Single Technology Appraisal

Nirmatrelvir plus ritonavir for treating COVID-19 (Partial Rapid Review of TA878) [ID6262]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nirmatrelvir plus ritonavir for treating COVID-19 (Partial Rapid Review of TA878) [ID6262]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance** from Pfizer

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. British Society for Heart Failure
   b. Cardiothoracic Transplant Patient Group
   c. Long COVID SOS
   d. UK Health Security Agency

3. **External Assessment Group critique of company comments on the Draft Guidance**
   a. EAG critique
   b. EAG addendum to critique

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 25 May 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Pfizer
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]	Not applicable – Representative of Pfizer

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Please state the name of the company, amount, and purpose of funding.	
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Executive summary of key points from the company response** The current analysis seeks to assess cost-effectiveness in groups of people who have an equivalent risk to people with any condition in the McInnes-defined high-risk group. The Department of Health and Social Care considered that based on the draft guidance papers, age 70 and over, diabetes, and obesity were important risk factors that should be taken into account in a cost-effectiveness analysis. While there might be uncertainty in the available data, the overall approach used in the committee's preferred analysis is scientifically flawed and will result in the lack of treatment options for these highly vulnerable population including those in care homes. Although the Edmunds report group might be at high risk for different reasons to those of the McInnes groups, they are nonetheless at similar and in some cases higher risk of severe outcomes than the McInnes-defined high risk group. Use of an underpowered trial that was not designed to demonstrate efficacy to drive assumptions in the analysis suggesting Paxlovid completely lacks treatment effect in vaccinated high-risk individuals is unjustified and is contrary to the UK regulatory license that Paxlovid is an efficacious medicine with acceptable safety profile in the label population. Any analyses including assumptions claiming lack of efficacy should not be considered for decision making. Furthermore, it does not consider a wealth of real-world evidence demonstrating the effectiveness of Paxlovid regardless of vaccination status from both the UK (OPENSAFELY noted by the committee as a robust study) and from around the world which was presented to the committee by the company throughout the appraisal process. In

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	addition, administration costs misaligned with the likely post-pandemic primary deployment model have become a barrier to patients' treatment access. The company agrees that there are evidence challenges for a constantly evolving disease such as COVID-19 and changing population dynamics. However, there is still enough evidence to make a decision that ensures patients at high-risk of severe outcomes are not deprived of treatment options. In this response, the company presents a set of base case assumptions supported by scientific evidence that support costs effectiveness in the 70+ population. The key points highlighted in this response and their corresponding sections are summarised below: **Comment 2:** EPIC-SR enrolment was stopped early due to availability of Paxlovid outside of the trial and was not designed nor statistically powered to demonstrate efficacy in COVID-19 hospitalisation or death endpoints among subgroups of patients; therefore, its use to inform Paxlovid clinical effectiveness in the economic model is inappropriate for decision making. EPIC-HR remains the most robust source of evidence available and should continue to be used as the primary source of Paxlovid efficacy in this appraisal. Real-world data from a vaccinated population (Lewnard et al.) support EPIC-HR as a plausible reflection of efficacy in the vaccinated population. **We suggest a value between the mean- and lower-efficacy data be chosen from EPIC-HR to inform the final economic modelling base case.** **Comment 3:** The administration costs (£410) applied in the EAG model are an overestimate compared to real-world costs, even in the most complex patient cases. New feedback from 36 HCPs concludes the likely time required when Paxlovid becomes routinely commissioned would be between £42.94 and £113.58. This supports our previously suggested medical review cost for care home residents of £117. These costs include those associated with a drug-drug interaction medical review which is required for some of the patients eligible for Paxlovid. **We therefore propose an admin cost of £117 be applied in the model.** **Comment 4:** The approach used to derive the confidence intervals in the NMA is inappropriate for the context in which it was used (given correction were required due to zero events); confidence interval lower bounds define the lower efficacy scenarios for EPIC-HR considered in this appraisal and are highly impactful on modelled cost effectiveness. The company present an alternative method of statistical analyses with resultant confidence intervals - further consideration should be given to the derivation of this data given the importance to decision making. **We propose the model base case assumption confidence intervals**

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	for the efficacy of Paxlovid on mortality be updated to these values (0.00, 0.1745)**.** **Comment 5**: Based on recent updates and scenarios developed by the EAG, there are inconsistencies in the decision problem. The company request clarity from NICE on their rationale for not considering alternative age-related data and how this relates to the final decision problem for this appraisal. Misaligned and constantly changing definitions of high-risk have consistently resulted in misalignment of evidence resulting in patients lacking access to treatments. **Comment 6**: The company has created resources aligned with the Paxlovid SmPC to support UK prescribers in the clinical management of drug-drug interactions and to improve the efficiency of clinical review and dispensing of oral antivirals for COVID-19. **Comment 7 and 8**: The company present their preferred base case based on changes reflecting appropriate Paxlovid administration costs and clinical effectiveness estimates. Details on exactly how the EAG model was updated are reported.
2	**<u>EPIC-SR was not designed and statistically powered to demonstrate efficacy in COVID-19 hospitalisation or death endpoints among subgroups of patients and its use to inform Paxlovid clinical effectiveness in the economic model is inappropriate for decision making</u>** **EPIC-SR enrolment was stopped early due to availability of Paxlovid outside of the trial, resulting in underpowering of the study and statistically non-significant results. As well as the data being statistically underpowered, the conclusions drawn may be medically inaccurate – this data is not appropriate for decision making in this appraisal.** **EPIC-HR is still the most robust source of evidence available and should continue to be used as the primary source of Paxlovid efficacy in this appraisal. Real-world data from a vaccinated population (Lewnard et al.[1]) support EPIC-HR as a plausible reflection of efficacy in the vaccinated population. To account for uncertainty, we propose the committee considered efficacy values between mean and low scenarios.** The company would like to reiterate that it is inappropriate to use data from EPIC-SR for decision making in this appraisal. As noted by the committee, EPIC-SR enrolment was stopped early. This resulted in underpowering of the study and therefore statistically non-significant results. Additional consideration is warranted regarding the suitable evidence to inform efficacy of Paxlovid in vaccinated

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	individuals in light of the evolving situation during the pandemic. Once Paxlovid received emergency use authorisation (EUA) in December 2021 from the US FDA for the treatment of mild-to-moderate Covid-19 in high-risk patients regardless of Covid-19 vaccination status, clinical equipoise was no longer met. Since vaccinated high-risk individuals could obtain Paxlovid outside of a trial setting, it was no longer ethical to continue to enrol patients into a placebo-controlled trial. Consequently, EPIC-SR had a limited number of vaccinated high-risk subjects, all of whom were enrolled prior to Paxlovid receiving EUA. Further subgrouping of the data as was done by the external assessment group (EAG) to focus on the vaccinated subgroup exacerbates the unreliability of the data. For the target patient population of concern, patients at high risk of progressing to severe COVID-19 illness, study EPIC-HR is the pivotal clinical trial in which efficacy of Paxlovid in COVID-19 related hospitalisation and all cause death has been established. EPIC-SR was not designed and statistically powered to demonstrate efficacy in COVID-19 hospitalisation or death endpoints among subgroups of patients. The company agrees that EPIC-SR has become increasingly important because it enrolled high risk patients who were vaccinated, a patient subset more representative of current high levels of population immunity acquired following vaccination, natural infection, or both. However, we disagree that EPIC-SR can be used to replace EPIC-HR as the pivotal study to support the endpoint of COVID-related hospitalisation or death. Because of the low rate of hospitalisation or death among the vaccinated patient population, EPIC-SR was underpowered for this endpoint. Therefore, estimates of the efficacy endpoints in EPIC-SR can only be used to “bridge”, but NOT to replace, the efficacy from the unvaccinated population to the vaccinated population, because these estimates did not have the required accuracy or well-defined 95% CI that would be achieved from an adequately powered clinical trial. This bridging is necessary because the Emergency Use Authorization (EUA) for Paxlovid has eliminated the clinical equipoise for repeating a placebo-controlled trial in vaccinated high-risk population. As a bridging study, EPIC-SR has shown that Paxlovid had efficacy consistent with the efficacy demonstrated in EPIC-HR. Similar to EPIC-HR, EPIC-SR reduced the following pre-specified endpoints relative to placebo: (1) the SARS-CoV-2 viral RNA level [redacted], (2) the proportion of participants with COVID-19-related hospitalization or all cause death [redacted], (3) the total number of COVID-19 related medical visits [redacted],and (4) the proportion of patients with post-baseline severe signs and symptoms [redacted],a result of both

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	(a) greater symptom improvement/alleviation among patients who had severe symptoms at baseline, and (b) less symptom worsening or deterioration among patients who did not already have severe symptom at baseline. It can be clearly concluded from these results in pre-specified efficacy endpoints that relative risk reduction from Paxlovid was consistent in the vaccinated (EPIC-SR) and unvaccinated (EPIC-HR) patient populations. The absolute risk reduction depended on risk level presented among the untreated patients in the placebo group. This conclusion was also supported by the analyses within subgroups of patients who were seropositive and who were seronegative: both subgroups had similar relative risk reductions, even though the absolute risk reduction was lower in the seropositive patient population whose background risk level was low.[2] In the EPIC-HR seropositive subgroup, 1/490 (<1%) Paxlovid recipients versus 8/479 (2%) placebo recipients met the composite endpoint of reduction of COVID-19-related hospitalization or death from any cause through day 28, resulting in a relative risk reduction of 88% (nominal p-value=0.02).[2] In conclusion, the company believes that to estimate the effect of Paxlovid in any high-risk patient population, the appropriate economic model should use the relative risk reduction estimates obtained from the EPIC-HR study and apply them to the background risk in the specific patient population of concern, so that the absolute risk reduction can be estimated appropriately. This specific patient population can be the vaccinated high-risk population in EPIC-SR, a patient population in a particular country, or patients within a specific geographic region affected by a pandemic or epidemic. Additionally, in the scenarios where EPIC-SR data was used by the EAG the latest draft guidance papers , the consideration of the lower efficacy scenario (confidence interval [CI] lower bounds for hospitalisation and mortality informing efficacy) is inappropriate. Whilst the company disagree with the use of EPIC-SR data in this capacity, the lower efficacy scenario was originally implemented as a compromise to address some of the uncertainty in treatment effectiveness among an unvaccinated population (EPIC-HR) and the generalisability of this data to a contemporary real-world population. As EPIC-SR included a sample with vaccinated participants, the rationale for the lower efficacy scenario no longer stands. Based on the underpowering of EPIC-SR, considering lower CI assumes nearly zero treatment effect for Paxlovid, an inappropriate assumption not supported by any data from EPIC-HR or real-world evidence (RWE) studies. In this circumstance, data collected under real-world use provides critical supportive evidence that complements and extends the available evidence of treatment efficacy, including to vaccinated individuals and also to time periods following the emergence of the Omicron variant.

