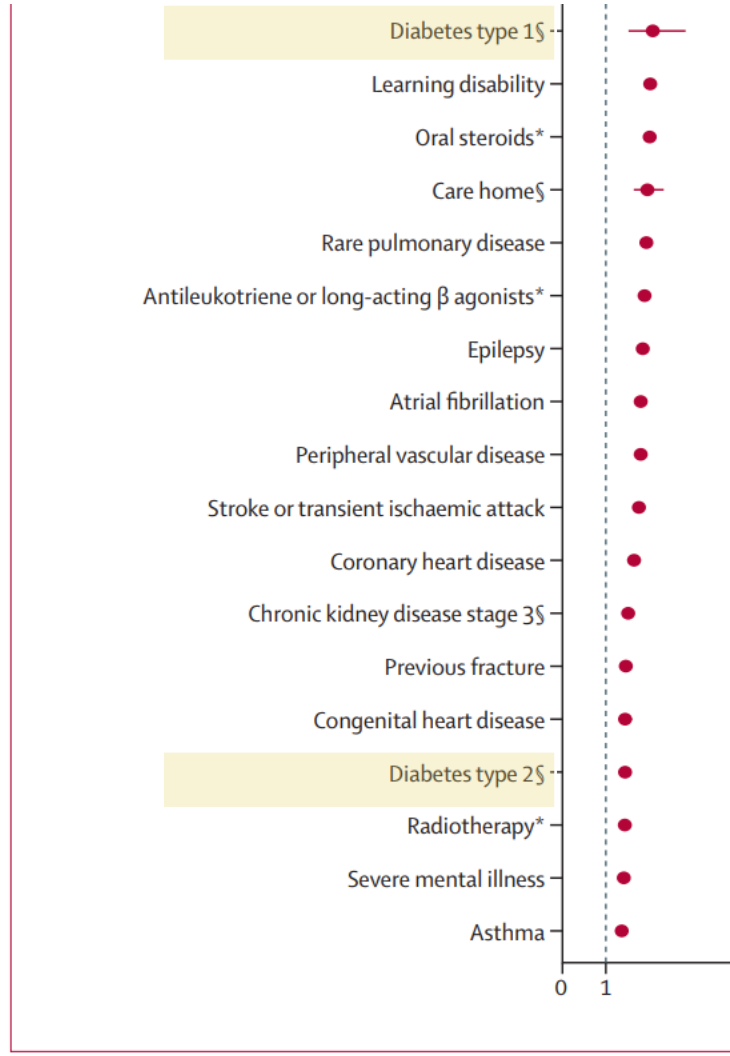
Consultation responses: patient and professional groups (1)

People with heart failure are being disadvantaged

- Patients with heart failure have increased risk of severe COVID outcomes
    - High mortality
    - Often have co-morbidities
    - Specific risks from becoming bed bound
- McInnes report identified heart failure as an additional risk factor but does not make any specific recommendation
- Hippisley-Cox et al. (2022) and Agrawal et al. (2022) show higher risk for people with heart failure compared with those with rheumatoid arthritis or lupus
- Concern regarding lack of representation and engagement with clinical cardiology community (membership of McInnes group does not include a cardiologist)

Adjusted rate associated with hospitalisation or death





Consultation responses: patient and professional groups (2)

Long COVID

- Healthcare and economic costs of long COVID not captured; welcome acknowledgement of this
- Future COVID models should include the impact on incidence and duration of long COVID
- Research evidence gap on who is most at risk of developing long COVID and the impact of subsequent infections in those with pre-existing long COVID
- Future clinical trials of COVID treatments should follow-up participants to establish the impact of treatment on subsequent development of long COVID

Consultation responses: company

1. EPIC-SR inappropriate for decision-making; efficacy estimates from EPIC-HR supported by RWE should be used, and a scenario between mean and low efficacy
2. Administration costs are too high – alternative lower costs should be used
3. Statistical method to account for low event rates inappropriate – alternative method proposed
4. Decision problem inconsistent – why have other age-related subgroups not been considered?
5. Resources have been provided to support prescribing (considered as part of point 2.)
6. Application of changes to the model (confirmed by EAG as appropriately implemented)
7. New preferred base case