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	Evidence supporting the real-world effectiveness of Paxlovid in contemporary clinical practice The company agrees with the committee that non-randomised evidence does not replace randomised clinical trials. However, in the absence of robust clinical trial data in vaccinated individuals and the omicron variant, RWE provides valuable information to support the generalisability of the EPIC-HR trial data. The committee for example "concluded that OpenSAFELY data provided support for the continuous hospitalisation and mortality benefit of nirmatrelvir plus ritonavir seen from the older trial". Furthermore, the committee concluded that there was no in vitro evidence showing reduced clinical efficacy of nirmatrelvir plus ritonavir across the variants tested. Throughout the appraisal process, Pfizer has provided multiple sources of real-world evidence which support the appropriate primary source of efficacy data for Paxlovid (EPIC-HR) as being generalisable to a vaccinated population in the current era of COVID-19. Real-world evidence has been critical to understanding the clinical effectiveness of COVID-19 treatments over the course of the pandemic against the constantly evolving virus in a heterologous setting of various levels of population immunity worldwide, acquired from vaccination, natural infection, or both. We acknowledge there are questions about generalisability of ex-UK RWE to UK populations, however, the committee should note that due to the current restriction to treatment access in the UK, it is not possible to generate these data. As such there is no UK RWE data outside of the McInnes population. However, these data are available from around the world. We are committed to continued monitoring of this data should access be broadened and to working with all stakeholders (UKHSA, NICE and NHSE) to generate, disseminate and assess the impact of new data on Paxlovid in the UK. Below we provide further real-world evidence to reduce the uncertainty in the efficacy estimates derived from the EPIC trials. Real-world studies conducted in Israel, Hong Kong, Canada and the United States have consistently across geographies demonstrated that Paxlovid is highly effective in reducing the risk of hospitalisation or death, during time periods predominated by multiple Omicron subvariants, including BA.1, BA.2, and BA.4/5.[1, 3-14] Estimates of effectiveness from real-world studies ranges from approximately 40% to 80% in both vaccinated (with or without a booster) and unvaccinated individuals,[1, 3, 8, 10, 13] with a clear overlap in effectiveness estimates between these two populations which demonstrates that data from an unvaccinated population may reasonable reflect clinical effectiveness in vaccinated individuals. Effectiveness has also been shown to not vary by other clinical characteristics including age group, and immunocompromised status.[10] Based on the totality and

	consistency of the scientific evidence, including data from real-world studies conducted in multiple countries, supportive results from EPIC-SR, and statistically significant results from EPIC-HR, the available data indicate that EPIC-HR efficacy is generalisable to the vaccinated population and therefore appropriate to inform efficacy of Paxlovid in vaccinated individuals. In particular, one real-world study conducted in the United States is uniquely informative on the effectiveness of Paxlovid in the vaccinated population. This matched cohort study by Lewnard et al.[1] used data from a large (7274 nirmatrelvir–ritonavir recipients and 126 152 non-recipients), integrated US healthcare system to assess effectiveness of Paxlovid against hospitalisation or death within 30 days of testing positive. This real-world study is the first – and currently only – published study to evaluate Paxlovid effectiveness according to timing of treatment initiation relative to timing of symptom onset (rather than testing positive). Evaluation based on timing of symptom onset is an important distinction to make in the appropriate assessment of Paxlovid effectiveness for real world UK practice as this is consistent with the wording in the MHRA label for Paxlovid use " Paxlovid should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 5 days of onset of symptoms".[15] Lewnard et al. included individuals aged 12 years and older, of whom 86% had received at least 2 Covid vaccine doses. The study period was April 8 to October 7, 2022, during which time Omicron BA.2 and BA.4/5 were in circulation and predominant. Against the endpoint of hospital admission or death within 30 days of an outpatient positive SARS-CoV-2 test, receipt of Paxlovid within 5 days of symptom onset (5472 (75·2%) treatment recipients and 84 657 (67·1%) non-recipients) was 80% effective overall, 83% effective among patients who had received at least 2 Covid vaccine doses, and 92% effective among patients who had received at least 3 Covid vaccine doses. **<u>Appropriate approaches for final decision making</u>** Given the limitations of EPIC-SR, the company believe this data should be considered as supportive clinical evidence alongside the multitude of real-world data in vaccinated populations, not as the primary source of evidence informing Paxlovid efficacy in this appraisal. Acknowledging the generalisability concerns of EPIC-HR in the contemporary vaccinated population, we believe this data is still the most robust source of evidence available and should continue to be used as the primary source of Paxlovid efficacy in this appraisal. As detailed above, real-world data from a vaccinated population (Lewnard et al.[1]) support EPIC-HR as a plausible reflection of efficacy in the vaccinated population. Whilst the mean efficacy estimates from EPIC-HR are consistent with the real world data in the vaccinated population[1], the company acknowledge that uncertainty remains, and that this should be

	accounted for in the decision making. The company agree with NICE's approach to consider mean- and low-efficacy scenarios when considering data from an unvaccinated population. As noted in the final draft guidance, the range between the mean- and lower-efficacy estimates should be considered for the data to be more suited to the current endemic setting. However, what has so far been unclear is the extent to which each scenario is considered for decision making. The lower-efficacy data from EPIC-HR should not be considered in isolation as this alone provides an overly pessimistic representation of Paxlovid's effectiveness. **We suggest a value between the mean- and lower-efficacy data be chosen from EPIC-HR to inform the final economic modelling base case.** Additional consideration should be given to the appropriate statistical methods used to derive the confidence intervals (Cis) informing the lower efficacy estimates, particularly given the impact these estimates have on cost effectiveness estimates of treatment. As described in greater detail in section 4, the company believe the methodology used to derive CI for mortality in the COVID-NMA should be reconsidered. **<u>The assumption of zero mortality benefit for Paxlovid cannot be considered appropriate in light of the evidence'</u>** Similar to the EPIC-HR trial, no deaths were observed in the Paxlovid arm of the EPIC-SR trial while deaths were observed in the placebo arm. The committee papers state that "The committee noted that the efficacy estimate from EPIC-SR had assumed no mortality benefit because it was not clear from the information available whether there had been any deaths in the trial." This is not factually correct. The press release from which the data used by the EAG in their analysis clearly states that "*Other not statistically significant findings included no PAXLOVID-treated patients admitted to the intensive care unit, compared to three in the placebo group, and* ***no deaths in patients who received PAXLOVID with one death in the placebo group***." As outlined in previous sections the company do not consider data from EPIC-SR to be appropriate for informing Paxlovid effectiveness estimates in the model. Notwithstanding this rationale, the fact remains that the assumption of zero mortality benefit for Paxlovid from EPIC-SR made by the EAG is factually inaccurate, contrary to the UK regulatory license that Paxlovid is an efficacious medicine with acceptable safety profile in the label population and any analyses including this assumption should not be considered for decision making.
3	**<u>The administration costs applied in the EAG model are an overestimate</u>** **Administration costs of £410 for Paxlovid currently modelled by the EAG is a vast overestimate, even in the most complex patient cases.**

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	The company present alternative costs reflective of the standard and complex patient scenarios which should be strongly considered given the large impact administration costs have on modelled cost-effectiveness estimates. These costs are conservative as they are based on the most complex medical review costs and are applied to all Paxlovid eligible patients despite only a proportion of the patients requiring additional medical review. **A survey amongst healthcare professionals has been conducted to elicit insight into clinical review and dispensing time for oral antivirals for COVID-19, HIV and other indications; results support the company preferred assumptions and highlight the currently modelled values as unrepresentative of UK clinical practice.** As noted in the company response to the draft guidance, we believe the administration costs applied for Paxlovid in the EAG model (£410) are an overestimation compared to the likely real-world costs once final guidance is implemented. Whilst the discussion of appropriate administration costs has been raised several times, we do not believe this has been given sufficient consideration in this appraisal; given the substantial impact these costs have on the cost effectiveness of Paxlovid in the EAG's economic modelling, it's crucial that these costs reflect those which will be realised when Paxlovid is available via routine post-pandemic delivery models. The committee papers state that "The committee considered the differences in administration costs in relation to the net monetary benefit outcomes, noting the uncertainty about future delivery models ". However, it is not clear if this was done in this partial review as the results were not presented. As noted above, alternative administration costs have been presented by the company in previous responses to the draft guidance; in brief, the following summarises the rationale behind the most conservative administration cost proposed: To model the administration process for Paxlovid for the average patient in primary care, we assume that clinical medical review, prescribing and dispensing will require a maximum of one hour of time (allowing for triage and clinical medical review) from a band 8a pharmacist or prescribing nurse: £75 based on Personal Social Services Research Unit (PSSRU) costs. [16] A scenario representing the more complex medical review required for care home patients should be considered as a conservative alternative. PSSRU review for this scenario found that "the average cost per resident of the multi-professional medication review intervention was £117".[16] This reflects the potential costs for patient with drug-drug interactions (DDIs) that would require complex medical review before prescribing. It should be noted that not all Paxlovid eligible patients have potential DDIs. This scenario which represents the most complex medical

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	review process and should be considered as the upper limit for oral antiviral administration cost. It is unclear what the source is for the £352.49 estimate noted by another stakeholder as noted in the draft guidance as the hourly cost of a pharmacist. This is clearly implausible since the highest salary band overall in the NHS (well beyond what is required to prescribe Paxlovid) incurs an hourly cost of £151. [16] As a result, we believe it is reasonable to consider the average cost of Paxlovid administration as falling between these values, reflecting the administration costs for standard patient (£75) and the conservative scenario for a complex patient requiring full DDI assessment (£117). Due to uncertainty in the proportion of patients that have potential DDIs, a conservative approach can be taken applying the admin costs for complex cases to all patients. **We therefore propose an admin cost of £117 be applied in the model.** **<u>Expert elicitation to validate the administration costs for Paxlovid in real-world clinical practice</u>** Originally, the EAG did not include administration costs for oral treatment in their model, but after consultation updated the model with costs provided by NHS England. The EAG concluded that future administration costs will be similar to those employed in the Covid Medicines Delivery Unit (CMDU) because the resources required to deliver treatment in future practice will be proportionately similar, although in the format of a permanent staffing structure. However, these administration cost calculations included elements not appropriate for a primary care delivery model for antivirals for example clinical consumables, stationery, room hire, office equipment and multiple staff costs. While these might be relevant in accessing the costs of setting up and running a CMDU (which do not have permanent structures), they do not reflect costs associated with routine delivery of an oral treatment in primary care. To consolidate the uncertainty on the exact administration costs of Paxlovid and the real-world resource requirements for DDI assessment, the company have conducted a brief survey among UK healthcare professionals (HCPs). The survey sought opinions from HCPs with insights into DDI assessment of oral antivirals on the time requirements and associated costs of antiviral delivery in clinical practice. The overall aim was to provide a contemporary estimate of DDI assessment costs and overall administration costs for oral antivirals, including those for the treatment of COVID-19. These costs may be used by NICE to validate the administration costs applied in economic model. <u>Method</u>

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	Detailed survey methodology, content and full results are uploaded alongside the company response as a study protocol and results report. In brief, the anonymous survey was sent to HCPs listed as a nurse, doctor or pharmacist with specialities alluding to experience in the prescription of oral antivirals for COVID-19, human immunodeficiency virus (HIV) or other oral antivirals in the community setting. Survey questions covered the NHS role of the HCP who conducts DDI assessments, the associated DDI review time and overall review and dispensing time requirements of oral antivirals for standard and complex patients with COVID-19, HIV and other indications. Questions were asked across these indications in order to capture expert input specific to COVID-19 but also oral antiviral delivery in a standard primary care environment. <u>Results</u> Overall, there were 36 HCPs responding to the questions relating to COVID-19, 25 responding to questions on HIV, and 23 responding to questions on oral antiviral administration in other indications. From the responses, the specialty and NHS banding of the HCP who performs the DDI review for oral antivirals is highly variable across departments/health boards. In relation to DDI reviews specifically for oral antivirals for COVID-19 via the CMDU, 46% stated this was conducted by a hospital-based doctor, 32% by a hospital based pharmacist, and 22% by a hospital based nurse. When compared to the responses relating to DDI checks for oral antiviral for HIV in the primary care setting, results are still varied but there is a higher proportion of assessments carried out by community pharmacists and nurses: 40% community-based nurse, 32% community-based pharmacist, and 28% general practitioner. These results suggest the majority of antiviral review and administration conducted in the primary care setting (future deployment of treatment for COVID-19 in the community) is done by higher banded nurses and pharmacists. When asked about the administration of oral antivirals for standard patients, HCP majority opinion suggests that the overall DDI review time across indications takes 15 minutes or less (61.1% in COVID; 52% in HIV; 52.2% across other indications; Figure 1). When asked about the time required for the overall clinical review, prescribing, and dispensing of oral antivirals, the majority of HCPs agreed that this takes 30 minutes or less (55.6% in COVID; 64% in HIV; 60.9% across other indications; Figure 2) When asked about the administration of oral antivirals for complex patients, the majority of HCP's reported a DDI review time of 45 minutes or less across indications (66.7% in COVID; 72% in HIV; Figure 1). When asked about the time requirement for overall clinical review, prescribing and dispensing time of oral

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antivirals for complex patients, the majority of HCP's reported that this takes one hour or less across indications (66.7% in COVID; 68% in HIV; Figure 2)

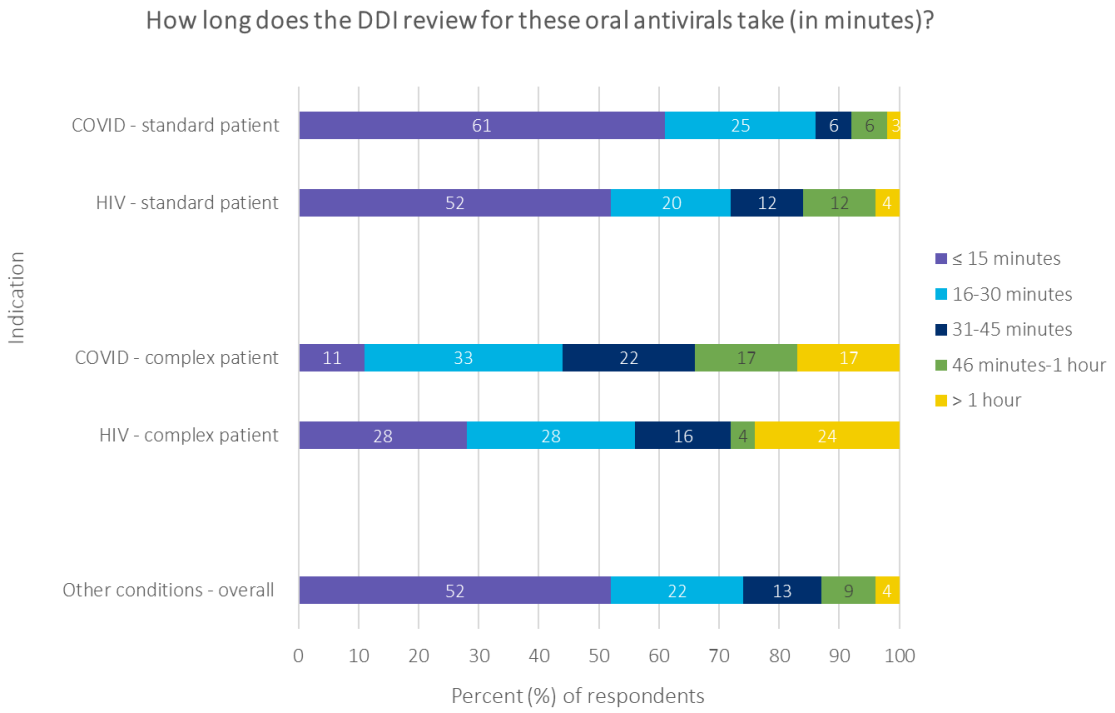

Figure 1. HCP responses to the question "How long does the DDI review for these oral antivirals take (in minutes)?"

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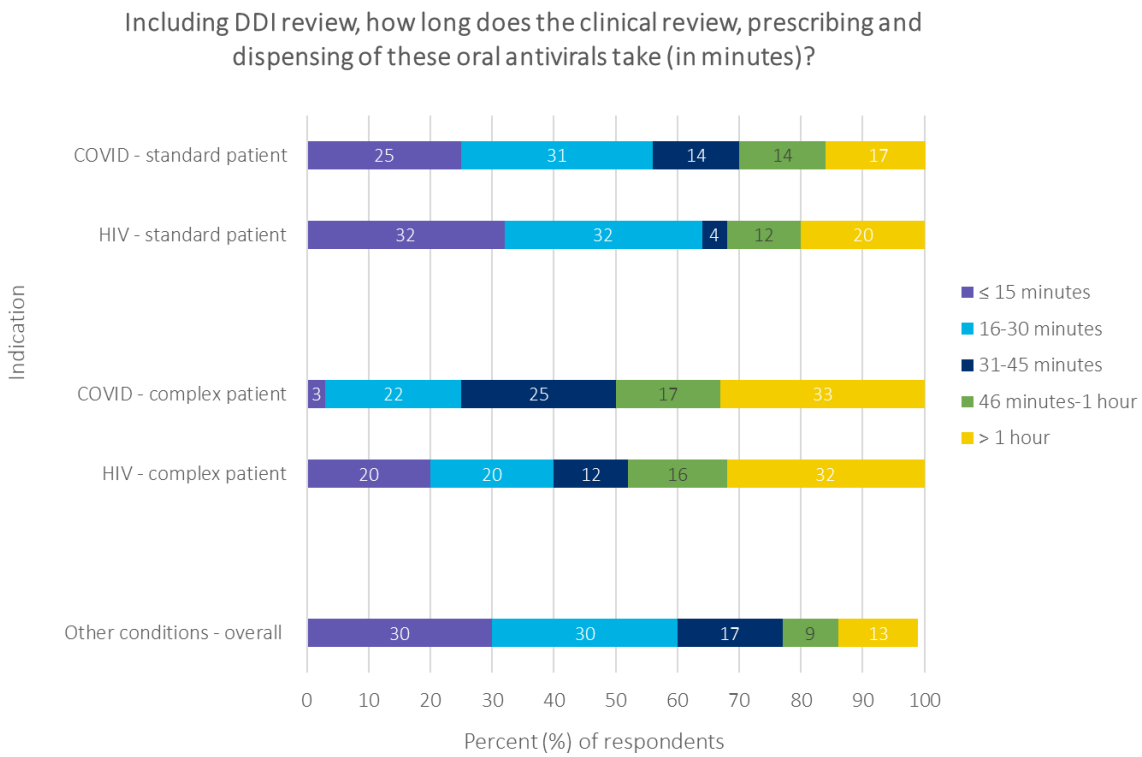

Figure 2. HCP responses to the question "Including DDI review, how long does the clinical review, prescribing and dispensing of these oral antivirals take (in minutes)?"

When the results on administration time for COVID-19 oral antivirals are stratified to only include HCPs with HIV experience too, we see that there are no substantial differences in DDI assessment or overall dispensing time for HCPs with or without experience prescribing oral antivirals for HIV (Figures 3 and 4). This data suggests that current administration times seen in clinical practice among antiviral specialists with HIV experience are representative of the overall administration times to be seen across broader practice in the future.

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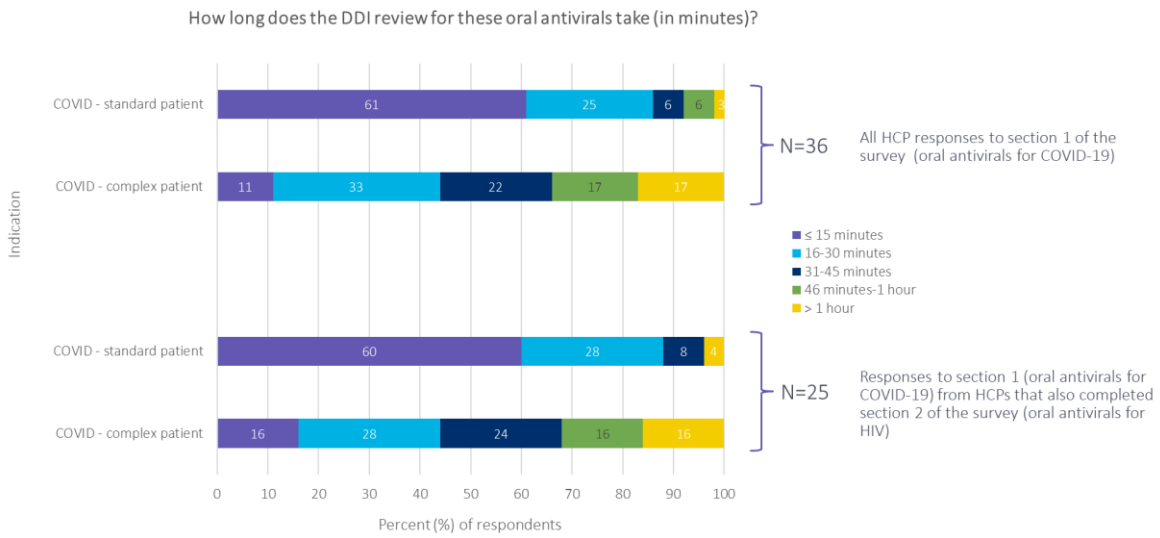

Figure 3. HCP responses to the question "How long does the DDI review for these oral antivirals take (in minutes)?" Data stratified by HCP respondents with and without HIV experience.

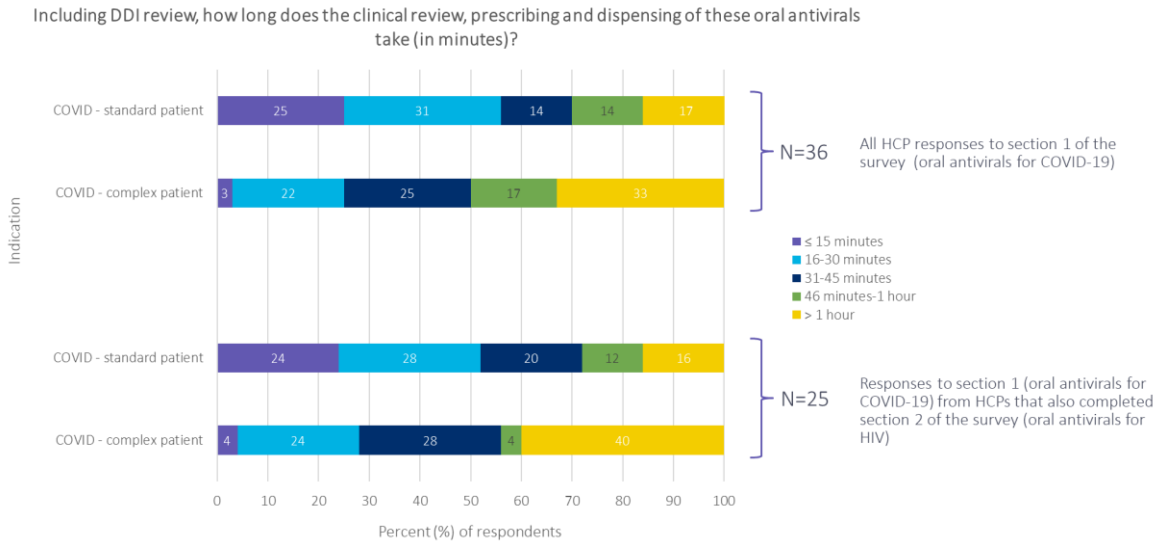

Figure 4. HCP responses to the question "Including DDI review, how long does the clinical review, prescribing and dispensing of these oral antivirals take (in minutes)?" Data stratified by HCP respondents with and without HIV experience.

Additional questions were asked on the use of tools and checklists to assist with DDI review; 50% of HCPs stated these were not currently used for clinical assessment of oral antivirals for COVID-19, suggesting there is room for further efficiencies in the time requirements of DDI assessment in future clinical practice in the primary care setting.

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The results from this survey support the assumption that overall administration time of oral antivirals (including DDI review) for COVID-19 would take no more than an hour for the average patient, including those that require more complex clinical review. Based on these results, the cost of DDI assessment and overall clinical review, prescribing and dispensing of oral antivirals for COVID-19 has been calculated using hourly reference costs from the PSSRU[17] (Table 1 below).