Note: company did not comment on the committee's conclusions on Edmunds report, except to state that although the Edmunds group may be at high risk for different reasons to those in the McInnes group, they are nonetheless at similar (some cases higher) risk than the McInnes group

Key issues for discussion

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Key issues for discussion

New cost-effectiveness analyses

Issue	ICER impact
1. Most appropriate source of efficacy data – EPIC-SR or EPIC-HR?	High
2. Which efficacy scenario is most appropriate – mean, low, or mean-low?	High
3. Which administration costs are most appropriate – £410 or £117?	Moderate
4. Which test is appropriate for computing confidence intervals with low event rates – Wald, likelihood ratio or score test?	Low

ICER, Incremental cost-effectiveness ratio

Source of efficacy data

EPIC-SR or EPIC-HR?

Company comments:

- EPIC-SR inappropriate for decision-making: underpowered for hospitalisation/death outcomes and stopped early because of low events
- EPIC-SR is supportive evidence of efficacy in vaccinated populations, alongside RWE, rather than the primary source of evidence
- EPIC-SR estimates can only be used to 'bridge' but not replace, efficacy from unvaccinated to vaccinated populations; results support consistent efficacy in viral load and COVID related medical visits etc
- EPIC-HR still the most robust evidence available, acknowledging generalisability concerns
- Extrapolating EPIC-HR estimates to vaccinated pop is supported by RWE from US, Israel, HK and Canada
- In particular, results from Lewnard et al. RWE are consistent with mean efficacy estimates from EPIC-HR; these estimates can therefore be applied to the baseline risk of the current population of interest

NICE technical team comments:

- TA878 concluded that EPIC-HR was not completely generalisable to the previous decision on the McInnes group – it considered RR estimates were likely to change from the original trial because of vaccination status and disease severity, and so considered mean and low efficacy scenarios in its decision-making

RWE, real-world evidence; RR, relative risk

EPIC-SR and EPIC-HR

Committee: EPIC-SR better reflects current endemic context and lower risk pop.

	EPIC-SR	EPIC-HR
Recruitment timing	Unknown (results first reported 14 December 2021)	16 July – 09 December 2021 (Delta)
Primary outcome	Self-reported sustained alleviation of COVID symptoms	Hospitalisation or death
Population	Standard risk (vaccinated and unvaccinated) and **vaccinated high risk**	Unvaccinated high risk

Inclusion criteria and baseline characteristics (definition of risk)	Baseline characteristics not reported
	
	Exclusion criteria states “at least **1 underlying medical condition** associated with increased risk of developing severe illness”
	
	However, 721/1153 (62%) vaccinated patients had **at least 1 risk factor** for progression to severe COVID-19
		• >=1 risk factor for severe disease including:
		  • age 60+ (~87% age ≥65)
		  • overweight (~80% BMI>25)
		  • current smoker (~39%)
		  • hypertension (~33%)
		  • diabetes (~12%)
		  • other risk factors with few participants (chronic lung disease, CKD, heart disease, active cancer, immunosuppressive disease).

EPIC-SR and EPIC-HR results

Committee: EPIC-SR better reflects current endemic context and lower risk pop.