NHS role	Hourly rate (PSSRU 2022 report)[17]
Nurse band 6	£53
Nurse band 7	£64
Nurse band 8a	£72
Nurse band 8b	£85
Pharmacist (band 8a)	£72
FY2	£50
specialist registrar (associate specialist)	£137
Consultant	£143

Weighted averages from the survey were calculated for 'time requirement for DDI review' and 'overall clinical review, prescribing and dispensing time' for both standard and complex patients. Conservative time estimates were taken, i.e where a HCP selected 16-30 minutes, 30 minutes were assumed, and 2 hours were assumed where ≥1 hour was selected. The HCP responses for 'role conducting DDI review' were mapped to PSSRU derived hourly rates (Table 1) and weighted averages of responses were calculated. Based on the above data, average costs of DDI review and overall clinical review, prescribing and dispensing of oral antivirals for standard and complex patients with COVID-19 has been calculated (weighted average time requirement * weighted average NHS role hourly cost):

Cost of DDI review for oral antivirals for a standard patient with COVID-19: **£42.94**

Cost of overall clinical review, prescribing and dispensing of oral antivirals for a standard patient with COVID-19: **£78.94**

Cost of DDI review for oral antivirals for a complex patient with COVID-19: **£85.88**

Cost of overall clinical review, prescribing and dispensing of oral antivirals for a complex patient with COVID-19: **£113.58**

These results support the company's original suggested scenarios for administration for a standard (£75) and complex patient (£117) as being

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	appropriate, and that the £410 currently modelled by the EAG is a vast overestimate, even in the most complex patient cases.
4	**<u>Unresolved issues with the assignment of mortality rates in the Paxlovid arm of the model</u>** **The approach used to derive the confidence intervals in the NMA is inappropriate for the context it was used.** **Confidence interval lower bounds define the lower efficacy scenarios for EPIC-HR considered in this appraisal, this approach underestimates the efficacy of Paxlovid on mortality – further consideration should be given to the derivation of this data given the importance to decision making.** In the original company submission, it was noted that the relative risk of death from any cause through day 28 after treatment with Paxlovid is implausible. The EAG model assumes this relative risk of death to be 0.15 (0.001-0.63), which is not in alignment with the informative EPIC-HR trial data in which no deaths were observed in the treatment arm. In their response, the EAG noted that these data are provided by COVID-NMA and commented that the distribution will utilise a continuity correction to adjust for small numbers of observed events. Where there are a small number of observations it can appear that the transition probabilities are more certain than they truly are, and it is common for continuity corrections to be performed to reduce this limitation. We acknowledge that in the case of low or no events in the data set, continuity correction is necessary in a network meta-analysis (NMA). However, we believe that the approach used to derive the confidence intervals (CI) in the NMA is inappropriate for the context it was used and that this issue of defining an appropriate mortality rate for Paxlovid in the economic model remains unresolved. The NMA protocol does not specify the method of continuity correction conducted, but it is likely that the Wald statistic was used as this produces the closest result to the reported values. Our calculations based on the modified Wald statistics (i.e., with continuity correction of 0.5 to each cell) results in a relative risk = 0.04 with 95% CI of (0.0024, 0.6792): $exp(log(0.5/1040/(12.5/1047)) + qnorm(0.975) * c(-1, 0, 1) * sqrt((1 - 0.5/1040)/0.5 + (1 - 12.5/1047)/12.5))$ Please note that the upper bound (0.6792) is slightly different from the 0.63 incorporated into the EAG model which could be a typo or differences in software used.

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	The Wald test is popular due to its simplicity and ease of implementation when calculating CI. However, it is too inaccurate when used for statistical inferences on small to moderate sample or event sizes. The method often results in marked under-coverage and lower CI endpoints that can fall below zero. It is widely recognised that Wald interval coverage probability is poor for sample proportions near zero or one[18, 19], and therefore, most statistical guidance and publications take this into account by requiring that this interval should be used only when min (np, n(1-p)) is at least five or ten (where p = population proportion and n = sample size). In the case of the EPIC-HR trial, although the overall sample size is large, the number of mortality events in the Paxlovid arm is not only small but zero. Consequently, the Likelihood Ratio test performs better than the Wald for determining CI in this setting. We therefore propose that the appropriate methodology for deriving CI be reconsidered, and that CI for the risk of death from any cause through day 28 after treatment with Paxlovid based on the Likelihood Ratio be implemented into the economic model. From our calculations this updated methodology results in risk of death from any cause through day 28 CI of **(0.00, 0.1745**). **We propose the model base case assumption be updated to these values.** Appendices to this comment below details the SAS code used to derive these CI using the Likelihood Ratio test. **Appendix – SAS code used to derive CI using the Likelihood Ratio test** *data epichr;* *input trt death counts;* *cards;* *1 0 1039* *1 1 0* *0 0 1034* *0 1 12* *;* *run;* *proc freq data=epichr order=data;* *table trt*death/relrisk (Column=2 CL=WALDMODIFIED);* *weight counts;* *run;* *proc freq data=epichr order=data;* *table trt*death/relrisk (Column=2 CL=SCORE);* *weight counts;* *run;* *proc freq data=epichr order=data;* *table trt*death/relrisk (Column=2 CL=LR);* *weight counts;*

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	run; */* *proc freq data=epichr order=data;* *table trt*death/relrisk (Column=2 CL=Exact);* *weight counts;* *exact relrisk method=score;* *run;* *proc freq data=epichr order=data;* *table trt*death/relrisk (Column=2 CL=Exact);* *weight counts;* *exact relrisk method=score2;* *run;* **/*
5	**<u>Inconsistencies in the decision problem</u>** Based on changes to the criteria used to inform the 'high risk' population and the EAG's recent report considering scenarios for age 70+ inclusion in this population, we request that NICE provide clarity on the final decision problem being considered in this appraisal, specifically which population is to be considered in the final economic model. We acknowledge there has been an evolving evidence base as this appraisal has progressed but following the recent EAG reporting we are unclear which age-related high-risk subgroups are being considered appropriate by NICE (draft guidance papers). When NICE requested additional data from the company to inform scenario analyses modelling by specific age groups in the mild COVID 19 setting, it was discussed that data relating to the 70+ subgroups would be provided where available, but that data from similar age groups (e.g. 65+) would be considered as a suitable alternative. In the company response this request was adhered to and data from the 70+ population was presented and explored alongside data from other age-related subgroups (60+ and 65+). Recent EAG critique of this evidence largely dismissed the company's approach and did not consider any alternative data presented alongside that available for the 70+ subgroup. As noted above, we request clarity from NICE on their rationale for not considering alternative age-related data and how this relates to the final decision problem for this appraisal.

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6	**Availability of tools to improve the efficiency of drug-drug interaction assessments for Paxlovid** In addition to the summary of patient characteristics (SmPC) for Paxlovid 150 mg/100 mg film-coated tablets[20], Pfizer Ltd UK has created resources aligned with the above SmPC to support UK prescribers in the clinical management of drug-drug interactions (DDI) including an online drug interaction checker.[21] Our Medical Information department has successfully responded to drug-drug interaction queries from UK healthcare professionals and continues to do so. In addition, Pfizer Ltd UK has also prepared resources that can be used by medical colleagues in response to individual unsolicited enquiries from members of the health professions or other relevant decision makers to offer continued support. Alongside the evidence provided in section 3, the availability and uptake of these resources in the primary care setting supports a reduction in the time requirements for DDI assessments which should be considered when defining the administration costs of Paxlovid applied in the economic model.
7	**Company suggested base case in 70+ population** The committee conclude that admin costs for Paxlovid are £410, whilst a complex medical review for care home residents' costs only £117. New feedback from 36 HCPs concludes the likely time required when Paxlovid becomes routinely commissioned would be between £42.94 and £113.58. We request the committee to consider a range of £75-£117. EPIC-SR was not designed and statistically powered to demonstrate efficacy in COVID-19 hospitalization or death endpoints among subgroups of patients and its use to inform Paxlovid clinical effectiveness in the economic model is inappropriate for decision making. EPIC-HR is still the most robust source of evidence available supported by RWE and should continue to be used as the primary source of Paxlovid efficacy in this appraisal. Accounting for uncertainty in the efficacy data we propose the committee considers mid-point efficacy values of mean efficacy and low scenario from the EPIC HR trial. The suggested base case inputs presented in the table below should be considered for final decision making. Changes to the EAG model reflect the changes to Paxlovid administration costs and clinical effectiveness estimates highlighted in sections 2 and 3:

Parameter	Base case value costs	Source

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Admin costs	[redacted]	PSSRU (average cost per resident of the multi-professional medication review intervention)[16]
Nirmatrelvir/ritonavir hospitalisation or death RR	[redacted]	EPIC HR mid-point of mean efficacy and low scenario values
Nirmatrelvir/ritonavir mortality D28 RR/ritonavir efficacy	[redacted]	EPIC HR mid-point of mean efficacy and low scenario values using updated confidence intervals for efficacy on mortality

Using these assumptions, we show that Paxlovid is cost-effective between £20,000 and £30,000 per QALY with an ICER of £[redacted]/QALY

	Total costs	**QALYs**	**ICER**	**NBM at £20K**	**NBM at £30K**
SoC	[redacted]	[redacted]			
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8

<u>Implementation of updated efficacy of Paxlovid on mortality in the model.</u>

Running scenario analyses with the model without a manual is challenging. It is unclear how exactly the EAG has been implementing changes related to mortality in the model given the inbuilt macro does not function. In the proposed base-case in section 7 we implemented changes to efficacy values as follows: In the "Baseline mortality outpatients" tab we updated D17 using the goal seek function to E17 by changing J17. In the "Parameters" tab we have updated the efficacy value in L98, L99, F98 and F99 to mid-point values or the low efficacy and mean efficacy scenarios. We have submitted the updated model alongside this response.

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.

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- Please underline all confidential information, and separately highlight information that is [redacted] and information that is [redacted]. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Society for Heart Failure

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	None
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The British Society of Heart Failure strongly believe patients with a diagnosis of heart failure should be offered out of hospital antiviral therapy should they contract COVID-19 in order to prevent the development of progressing to severe disease. The draft recommendation does not have heart failure as an inclusion for eligibility, and we feel this should be amended. Patients with heart failure have an increased risk of infection-related morbidity and mortality (1). A number of studies have specifically shown worse clinical outcomes in patients with heart failure who are admitted to hospital with COVID-19 when compared to those without (2). The mortality risk of heart failure even without COVID is high, with 1 in 10 patients not surviving a hospital admission. 1 in 3 of those who do reach discharge from hospital do not subsequently survive beyond 1 year. Furthermore, 80% of our patients are diagnosed with heart failure when they present in an acutely unwell decompensated state, thus proving the seriousness of the condition. Our patients also often have multiple comorbidities that make them more vulnerable,

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	including 30% having chronic kidney disease, and 30% having diabetes. This puts these patients at even higher risk of immunocompromise, complications of infection and need for hospitalisation if they develop COVID. Heart failure patients are at particular risk if they become bed bound from a severe COVID-19 infection, as they develop systemic inflammation and coagulation issues. Being hypoxic from infections such as COVID-19 increases oxidative stress which leads of intracellular acidosis, damage to mitochondria, and cell death. Fever and enhanced sympathetic activity can cause tachycardia which increases myocardial oxygen consumption and is a particular issue in patients with heart failure who do not have the cardiac reserve to tolerate this. Furthermore COVID-19 can cause a cytokine storm and active the coagulation cascade causing thrombosis. Therefore, patients with heart failure are at increased risk of end organ damage if they contract severe COVID-19 infection and need to be protected against this. We strongly feel offering out of hospital anti-viral therapy to these patients is extremely important. References- 1) Italia L, Tomasoni D, Bisegna S, et al. COVID-19 and heart failure: from epidemiology during the pandemic to myocardial injury, myocarditis, and heart failure sequelae. Front Cardiovasc Med. 2021;8:713560. (2) Yonas E, Alwi I, Pranata R, et al. Effect of heart failure on the outcome of COVID-19—a meta analysis and systematic review. Am J Emerg Med. 2021;46:204-211.
2	The BSH are concerned that the draft recommendations do not include people with an active diagnosis of heart failure and as a result the population with this specific disability are being disadvantaged. The draft recommendations have retained the specific link for access to Niramtrelvir plus ritonavir treatment to the population defined in the updated McInnes Report. The updated McInnes Report clearly states that it has “identified several cardiovascular diseases, particularly heart failure [as additional risk factors]” but has not made any specific recommendations around these conditions. The BSH consider that NICE must assess the best evidence available for relative severe Covid 19 risk for people with heart failure and draw its own conclusions. The two Omicron era studies referenced in the NICE assessment, Hippesley – Cox et al (2022) and Agrawal et al (2022) both evidence higher severe Covid 19 risk in people with heart failure compared to some conditions included in the McInnes list, such as the immune mediated inflammatory disorders of rheumatoid arthritis or systemic lupus erythematosus. Hippisley – Cox et al (2022), demonstrate a relative risk of death from Covid 19 in men from heart failure of 1.41 compared to 1.24 in rheumatoid arthritis or systemic lupus erythematosus and for women 1.63 compared to 1.18. Agrawal et all (2022) demonstrate an adjusted relative risk of hospitalisation or death from Covid 19 in the vaccinated and boosted population of 2.38 for heart failure compared to 2.32 for people with rheumatoid arthritis or systemic lupus erythematosus. The BSH believe that there is sufficient evidence for NICE to recommend people with heart failure are included in the groups able to access Nirmatrelvir plus ritonavir for treating mild Covid 19. Failure to include this patient group could discriminate against people with heart failure compared to people who will be able to access this treatment despite having a lower underlying risk of severe Covid 19 disease progression.

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3	The BSH are concerned at the lack of representation and engagement with the clinical cardiology community and notes that the membership of the McInnes Advisory Group does not include a cardiologist. The group includes members from all clinical specialities that are listed in Box 1 but is lacking direct input from cardiology despite evidence suggesting that people with certain cardiac conditions may have similar or a greater risk of severe Covid 19 to conditions included in the recommendations. We hope you consider our comments and are willing to provide more information if necessary.
4	
5	
6	

Insert extra rows as needed

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- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Cardiothoracic Transplant Patient Group at NHS Blood and Transplant

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Nirmatrelvir plus ritonavir for treating COVID-19 (Partial Rapid Review of TA878) [ID6262]

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	None
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The Cardiothoracic Transplant Patient Group are concerned that the draft recommendations do not include people with an active diagnosis of heart failure and as a result the population with this specific disability are being disadvantaged. The draft recommendations have retained the specific link for access to Niramtrelvir plus ritonavir treatment to the population defined in the updated McInnes Report. The updated McInnes Report clearly states that it has "identified several cardiovascular diseases, particularly heart failure … as additional risk factors." but has not made any "specific recommendations around these conditions…". The Cardiothoracic Transplant Patient Group consider that NICE must assess the best evidence available for relative severe Covid 19 risk for people with heart failure and draw its own conclusions.

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	The two Omicron era studies referenced in the NICE assessment, Hippesley – Cox et al (2022) and Agrawal et al (2022) both evidence higher severe Covid 19 risk in people with heart failure compared to some conditions included in the McInnes list, such as the immune mediated inflammatory disorders of rheumatoid arthritis or systemic lupus erythematosus. Hippisley – Cox et al (2022), demonstrate a relative risk of death from Covid 19 in men from heart failure of 1.41 compared to 1.24 in rheumatoid arthritis or systemic lupus erythematosus and for women 1.63 compared to 1.18. Agrawal et all (2022) demonstrate an adjusted relative risk of hospitalisation or death from Covid 19 in the vaccinated and boosted population of 2.38 for heart failure compared to 2.32 for people with rheumatoid arthritis or systemic lupus erythematosus. The Cardiothoracic Transplant Patient Group believe that there is sufficient evidence for NICE to recommend people with heart failure are included in the groups able to access Nirmatrelvir plus ritonavir for treating mild Covid 19. Failure to include this patient group could discriminate against people with heart failure compared to people who will be able to access this treatment despite having a lower underlying risk of severe Covid 19 disease progression.
2	The Cardiothoracic Transplant Patient Group are concerned at the lack of representation and engagement with the clinical cardiology community. The Cardiothoracic Transplant Patient Group notes that the membership of the McInnes Advisory Group does not include a cardiologist. The group includes members from all clinical specialities that are listed in Box 1 but is lacking direct input from cardiology despite evidence suggesting that people with certain cardiac conditions may have similar or a greater risk of severe Covid 19 to conditions included in the recommendations. The Cardiothoracic Transplant Patient Group recommends that the NICE appraisal process the panel seek the expert opinion from a professional cardiac body, such as The British Society For Heart Failure.
3	
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Insert extra rows as needed

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following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Long Covid SOS

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Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We welcome the acknowledgement in 3.18 last para 'model was not sensitive to other benefits of treatment like faster resolution of symptoms (hospital setting)'. The model is still considered most appropriate for the access to first line treatments to Covid-19 and we are concerned that the healthcare and economic costs of Long Covid are not captured as this data is harder to resource.
2	We are in agreement that future Covid-19 models should include the 'impact on incidence and duration of long COVID' as stated in the uncaptured benefit in 3.28
3	There is a research evidence gap as it has not been determined who is most at risk of developing Long Covid and the impact of subsequent infections of Covid-19 in those with pre-existing Long Covid.
4	We urge that future clinical trials into anti-viral and Covid-19 treatments should follow up participants to establish the impact of the treatment on the subsequent development of Long Covid or any changes to a Long Covid condition if used on subsequent Covid-19 infections.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UK Health Security Agency – COVID-19 Therapeutics Programme

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Example 1	We are concerned that this recommendation may imply that ……..
1	There is no current option for the treatment of severe COVID-19 in children in proposed NICE guidance. Thank you for reviewing the role of nirmatrelvir/ritonavir in this population, as safety and efficacy data show it can be used in children 12 years and older.
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Insert extra rows as needed

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Therapeutics for people with COVID-19. An economic evaluation:
EAG additional analysis post NICE Appraisal Consultation Document

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Abdullah Pandor, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Shijie Ren, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
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Date completed	2nd June 2023

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Declared competing interests of the authors

No author declares a conflict of interest.

1 Introduction

This appraisal (ID6262) has evolved from ID4038 which covered therapeutics for people with COVID-19. NICE did this such that guidance could be published for the majority of treatments appraised with recommendations on the use of nirmatrelvir plus ritonavir (henceforth nirmatrelvir/ritonavir) in older patients following and not causing a delay to the recommendations in ID4038. Recommendations for ID4038 have been published in NICE Technology Appraisal 878 (TA788[1]). Nirmatrelvir/ritonavir is recommended for adults with COVID-19 provided they do not need supplemental oxygen and have an increased risk for progression to severe COVID-19 as defined in an independent advisory group report commissioned by the Department of Health and Social Care.[2] This report has been referred to by NICE as the 'McInnes report'.

This document should be read in conjunction with the initial EAG report[3], erratum[4], and EAG report following the NICE Appraisal Consultation Document[3] for TA878, which provide more details on the work which has been undertaken. Additionally, the company's (Pfizer) submission related to the use of nirmatrelvir/ritonavir in older patients and an EAG document critiquing this submission and containing EAG-generated ICERs expressed in terms of cost per quality-adjusted life year (QALY) gained should be read; these documents are contained on the NICE website.[5]

Section 2 summarises the seven comments made by the company in response to NICE's Appraisal Consultation Document (ACD); for cross-referencing purposes, the EAG has retained the numbers in the company's document resulting in these being Comment 2 to Comment 8. Section 2 also provides EAG critiques of the comments made by the company.

Section 3 details the analyses undertaken by the EAG and the generated ICERs. Section 4 provides the results generated by the EAG. Section 5 provides a discussion on the results generated by the EAG and by the company.

2 A summary of the company's comments

The seven comments made by the company are bulleted here and then discussed in more detail in following sub-sections. Not all comments relate to the EAG, and this has been noted where appropriate. The numbering of comments is as in the company's document.

- EPIC-HR is more appropriate to model the efficacy of nirmatrelvir/ritonavir than EPIC-SR
- The administration costs of providing nirmatrelvir/ritonavir are too high
- The statistical analysis undertaken by COVID-NMA is inappropriate
- Clarity requested from NICE regarding the ages considered in the decision problem
- Resources provided by the company to support providers in management of drug-drug interactions
- New base case analyses
- Methods for amending the EAG's model

More details on each of these points are provided in the company's submission. The EAG has provided a critique of the company's position within each sub-section to improve readability.

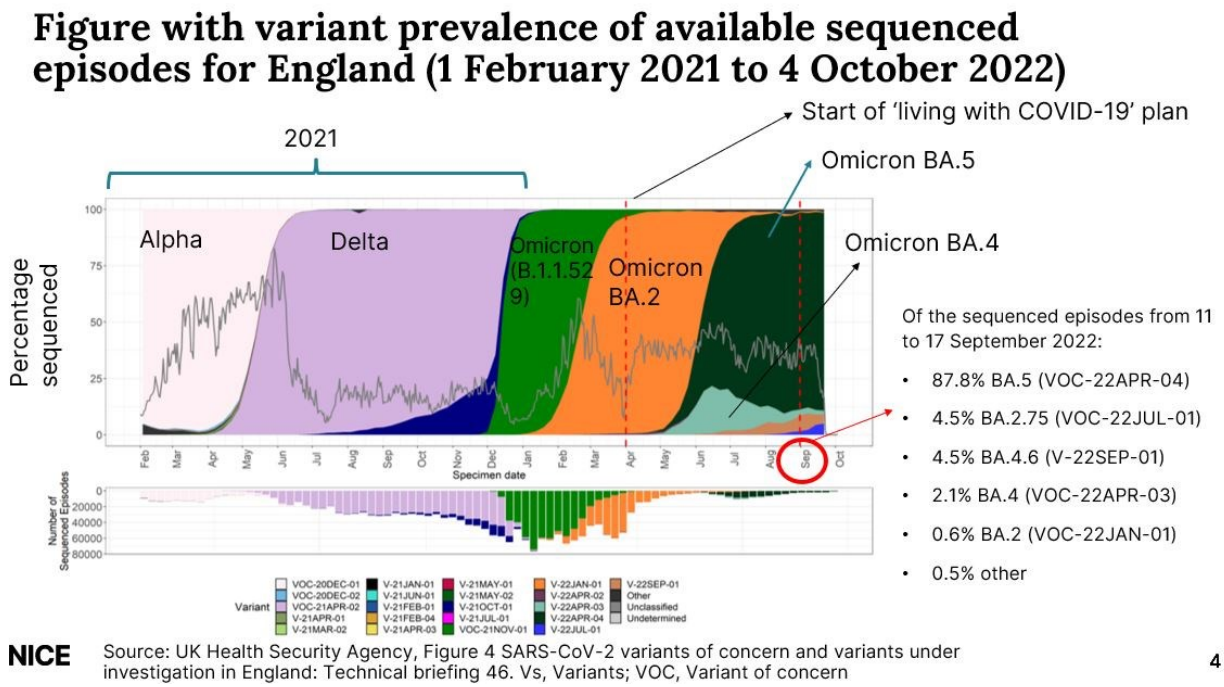
2.1 Comment 2: EPIC-HR is more appropriate to model the efficacy of nirmatrelvir/ritonavir than EPIC-SR

For information, brief details of the two EPIC studies (EPIC High Risk (EPIC-HR) and EPIC Standard Risk (EPIC-SR) are provided.

The EPIC-HR study recruited symptomatic, unvaccinated, non-hospitalised adults at high risk for progression to severe COVID-19 (n=2246). Recruitment centres were worldwide (predominantly in the United States and with none in the UK) with patients enrolled between the 16th of July 2021 and the 9th of December 2021.[6] This time period would have been largely aligned with the Delta SARS-CoV-2 variant (see Figure 1).