	EPIC-SR Standard risk (vaccinated and unvaccinated)			EPIC-SR Vaccinated high risk			EPIC-HR Unvaccinated high risk		
	Nirm/rit	Placebo	RRR	Nirm/rit	Placebo	RRR	Nirm/rit	Placebo	RRR
N	[redacted]	[redacted]		[redacted]	[redacted]		1,039	1,046	
Hospitalisation (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8 (0.77)	65 (6.21)	**88%**
Death (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	12 (1.15)	N/A

	Calculation of mean value (with different methods for continuity correction)								
	Wald	Likelihood	Score	Wald	Likelihood	Score	Wald	Likelihood	Score
Median	N/R	N/R	N/R	[redacted]	[redacted]	[redacted]	88%	88%	88%
Mean	N/R	N/R	N/R	[redacted]	[redacted]	[redacted]	87%	87%	87%

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RRR, relative risk reduction

Non-randomised evidence n.b not systematically reviewed

Study	Study design and results overview
Lewnard et al (2023)	• Retrospective matched cohort, USA (California) health records. N=7274 received nirm/rit. • Adjusted estimate of effectiveness of preventing hospitalisation or death: 53.6% (7–77%) for all comers or 79.6% (34–94%) if dispensed within 5 days of symptom onset
Aggarwal et al (2023)	• Retrospective matched cohort, USA (Colorado) health records. N=9881 received nirm/rit. • Adjusted odds ratio of 0.45 (0.33-0.62) for hospitalisation and 0.15 (0.03-0.50) for death.
Kaboré et al (2023)	• Retrospective matched cohort, Canada (Quebec) health records. N=8402 had nirm/rit • 69% reduced relative risk of hospitalisation. No benefit found in those with a complete primary vaccination course RR: 0.93 (0.78-1.08)
Shah et al (2022)	• Large electronic health record, USA. N=699,848 received nirm/rit. • Associated with a lower hospitalisation rate - adjusted hazard ratio 0.49 (0.46–0.53). 28.4% received a nirm/rit prescription within 5 days of COVID-19 diagnosis
Xie et al (2023)	• Ehealth record trial emulation, USA. N=31,524 had nirm/rit within 5 days of diagnosis. • Relative risk reduction in hospitalisation or death of 0.65 (0.57-0.74) in people who had 1 or 2 doses of vaccine.
Najjar-Debbiny et al (2023)	• Database study, Israel healthcare provider. N=4737 received nirm/rit. • Adjusted analysis showed reduction in rate of severe COVID-19 or mortality with adjusted HRs of 0.54 (0.39–0.75) and 0.20 (0.17–0.22)

Comments on real world evidence

Results of non-randomised studies that have not had risk of bias/confounding assessed should be interpreted cautiously – prognostic factors will not be equally distributed

EAG comments:

- Results should be interpreted with caution due to limitations with methods and generalisability
- Statistical approaches (e.g. variable selection and matching processes) and data quality issues may impact estimation of treatment effects (e.g. recall and ascertainment bias, missing data and misclassification of immunity, unmeasured confounding)

NICE technical team comments:

- Real-world evidence can be important to help resolve gaps in knowledge
- Can supplement RCT data and provide reassurance around generalisability issues
- Not common to use as a substitute for RCTs in determining efficacy
- There are recognised challenges in generating robust results from real-world data
- Inherent biases in study design mean complex statistical techniques are needed
- Data preparation and methods of analysis can have important effects on the estimates
- See: NICE's Real-world evidence framework

Efficacy scenarios

Mean, low, or between mean and low?

Company comments:

- Agree with considering mean and low estimates when using data from unvaccinated population
- TA878 considered mean and low efficacy for nirm/rit (when using EPIC-HR as primary efficacy data)
- Low efficacy scenario is not appropriate for EPIC-SR data because this trial included vaccinated patients
- A value between the mean- and low-efficacy scenarios is more appropriate when using EPIC-HR

EAG comments:

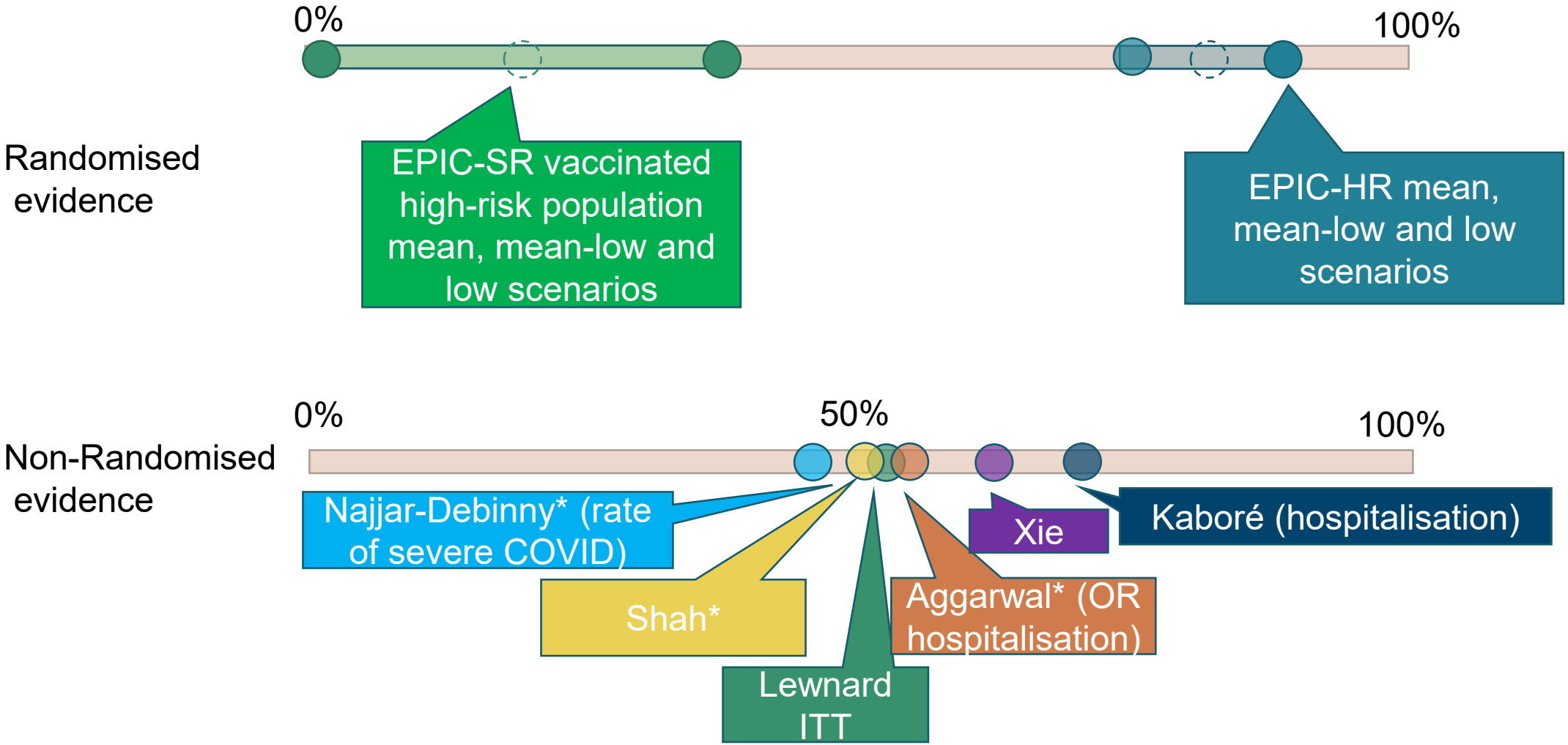
- Mean, low, and mean-low efficacy scenarios are presented
- Mean-low values derived from the mid-point between the mean and low point estimates of relative risk reduction in hospitalisation or death (the average between the 2 estimates)

NICE technical team comments:

- Mean scenario assumes conditions are the same as at the time of the trial
- Low scenarios considered to account for generalisability concerns with the original trial data to the current endemic setting (variant, disease severity, vaccination status)
- TA878 notes that there was no in vitro evidence showing reduced activity of antivirals across variants tested

Relative risk reduction – summary of evidence

Relative risk reduction of hospitalisation or death



ITT, intention to treat; OR, odds ratio

*NB: hazard ratios assumed to be relative risk and inverted to show reduction

Administration costs

Key choice between CMDU estimated costs and company survey

Company comments:

- £410 an overestimate as it is based on CMDU costs (incl. staffing, admin support, dispensing, consumables, couriering medicines, travel, stationery and hiring rooms, but excl. medical review of drug-drug interactions)
- Costs of medical review, prescribing and dispensing, are likely to be lower in post-pandemic delivery models:
  - Average patient in primary care: £75 (PSSRU)
  - More complex patients in care homes: £117 (PSSRU)
- Analysis of results from a company survey of 36 health care professionals (nurse, doctor or pharmacist with experience of prescribing oral antivirals) found the average cost for a complex patient was £114
- Company has provided resources to support prescribers in the clinical management of drug-drug interactions
- Company propose costs of £117 as a conservative estimate

EAG comments:

- £117 per patient is plausible admin cost; scenarios analyses replacing £410 with £117 are provided

NICE technical team comments:

- £410 figure was from early in the pandemic; committee considered difference in NMB when assuming different admin costs, given uncertainty around future delivery models

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CMDU, COVID medicines delivery unit; PSSRU, Personal Social Services Review Unit; NMB, net monetary benefit

Company survey

Methods

- Survey of UK healthcare professionals with insight into drug-drug interaction assessment for oral antivirals on the time requirements and associated costs of antiviral delivery in clinical practice
- Aim: to provide a contemporary estimate of drug-drug interaction assessment costs and overall administration costs
- Anonymous survey sent to nurses, doctors or pharmacists with experience in the prescription of oral antivirals for COVID, HIV, or other oral antivirals in community setting