The EPIC-SR study recruited patients who are at standard risk for developing severe COVID-19. Recruitment centres were worldwide (predominantly in the United States and with none in the UK[7]). Patients were enrolled from the 25th of August 2021 with the last updated results reported in December 2021. 1153, patients had been enrolled with 721 of these patients vaccinated adults with at least one risk factor for progression to severe COVID-19.[8] This time period would have been largely aligned with the Delta SARS-CoV-2 variant (see Figure 1).

Figure 1: Slide presented at a NICE Appraisal Committee related to the prevalence of SARS-CoV-2 variants.



The company states that the use of EPIC-SR to inform clinical effectiveness is inappropriate as the study was not statistically powered to demonstrates efficacy within subgroups (such as vaccinated patients) and that enrolment was stopped due to the availability of nirmatrelvir/ritonavir outside of the study. The company contends that EPIC-HR is the most robust source of clinical evidence and that this is supported by real world data from a vaccinated population.[9]

Whilst the company "*agrees that EPIC-SR has become increasingly important because it enrolled high risk patients who were vaccinated, a patient subset more representative of current high levels of population immunity acquired following vaccination, natural infection, or both*" it disagrees "*that EPIC-SR can be used to replace EPIC-HR as the pivotal study to support the endpoint of COVID-related hospitalisation or death*" as there was a low number of events and because EPIC-SR was not powered for this endpoint.

The company states that both EPIC-HR and EPIC-SR reduced pre-specified endpoints relative to placebo and that EPIC-SR had results consistent with EPIC-HR, although the results were not provided in the company's response to allow a comparison. The pre-specified endpoints listed by the company were: the SARS-CoV-2 viral RNA level; the proportion of participants with COVID-19-related hospitalisation or all cause death; the total number of COVID-19 related medical visits; and the proportion of patients with post-baseline severe signs and symptoms. The company states that the relative risk reduction (RRR) was similar for the seropositive subgroup and seronegative subgroup with

values of 88% and 85% respectively.[10] The RRR in the EPIC-SR vaccinated high-risk subgroup was 58% which was described in the FDA briefing document as similar to the 88% and 85% values[10] as all were over 50%. The company that "*the appropriate economic model should use the relative risk reduction estimates obtained from the EPIC-HR study and apply them to the background risk in the specific patient population of concern, so that the absolute risk reduction can be estimated appropriately*."

The company also states that were EPIC-SR to be used in the economic analyses that "*the consideration of the lower efficacy scenario (confidence interval [CI] lower bounds for hospitalisation and mortality informing efficacy) is inappropriate*" as "*the lower efficacy scenario was originally implemented as a compromise to address some of the uncertainty in treatment effectiveness among an unvaccinated population (EPIC-HR) and the generalisability of this data to a contemporary real-world population*" and that EPIC-SR included a sample of vaccinated patients.

The company states that real-world evidence (RWE) studies "*provides critical supportive evidence that complements and extends the available evidence of treatment efficacy, including to vaccinated individuals and also to time periods following the emergence of the Omicron variant*". The company also states that "*RWE provides valuable information to support the generalisability of the EPIC-HR trial data*" and that "*the committee concluded that there was no in vitro evidence showing reduced clinical efficacy of nirmatrelvir plus ritonavir across the variants tested*". The company states that the estimates of effectiveness from RWE studies "*ranges from approximately 40% to 80% in both vaccinated (with or without a booster) and unvaccinated individuals, with a clear overlap in effectiveness estimates between these two populations which demonstrates that data from an unvaccinated population may reasonable reflect clinical effectiveness in vaccinated individuals*."[9, 11-14] The company adds that "*Effectiveness has also been shown to not vary by other clinical characteristics including age group, and immunocompromised status*."[13]

The company highlights that the Lewnard study[9] assessed the efficacy of nirmatrelvir/ritonavir relative to the timing of treatment from symptom onset. This study was undertaken between the 8th of April and the 7th of October (when Omicron BA.2, BA.4 and BA.5) were most prevalent (see Figure 1). The company reports that nirmatrelvir/ritonavir "*was 80% effective overall, 83% effective among patients who had received at least 2 Covid vaccine doses, and 92% effective among patients who had received at least 3 Covid vaccine doses.*"

Based on these data the company proposes that "*a value between the mean- and lower-efficacy data be chosen from EPIC-HR to inform the final economic modelling base case*". The EAG notes that in this suggestion the median is used rather than the mean and that the estimation of the upper limit of the 95%

confidence interval (CI) for death is from the likelihood ratio rather than that reported by COVID-NMA (see Comment 4).

EAG critique: The EAG acknowledges the large uncertainty in the efficacy of nirmatrelvir/ritonavir related to the randomised studies, EPIC-HR and EPIC-SR (which enrolled the more appropriate population but where there were only a small number of observed events).

The EAG notes that the RWE studies are subject to a number of limitations. For example, the EAG believes that the results of the RWE study reported by Lewnard *et al.*[9] (conducted among US outpatients with COVID-19 in the Kaiser Permanente Southern California health-care system) should be interpreted with some degree of caution and its generalisability to the UK context is unclear. Methodological limitations may have further impacted the estimates of effectiveness. In this retrospective study, statistical approaches (e.g., variable selection and matching process) and data quality issues may have impacted on the estimation of treatment effects (e.g., recall and ascertainment bias, missing data and misclassification of immunity due to undiagnosed previous SARS-CoV2 infections or those never reported to the health-care system, unmeasured confounding; and adherence to nirmatrelvir/ritonavir). In addition, as noted by Molina et al,[15] '*the rates of 30-day hospitalisation and death reported by Lewnard and colleagues are notably lower than those reported for a subgroup of vaccinated patients with more than one risk factor for progression in the EPIC-SR trial, which was terminated early because of the low event rate*' and '*The requirement of a positive SARS-COV-2 test for study inclusion could have introduced substantial selection bias, because other studies show that up to 80% of patients who receive treatment have missing tests in electronic health records*'. Lewnard *et al*. [9] also note that their findings '*might not be generalisable to patients tested for SARS-CoV-2 infection outside clinical settings'*.

The EAG has run multiple analyses to allow the committee to select the scenario(s) which most closely resemble(s) its judgement on the efficacy of nirmatrelvir/ritonavir noting that the NICE appraisal consultation document stated that the "*committee agreed to consider the mean- and low-efficacy estimates from EPIC-SR alongside the mean and low efficacy estimates from EPIC-HR in its decision making for this population*".[16] Due to this and the proposed suggestion by the company, the EAG has not run any scenario analyses where the efficacy was greater than the mean.

2.2 Comment 3: The administration costs of providing nirmatrelvir/ritonavir are too high

The company states that the cost of £410 provided to the EAG by NICE for administering nirmatrelvir/ritonavir is too high; this cost was taken from the COVID Medicines Delivery Units and costs included elements for: staffing, administrative support, dispensing, clinical consumables, couriering medicines, travel, stationary, and hiring rooms, but excluded medical review to assess drug interactions and any changing in permanent staffing structures.

The company notes that it is not clear whether the committee considered the uncertainty in costs related to future delivery models in ID6262 (this appraisal). The company highlights that a PSSRU review found that "*the average cost per resident of the multi-professional medication review intervention was £117*"[17] for "*the more complex medical review required for care home patients*". The company states "t*his scenario which represents the most complex medical review process and should be considered as the upper limit for oral antiviral administration cost*".

To support its position the company undertook a survey of healthcare professionals (HCP) to '*elicit insight into clinical review and dispensing time for oral antivirals for COVID-19, HIV and other indications.*' The anonymous survey was sent to HCPs listed as a nurse, doctor or pharmacist with experience in the prescription of oral antivirals. Questions were asked about the time required to review and dispense oral antivirals for complex patients with COVID-19, human immunodeficiency virus (HIV) or other conditions. 36 HCPs responded to COVID-19 questions, 25 to HIV questions and 23 for other indications. Comprehensive analyses of the results are provided in the company's response, along with the methodology for estimating the costs of "*overall clinical review, prescribing and dispensing of oral antivirals for a complex patient with COVID-19*" which was £114, which is supportive of the cost of £117 that the company proposes should be used for administration costs related to nirmatrelvir/ritonavir.

EAG critique: The EAG believes that the costs of £117 per patient are plausible and has run scenario analyses where the NICE committee preferred value of £410 has been replaced with a cost of £117.

2.3 Comment 4: The statistical analysis undertaken by COVID-NMA is inappropriate

The EAG provided analyses to the appraisal committee based on the mean of the distribution and the upper and lower limits of the 95% CI. As such, changes in the confidence intervals would impact on all three analyses. The company contends that the method used by COVID-NMA when applying a continuity correction to account for zero events is inappropriate. The company states that the method used by COVID-NMA is not specified, although the company suggests that it is likely that the modified

Wald test was used as "*this produces the closest result to the reported values*" although the upper limit of the 95% CI is calculated to be 0.68 rather than the 0.63 reported by COVID-NMA. The company notes that the differences "*could be a typo or differences in software used*".

The company states that the Wald test "*is too inaccurate when used for statistical inferences on small to moderate sample or event sizes. The method often results in marked under-coverage and lower CI endpoints that can fall below zero. It is widely recognised that Wald interval coverage probability is poor for sample proportions near zero or one*[18, 19] *and therefore, most statistical guidance and publications take this into account by requiring that this interval should be used only when min (np, n(1-p)) is at least five or ten (where p = population proportion and n = sample size). In the case of the EPIC-HR trial, although the overall sample size is large, the number of mortality events in the Paxlovid arm is not only small but zero.*"

The company proposes that the likelihood ratio test is more appropriate that the Wald test in this circumstance. The calculations performed by the company estimate the confidence interval for the relative risk (RR) of death from any cause to day 28 of (0.00 to 0.1745). The company did not alter the RR for death or hospitalisation presumably as both the Wald test and the likelihood ratio gave very similar answers.

EAG critique: The EAG agrees with the company that COVID-NMA may have used the modified Wald test with 0.5 continuity correction to each cell as the EAG manages to reproduce the results presented by COVID-NMA using the modified Wald test. However, the EAG disagrees with the company that the difference in the estimation of the upper confidence interval limit is due to either a typo or differences in software used. The EAG believes that the difference is due to a different population being used in the calculation. COVID-NMA used the intention to treat population (0/1120 vs. 13/1126 for all-cause day 28 mortality) and the company used a subgroup population where patients were treated ≤5 days after onset of symptoms (0/1139 vs. 12/1046 for all-cause day 28 mortality). The EAG agrees with the company to use the subgroup population as it aligns with the licence.

The EAG notes that there are many ways to compute the confidence intervals for categorical data and a common approach is to invert significance tests based on either the Wald test, or the score test, or the likelihood ratio rest.[20] These three methods are asymptotically equivalent under the null hypothesis. In practice, the Wald test is popular because of simplicity. These three methods would provide similar confidence interval limits in the case of large sample size and when proportions are neither near zero nor one. In the case of zero events, the Wald confidence interval limits cannot be computed without applying for continuity corrections. Hence, the Wald confidence interval limits would vary with the choice of continuity correction. Both score and likelihood ratio intervals do not depend on the continuity

correction. Statistical literature suggests that the score and likelihood intervals have several advantages over the Wald intervals.[21] When the sample size is small or the proportion is near zero or one, score tests sometimes perform better than likelihood ratio tests.[22]

The EAG highlights that the company only states that the likelihood ratio test performs better than the Wald test for computing confidence interval with zero events and presents a confidence interval derived using the likelihood ratio test. The company does not discuss the score test and does not present a confidence interval based on the score test. However, the SAS code provided by the company includes computing the confidence interval using the score test, so the company is aware of this method.

The company highlights that it is factually inaccurate for the Appraisal Committee to state that "*the efficacy estimate from EPIC-SR had assumed no mortality benefit because it was not clear from the information available whether there had been any deaths in the trial*" and states that the press release from which the data used by the EAG are taken "*clearly states that "Other not statistically significant findings included no PAXLOVID-treated patients admitted to the intensive care unit, compared to three in the placebo group, and* ***no deaths in patients who received PAXLOVID with one death in the placebo group***." The EAG notes that in response to NICE the company confirmed that there had been one death in the vaccinated subgroup within the placebo arm.