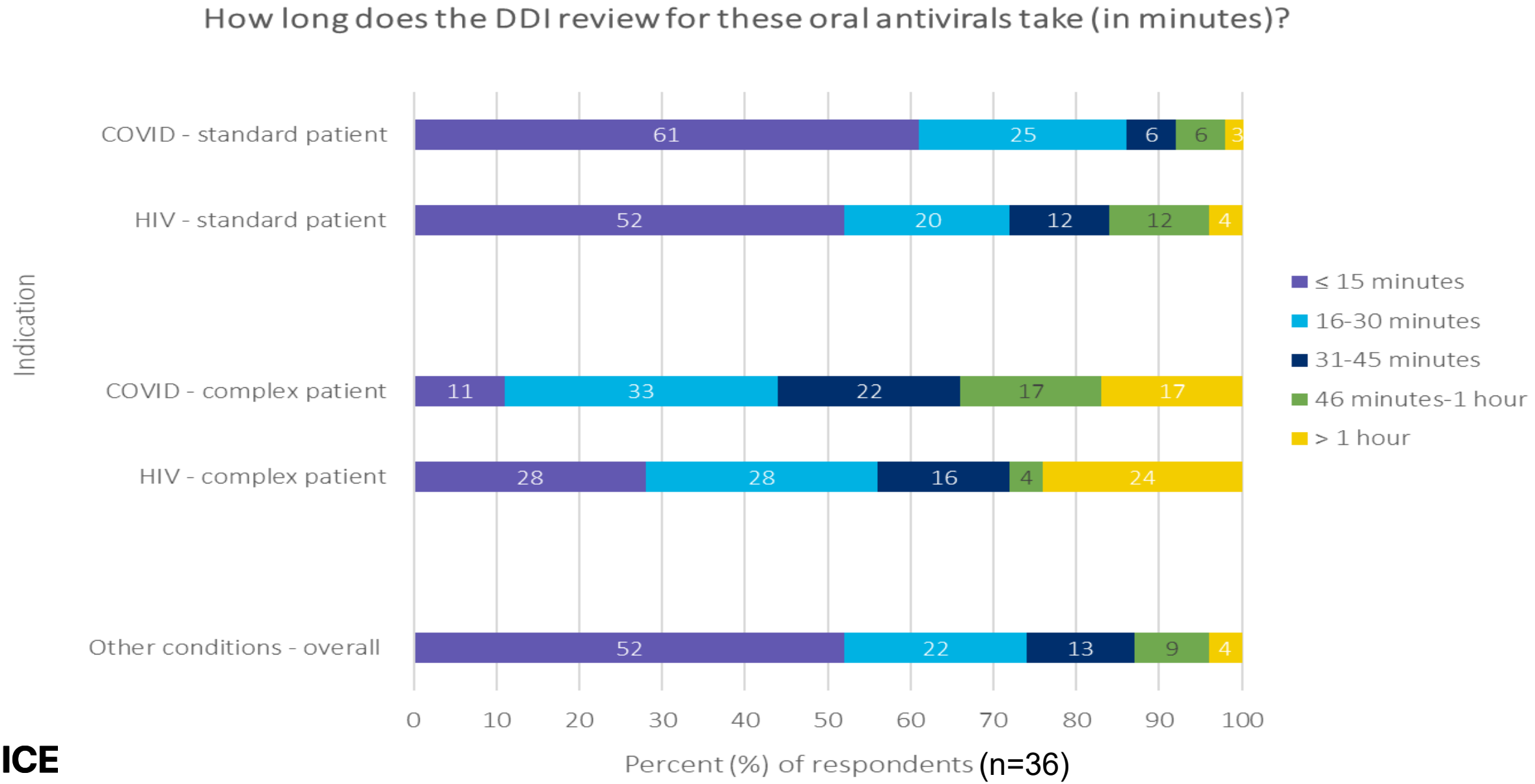
Survey questions

- NHS role of healthcare professional conducting drug-drug interaction assessments
- Drug-drug interaction review time
- Overall review and dispensing time requirements for standard and complex patients with COVID, HIV and other indications

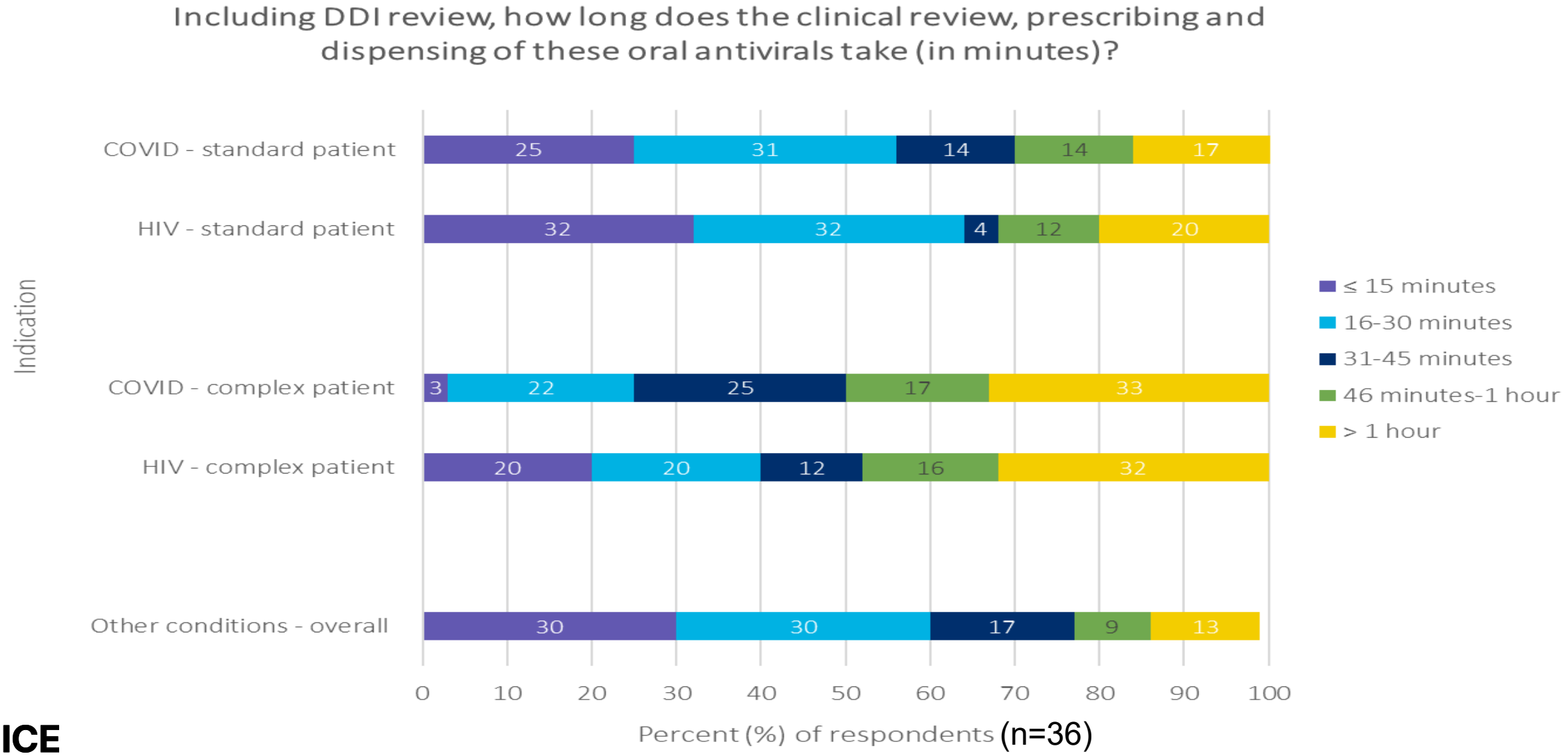
- 36 healthcare professionals responded to questions relating to COVID