The EAG re-calculated the 95% CI for relative risk for hospitalisation or death, and call-cause day 28 mortality using the Wald test, score and the likelihood ratio. The results are shown in Table 1.

Table 1: Results of RR for hospitalisation or death and all-cause day 28 mortality for EPIC-HR and EPIC-SR

	Paxlovid	Placebo	Wald test (95% CI)	Score (95% CI)	Likelihood ratio (95% CI)
EPIC-HR[1]					
Hospitalisation or death	8/1039	66/1046	Median: 0.122 (0.059, 0.253) Mean: 0.131	Median: 0.122 (0.060, 0.249) Mean: 0.130	Median: 0.122 (0.054, 0.238) Mean: 0.131
All-cause day 28 mortality	0/1039	12/1046	Median: 0.0403[2] (0.0024, 0.6792)[2] Mean: 0.114	Median: 0 (0, 0.3215) Mean: 0.008[3]	Median: 0 (0, 0.1745) Mean: 0.006[3]
EPIC-SR					
Hospitalisation or death	3/361	7/360	Median: 0.4654[2] (0.1320, 1.6412)[2] Mean: 0.572	Median: 0.4274 (0.121, 1.5045) Mean: 0.526	Median: 0.4274 (0.0927, 1.5242) Mean: 0.552
All-cause day 28 mortality	0/361	1/360	Median: 0.3324[2] (0.0136, 8.1327)[2] Mean: 1.257	Median: 0 (0, 3.8277) Mean: 0.037[3]	Median: 0 (0, 5.7961) Mean: 0.050[3]

[1] A subgroup population where patients were treated ≤5 days after onset of symptoms, [2] Continuity correction applied when minimum (np, n(1-p)) is less than five or ten (where p = population proportion and n = sample size). [3] When calculating the mean with median and lower limits of zero, we assumed that the median=0.001 and the lower limit of the 95% CI =0.0001
CI – confidence interval.

2.4 Comment 5: Clarity requested from NICE regarding the ages considered in the decision problem

In its initial submission related to older patients the company evaluated the cost-effectiveness of nirmatrelvir/ritonavir in people under the age of 70 years. However, NICE explicitly instructed the EAG to exclude these and focus only on the analyses provided for the subgroup of patients without a high-risk condition that were 70 years or older, which were combined with patients at high-risk. The company has requested "*clarity from NICE on their rationale for not considering alternative age-related data and how this relates to the final decision problem for this appraisal.*" This is not a matter for the EAG who make no comment on this.

EAG critique: None.

2.5 Comment 6: Resources provided by the company to support providers in management of drug-drug interactions

The company states that it '*has created resources aligned with the above SmPC to support UK prescribers in the clinical management of drug-drug interactions (DDI) including an online drug interaction checker*' and that '*Our Medical Information department has successfully responded to drug-drug interaction queries from UK healthcare professionals and continues to do so. In addition, Pfizer Ltd UK has also prepared resources that can be used by medical colleagues in response to individual unsolicited enquiries from members of the health professions or other relevant decision makers to offer continued support.*' The company uses this as supportive evidence that the costs reported by NHSE for administering nirmatrelvir/ritonavir (see Comment 3) are too high.

EAG critique: The EAG notes the company's comments and has run scenario analyses where the NICE committee preferred value of £410 has been replaced with a cost of £117.

2.6 Comment 7: New base case analyses

The company produce new base case results amending the administration costs from £410 to £117, changing the relative risk (RR) of hospitalisation or death associated with nirmatrelvir/ritonavir treatment to 0.200, and changing the RR of death associated with nirmatrelvir/ritonavir treatment to 0.1073. These values are obtained from averaging the median value and the upper limit of the 95% CI. The results from the company's base case are shown in Table 2. The company's base case ICER is [redacted].

Table 2: Results from the company's base case

	Costs (£)	QALYs	Inc Costs (£)	Inc QALYs	ICER
SoC	[redacted]	[redacted]			
N/R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N/R – nirmatrelvir/ritonavir; QALYs – quality-adjusted life years; SoC – standard of care

EAG critique: The EAG has provided alternative scenarios which are detailed in Section 3.

2.7 Comment 8: Methods for amending the EAG's model.

The EAG did not produce a user manual for the model due to the time deadlines. As such, the company were not certain that they had made the intended changes within the model and provided details of the changes made.

EAG critique: The EAG confirms that the company ran the model as intended.

3 The analyses run by EAG

The EAG used the same model structure as previously detailed but needed to update a number of parameters to represent a population aged 70 years and over.

The EAG ran multiple analyses. All used the mean age of hospitalised ([redacted] years) and non-hospitalised patients ([redacted] years) for a cohort 70 years and over and the probability of hospitalisation [redacted] and death [redacted] associated with standard of care (SoC) in this cohort. These data were supplied as academic-in-confidence data from the PANORAMIC group.

The EAG has run 36 scenarios: 18 with an administration cost of £420 per person and 18 with an administration cost of £117 per person. The 18 scenarios are split into 9 that are based on EPIC-HR data and 9 that are based on EPIC-SR data. The 9 scenarios are the combinations of three methods for calculating confidence intervals for relative risk (Wald test, likelihood ratio test and score test) and three assumed efficacies (mean, low and mean-low).

Data on the number of events for EPIC-HR has been taken from a subgroup of EPIC-HR where patients were treated ≤5 days after onset of symptoms.[6] For estimating the RRs for hospitalisation or death the EAG calculated the mean value from the distribution estimated from each confidence interval method and used this in the 'Mean' scenario; this and the estimated 95% CIs can be found in Table 1. The EAG used the upper limit of the 95% CI for the 'Low' scenario and used the average value of the mean and the low scenario to form the 'Mean-Low' scenario. As detailed in Comment 4, the mean values associated with deaths were believed to be implausible low (with RRR of greater than 99% for score and the likelihood ratio – see Table 1). As such, the EAG set the mean value to the mean value of the relevant distribution for hospitalisation and death combined; it is unclear if this will be favourable or unfavourable for nirmatrelvir/ritonavir.

Data for EPIC-SR has been taken from a Pfizer press release (June 2022)[8]. This reported that 3/361 vaccinated adults with at least one risk factor for progression to severe COVID-19 were hospitalised or died in the nirmatrelvir/ritonavir arm compared with 7/360 vaccinated adults with at least one risk factor for progression to severe COVID-19 in the placebo arm. The same method used to derive the Mean, Low, and Mean-Low scenarios for hospitalisation or death and for death for EPIC-HR was applied to EPIC-SR, with the exception that where the upper limit of the 95% CI exceeded unity this was set to unity. Again, the mean value had been set to the RR associated with hospitalisation and death combined as the RRR predicted by the likelihood ratio and score were approximately 0.95 and higher – see Table 1. The values used in the 18 scenarios are reported in Table 3. For completeness, the company's proposed base case is also contained in this table.

The EAG stresses that it does not know which of the 18 scenarios is most plausible, although the Wald test may may be inappropriate for computing confidence interval for RRs for death due to zero events. However, by providing this range of scenarios (alongside the company's base case) it allows the Appraisal Committee to select its preference or to infer ICERs from interpolating between scenarios.

Table 3: Parameter values used in the EAG's analyses

Scenario	Study Used	Continuity Correction Approach	Efficacy scenario	Nirmatrelvir /ritonavir hospitalisation or death RR	Nirmatrelvir /ritonavir death RR
CBC	EPIC-HR	Likelihood Ratio	Mean-Low	0.200	0.107
1	EPIC-HR	Wald Test	Mean	0.131	0.131†
2	EPIC-HR	Wald Test	Low	0.253	0.679
3	EPIC-HR	Wald Test	Mean-Low	0.192	0.405
4	EPIC-HR	Likelihood Ratio	Mean	0.131	0.131†
5	EPIC-HR	Likelihood Ratio	Low	0.238	0.175
6	EPIC-HR	Likelihood Ratio	Mean-Low	0.184	0.153
7	EPIC-HR	Score	Mean	0.130	0.130†
8	EPIC-HR	Score	Low	0.249	0.322
9	EPIC-HR	Score	Mean-Low	0.190	0.226
10	EPIC-SR	Wald Test[1]	Mean	0.572	0.572†
11	EPIC-SR	Wald Test[1]	Low	1.000[2]	1.000[2]
12	EPIC-SR	Wald Test[1]	Mean-Low	0.786	0.786
13	EPIC-SR	Likelihood Ratio	Mean	0.552	0.552†
14	EPIC-SR	Likelihood Ratio	Low	1.000[2]	1.000[2]
15	EPIC-SR	Likelihood Ratio	Mean-Low	0.776	0.776
16	EPIC-SR	Score	Mean	0.526	0.526†
17	EPIC-SR	Score	Low	1.000[2]	1.000[2]
18	EPIC-SR	Score	Mean-Low	0.763	0.763

[1] Continuity Corrected, [2] The 95% upper CI was capped at 1 for this scenario CBC: - Company's base case †The EAG set this equal to the RR of Nirmatrelvir /ritonavir in hospitalisation or death

As with the initial EAG report for this STA, the survival distributions for patients requiring supplemental oxygen and patients not requiring supplemental oxygen were calibrated so that the 28-day mortality rate for patients receiving SoC equalled [redacted]. No changes were made to data regarding time to discharge or change of patients' distributions between ordinal scales when in hospital as the EAG could not identify alternative data sources for this subgroup.

4 The results generated by the EAG

The results generated by the EAG are presented grouped by mean efficacy scenarios, Low efficacy scenarios, and Mean-Low efficacy scenarios. The majority of results use the £410 administration costs preferred by the Appraisal Committee although the ICER when this is reduced to £117 is also provided. The net monetary benefits (NMB) when the administration cost is reduced to £117 can be obtained by subtracting £293 (£410 - £117) from the NMB values generated using the higher administration cost.

4.1 Mean efficacy results

The results of the mean efficacy analysis are shown in Table 4. There is a clear distinction in the ICER dependent on whether EPIC-HR or EPIC SR is preferred. The only ICERs below [redacted] are using EPIC-HR and an administration cost of £117; if the administration cost increases to £410 the ICERs for the EPIC-HR scenarios are approximately [redacted].

Table 4: Mean efficacy results

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY compared with SoC (£)Δ
Standard of Care (all scenarios)						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Scenario 1 (EPIC-HR using the Wald test)						
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4 (EPIC-HR using the likelihood ratio)						
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7 (EPIC-HR using score)						
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 10 (EPIC-SR with the Wald test with continuity correction)						
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 13 (EPIC-SR using the likelihood ratio)						
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 16 (EPIC-SR using score)						
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained
Δ Assuming an administration cost of £117 per person.
QALY – quality-adjusted life years

4.2 Low efficacy results

The results of the low efficacy analyses are shown in Table 5. There is a clear distinction in the ICER dependent on whether EPIC-HR or EPIC SR is preferred. No ICERs are below [redacted], although using EPIC-HR and an administration cost of £117 the ICERs are below [redacted]; if the administration cost increases to £410 the ICERs for the EPIC-HR scenarios are greater than [redacted]. If data from EPIC-SR are used, nirmatrelvir/ritonavir is [redacted], although this assumed (probably implausibly that nirmatrelvir/ritonavir has no impact on either hospitalisation or death).