HCP, healthcare professional; DDIs, drug-drug interaction

Company survey results: time for drug-drug interaction review



Company survey results: time for review, prescribing and dispensing



Company survey results: administration costs

Conclusion: overall administration would take no more than 1 hour for the average patient (including complex patients)

- Specialty and banding of healthcare professional undertaking drug-drug interaction review highly variable
- Weighted averages of responses were calculated and mapped to hourly rates

Cost of DDI review for oral antivirals for a standard patient with COVID	**£42.94**
Cost of overall clinical review, prescribing and dispensing of oral antivirals for a standard patient with COVID	**£78.94**
Cost of DDI review for oral antivirals for a complex patient with COVID	**£85.88**
Cost of overall clinical review, prescribing and dispensing of oral antivirals for a complex patient with COVID	**£113.58**

Statistical tests

Wald, likelihood ratio or score test?

Company comments:

- Approach used to derive confidence intervals for mortality benefit in the NMA is inappropriate
- NMA Relative Risk for death used in EAG model takes account of the application of a continuity correction to adjust for small numbers of events (assumed to be Wald test)
- Wald method is too inaccurate when used for statistical inferences on small sample/event sizes
- Because there were zero events in EPIC-HR, the likelihood ratio test is more appropriate

EAG comments:

- Agree that Wald is likely to be the method that was used in the COVID-NMA
- There are several ways to compute confidence intervals, and in the case of zero events, Wald confidence interval limits cannot be computed without applying continuity correction
  - so the intervals would vary with the choice of continuity correction
- Score and likelihood ratio tests do not depend on the continuity correction and have several advantages over the Wald method (score tests sometimes perform better than likelihood ratio tests)
- Confidence intervals re-calculated using all 3 statistical tests and presented in scenario analyses
- Note that this has a greater impact on ICERs using EPIC-SR efficacy where there are zero events

CI, Confidence interval; RR, relative risk; NMA, network meta-analysis; EAG, Evidence Assessment Group