Table 5: Low efficacy results

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY compared with SoC (£)Δ
Standard of Care (all scenarios)						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Scenario 2 (EPIC-HR using the Wald test)						
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5 (EPIC-HR using the likelihood ratio)						
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8 (EPIC-HR using score)						
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 11 (EPIC-SR with the Wald test with continuity correction)						
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 14 (EPIC-SR using the likelihood ratio)						
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 17 (EPIC-SR using score)						
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained
Δ Assuming an administration cost of £117 per person.
QALY – quality-adjusted life years

4.3 Mean-Low efficacy results

The results of the Mean-Low efficacy analysis for patients at high-risk of hospitalisation are shown in Table 6. There is a clear distinction in the ICER dependent on whether EPIC-HR or EPIC SR is preferred. No ICERs are below [redacted], although using EPIC-HR and an administration cost of £117 the ICERs are below [redacted]; if the administration cost increases to £410 the ICERs for the EPIC-HR scenarios are [redacted]. If data from EPIC-SR are used, all ICERs are above [redacted].

Table 6: Mean-Low efficacy results for people at high-risk of hospitalisation

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC† (£)	NMB compared with SoC†† (£)	Cost per QALY compared with SoC (£)Δ
Standard of Care (all scenarios)						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Scenario 3 (EPIC-HR using the Wald test)						
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6 (EPIC-HR using the likelihood ratio)						
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 9 (EPIC-HR using score)						
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 12 (EPIC-SR with the Wald test with continuity correction)						
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 15 (EPIC-SR using the likelihood ratio)						
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 18 (EPIC-SR using score)						
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† Assuming a threshold of £20,000 per QALY gained †† Assuming a threshold of £30,000 per QALY gained
Δ Assuming an administration cost of £117 per person.
QALY – quality-adjusted life years

4.4 Sensitivity Analysis Results

The EAG ran two sets of the sensitivity analyses: amending the duration for long COVID (by doubling and halving the base case value of 113.6 weeks) and changing the standardised mortality rate (SMR) values associated with long COVID from 7.7 to 5 and 10. Due to the timescales of the project and the broad similarity in changes across scenarios the EAG has run these sensitivity analyses only for Scenarios 7, 8 and 9 which have ICERs between [redacted] and [redacted] when assuming an administration cost of £410 and ICERs between [redacted] and [redacted] when an administration cost of £117 per person was used. The Appraisal Committee may be required to make inferences on the remaining scenarios, or request ICERs for specific scenarios from the EAG. Scenarios 7 to 9 are those that use EPIC-HR data at Mean, Low and Mean-Low efficacy where confidence intervals have been calculated using score and the EAG has set the Mean efficacy RR for death to the RR for hospitalisations and death (a value of 0.130)

As anticipated, the doubling of the impacts of long COVID reduced the ICER whereas halving the duration increased the ICER. These changes are due to nirmatrelvir/ritonavir having a beneficial effect on reducing hospitalisations, with the assumption that 100% of patients hospitalised would have long COVID compared with 10% of people not hospitalised. The range between the ICERs in the doubled and halved duration was approximately [redacted] assuming an administrative cost of £410 and approximately [redacted] assuming an administrative cost of £117 per person.

Also, as anticipated, for the reasons just described, increasing the SMR decreased the ICER whereas reducing the SMR increased the ICER. The results from the sensitivity analyses are presented in Table 7 when the duration of long COVID is altered and in Table 8 when the SMR associated with long COVID is changed. The range between the ICERs in the SMR of 5.0 and the SMR of 10.0 was approximately [redacted] assuming an administrative cost of £410 and approximately [redacted] assuming an administrative cost of £117 per person.

Whilst there is uncertainty in the duration of long COVID and the SMR during the long COVID period, there is no reason to believe alternative values are more plausible than those used in the EAG basecase.

Table 7: Sensitivity Analysis results – changing the duration of long COVID.

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC[†](£)	NMB compared with SoC[††] (£)	Cost per QALY compared with SoC (£)[Δ]
Scenario 7 (EPIC-HR using score) – Mean efficacy: Long COVID duration 113.6 weeks						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7 (EPIC-HR using score) – Mean efficacy: Long COVID duration 56.8 weeks						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7 (EPIC-HR using score) – Mean efficacy: Long COVID duration 227.2 weeks						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8 (EPIC-HR using score) – Low efficacy: Long COVID duration 113.6 weeks						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8 (EPIC-HR using score) – Low efficacy: Long COVID duration 56.8 weeks						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8 (EPIC-HR using score) – Low efficacy: Long COVID duration 227.2 weeks						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 9 (EPIC-HR using score) – Mean-Low efficacy: Long COVID duration 113.6 weeks						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 9 (EPIC-HR using score) – Mean-Low efficacy: Long COVID duration 56.8 weeks						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 9 (EPIC-HR using score) – Mean-Low efficacy: Long COVID duration 227.2 weeks						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[†] Assuming a threshold of £20,000 per QALY gained [††] Assuming a threshold of £30,000 per QALY gained
[Δ] Assuming an administration cost of £117 per person.
QALY – quality-adjusted life years

Table 8: Sensitivity Analysis results – changing the SMR associated with long COVID.

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC[†](£)	NMB compared with SoC[††] (£)	Cost per QALY compared with SoC (£)[Δ]
Scenario 7 (EPIC-HR using score) – Mean efficacy: SMR of 7.7						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7 (EPIC-HR using score) – Mean efficacy: SMR of 5.0						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7 (EPIC-HR using score) – Mean efficacy: SMR of 10.0						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8 (EPIC-HR using score) – Low efficacy: SMR of 7.7						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8 (EPIC-HR using score) – Low efficacy: SMR of 5.0						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8 (EPIC-HR using score) – Low efficacy: SMR of 10.0						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 9 (EPIC-HR using score) – Mean-Low efficacy: SMR of 7.7						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 9 (EPIC-HR using score) – Mean-Low efficacy: SMR of 5.0						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 9 (EPIC-HR using score) – Mean-Low efficacy: SMR of 10.0						
Standard of Care	[redacted]	[redacted]	-	-	-	-
Nirmatrelvir/ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[†] Assuming a threshold of £20,000 per QALY gained [††] Assuming a threshold of £30,000 per QALY gained
[Δ] Assuming an administration cost of £117 per person.
QALY – quality-adjusted life years; SMR – standardised mortality rate

5 Discussion of the results generated by the EAG and those generated by Pfizer

The results generated by the EAG are heavily dependent on the data used to populate the model and to a lesser extent the administration costs assumed in providing nirmatrelvir/ritonavir and the point estimates used for the RRs of hospitalisation and death, and death.

The more favourable base case estimates for nirmatrelvir/ritonavir are generated when data from EPIC-HR are assumed to be generalisable, administration costs of £117 per person are assumed and Mean efficacy is used; in these scenarios ICERs are less that [redacted]. The more favourable results generated by the EAG are relatively similar to the ICER estimated by the company.

The least favourable base case estimates for nirmatrelvir/ritonavir are generated when data from EPIC-SR are used, administration costs of £410 per person are assumed and Low efficacy is used; in these scenarios nirmatrelvir/ritonavir is [redacted], which is probably implausible, however the ICERs are greater than [redacted] when 'Mean-Low' efficacy is used rather than Low efficacy.

There is considerable uncertainty in the decision problem as both EPIC-HR and EPIC-SR recruited patients when the Delta variant was most prevalent, and it is possible that the efficacy of treatment has changed as the variant changed. Whilst EPIC-SR was more representative as it recruited patients who were vaccinated this study was stopped early with a low number of events.

The small number of deaths in both EPIC-HR and EPIC-SR causes problems for estimating the RR of nirmatrelvir/ritonavir in preventing death. The EAG has changed approach and has set the value for the mean RR of death to the Mean value of hospitalisation and death, whilst this is subjective and uncertain, the authors think that this is a reasonable decision. The RR for death in the Low scenario has been generated using three different methods for calculating the confidence intervals for RR (Wald test, likelihood ratio test and score test). For EPIC-SR this did not influence the results as the upper limit of the 95% CI was set to unity for all methods, although this did impact on the Low values when using EPIC-HR which were 0.175 (likelihood ratio), 0.322 (score) and 0.679 (Wald test), although the EAG notes that the Wald test may may be inappropriate for computing confidence interval for RRs for death due to zero events.

The EAG cannot put forward a preferred ICER as there are too many subjective decisions that need to be made in the face of considerable uncertainty, but reitarates that the decision on which study to use is pivotal. If the decision had been to accept a Mean-Low scenario and to use score as the method for calculating confidence intervals then the ICERs are [redacted] (£410 administration cost per person) and

[redacted] (£117 administration cost per person) when EPIC-HR is used and [redacted] (£410 administration cost per person) and [redacted] (£117 administration cost per person) when EPIC-SR is used.

The results were shown to moderately sensitive to the assumed duration of long COVID and also to the SMR associated with long COVID. Attaining accurate parameter values for these variables may be important if the Appraisal Committee chooses scenarios that have ICERs close to the Appraisal Committee's perceived cost per QALY threshold for nirmatrelvir/ritonavir. However, there is considerable uncertainty in the values due to changing SARS-CoV-2 variants, vaccination status, prior infection and changes in standard of care for patients hospitalised with COVID-19.

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Declared competing interests of the authors

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1 Introduction

This addendum explores the potential impact of adverse event (AEs) associated with nirmatrelvir/ritonavir on the incremental cost effectiveness ratio (ICER) as these were not considered in the report dated the 2nd of June 2023.

2 The analyses run by EAG

The external assessment group (EAG) has selected three scenarios to explore the impact of AEs. These scenarios are detailed in Table 1 with the numbering maintained as in the earlier report.

Table 1: Parameter values used in the EAG's analyses

Scenario	Study Used	Continuity Correction Approach	Efficacy scenario	Nirmatrelvir /ritonavir hospitalisation or death RR	Nirmatrelvir /ritonavir death RR
9	EPIC-HR	Score	Mean-Low	0.190	0.226
16	EPIC-SR	Score	Mean	0.526	0.526†
18	EPIC-SR	Score	Mean-Low	0.763	0.763

†The EAG set this equal to the RR of Nirmatrelvir /ritonavir in hospitalisation or death

The EAG has assumed three average QALY losses associated with AEs for each person receiving nirmatrelvir/ritonavir treatment. These values are: 0.0001, 0.0010 and 0.0027; the last value is equivalent to all people receiving nirmatrelvir/ritonavir losing one day at a utility of 1.0 on average.

3 The results generated by the EAG

The results for Scenario 9 are shown in Table 2, for Scenario 16 in Table 3 and in Table 4 for Scenario 18

Table 2: Exploring the impact of AEs on the ICER for Scenario 9

QALY loss from AEs	Incremental discounted QALY	Cost per QALY compared with SoC (£)	Cost per QALY compared with SoC (£)[Δ]
Zero	[redacted]	[redacted]	[redacted]
0.0001	[redacted]	[redacted]	[redacted]
0.0010	[redacted]	[redacted]	[redacted]
0.0027	[redacted]	[redacted]	[redacted]

[Δ] Assuming an administration cost of £117 per person.
AEs – adverse events; QALY – quality-adjusted life years; SOC – standard of care

Table 3: Exploring the impact of AEs on the ICER for Scenario 16

QALY loss from AEs	Incremental discounted QALY	Cost per QALY compared with SoC (£)	Cost per QALY compared with SoC (£)[Δ]
Zero	[redacted]	[redacted]	[redacted]
0.0001	[redacted]	[redacted]	[redacted]
0.0010	[redacted]	[redacted]	[redacted]
0.0027	[redacted]	[redacted]	[redacted]

[Δ] Assuming an administration cost of £117 per person.
AEs – adverse events; QALY – quality-adjusted life years; SOC – standard of care

Table 4: Exploring the impact of AEs on the ICER for Scenario 18

QALY loss from AEs	Incremental discounted QALY	Cost per QALY compared with SoC (£)	Cost per QALY compared with SoC (£)[Δ]
Zero	[redacted]	[redacted]	[redacted]
0.0001	[redacted]	[redacted]	[redacted]
0.0010	[redacted]	[redacted]	[redacted]
0.0027	[redacted]	[redacted]	[redacted]

[Δ] Assuming an administration cost of £117 per person.
AEs – adverse events; QALY – quality-adjusted life years; SOC – standard of care