Impact on efficacy estimates of using different statistical tests

Impact is greater on EPIC-SR results

	Nirm/ rit	Placebo	Wald test (95% CI)	Score test (95% CI)	Likelihood ratio (95% CI)
EPIC-HR					
Hospitalisation/ death	8/1,039	66/1,046	Median: 0.122 (0.059, 0.253) Mean: 0.131 Mean-low: 0.192	Median: 0.122 (0.060, 0.249) Mean: 0.130 Mean-low: 0.190	Median: 0.122 (0.054, 0.238) Mean: 0.131 Mean-low: 0.200
Death	0/1,039	12/1,046	Median: 0.0403 (0.0024, 0.6792) Mean: 0.114 Mean-low: 0.405	Median: 0 (0, 0.3215) Mean: 0.008 Mean-low: 0.226	Median: 0 (0, 0.1745) Mean: 0.006 Mean-low: 0.107
EPIC-SR (vaccinated subgroup)					
Hospitalisation/ death	3/361	7/360	Median: 0.4654 (0.1320, 1.6412) Mean: 0.572 Mean-low: 0.786	Median: 0.4274 (0.121, 1.5045) Mean: 0.523 Mean-low: 0.763	Median: 0.4274 (0.0927, 1.5242) Mean: 0.552 Mean-low: 0.776
Death	0/361	1/360	Median: 0.3324 (0.0136, 8.1327) Mean: 1.257 Mean-low: 0.786	Median: 0 (0, 3.8277) Mean: 0.037 Mean-low:0.763	Median: 0 (0, 5.7961) Mean: 0.050 Mean-low: 0.776

Updated cost-effectiveness results

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Company's preferred base case

	Total costs	Inc Costs	Total QALYs	Inc QALYs	ICER	NMB at £20k	NMB at £30k
SOC	[redacted]	-	[redacted]	-	-	-	-
Nirm/rit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key discussion point	Company preference
1. Source of efficacy data	EPIC-HR
2. Efficacy scenario	Mean-low
3. Administration cost	£117
4. Statistical test	Likelihood ratio test
Note: EAG provides scenarios for all options for the 4 key discussion points	

SOC, standard of care; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; EAG, Evidence Assessment Group

EAG results: summary ICERs

ICERs only <£30k per QALY gained when EPIC-HR used

ICERs only <£20k per QALY gained when EPIC-HR used and admin costs £117

	Admin costs: £117			Admin costs: £410		
EPIC-HR	**Wald**	**Likelihood**	**Score**	**Wald**	**Likelihood**	**Score**
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean-Low	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Admin costs: £117			Admin costs: £410		
EPIC-SR	**Wald**	**Likelihood**	**Score**	**Wald**	**Likelihood**	**Score**
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean-Low	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Impact of adverse events on ICERs

Tested with 3 scenarios, and 3 values for average QALY losses associated with adverse events for each person receiving nirmatrelvir plus ritonavir

Scenario 9: Efficacy from EPIC-HR, mean-low scenario, score test			
QALY loss from AEs	**Incremental discounted QALY**	**Cost/QALY compared with SoC**	**Cost/QALY compared with SoC**
Zero	[redacted]	[redacted]	[redacted]
0.0001	[redacted]	[redacted]	[redacted]
0.0010	[redacted]	[redacted]	[redacted]
0.0027	[redacted]	[redacted]	[redacted]

Scenario 16: Efficacy from EPIC-SR, mean scenario, score test			
QALY loss from AEs	**Incremental discounted QALY**	**Cost/QALY compared with SoC**	**Cost/QALY compared with SoC**
Zero	[redacted]	[redacted]	[redacted]
0.0001	[redacted]	[redacted]	[redacted]
0.0010	[redacted]	[redacted]	[redacted]
0.0027	[redacted]	[redacted]	[redacted]

Scenario 18: Efficacy from EPIC-SR, mean-low scenario, score test			
QALY loss from AEs	**Incremental discounted QALY**	**Cost/QALY compared with SoC**	**Cost/QALY compared with SoC**
Zero	[redacted]	[redacted]	[redacted]
0.0001	[redacted]	[redacted]	[redacted]
0.0010	[redacted]	[redacted]	[redacted]
0.0027	[redacted]	[redacted]	[redacted]

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Thank you.