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Dear Dr. Chakravarty

Re: Response to Initial Scrutiny Letter – molnupiravir for the treatment of people with COVID-19 [ID 4038]

MSD is grateful for your detailed review of our Appeal Letter, and for your view in the Initial Scrutiny Letter that our appeal grounds 1a.1, 1a.2, 1a.3, 1a.4, 1a.6 and 1a.7 are admissible, albeit in some cases with certain qualifications. In addition, we note that you are minded to admit our appeal ground 1b.1, but would like further clarification. MSD is grateful for the opportunity to respond. For consistency, we have followed the order of grounds in our Appeal Letter, and as initially numbered.

Appeal point 1a.1

MSD appreciates that you are minded to refer this appeal point to the Appeal Panel, save that you are not minded to admit challenges against the the NICE Health Technology Evaluations Manual (the "Guidance Manual") or the Process Statement *per se*. In this respect, we ask you to consider the following observations in your final decision:

a) The relevant appeal ground asks simply whether NICE has acted fairly. MSD appreciates that NICE has adopted an approach that a generic challenge to the Guidance Manual (*i.e.*, one that would apply to all appraisals) is not for an individual Appeal Panel to consider. Although that caveat is not to be found in Regulation 9 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 (the "Regulations"), MSD does not take issue with it for the purposes of this appeal.

b) There is no intention in this appeal to challenge the content of the Guidance Manual itself. Pragmatically we accept an Appeal Panel will not entertain such a challenge. As you note, the argument in respect of the Guidance Manual is that the procedure adopted in ID4038 did not adhere to the procedure and safeguards contained in the Guidance Manual (and at times in fact undermined those safeguards).

c) The Process Statement, however, differs fundamentally from the Guidance Manual, and we do not accept that the Process Statement cannot be the proper subject of an appeal. First, as we noted above, Regulation 9 does not appear to allow NICE to exclude any allegation of unfairness, no matter the cause.[1] While we

[1] The observation in the "Guide to the technology appraisal and highly specialised technologies appeal process" that "[a]*n appellant who believes that they have not been treated fairly by NICE or the advisory committee because the published*

(continued…)

do not challenge NICE's practice *vis-à-vis* the Guidance Manual, at least in this appeal, we do not make the same concession *vis-à-vis* a "process statement." We note here that the Regulations put the issue of fairness into the hands of an independent Appeal Panel consisting of individuals appointed by the Secretary of State, and not into the hands of NICE. Second, as far as MSD is aware, the Process Statement is not an established procedural document. We are unaware of any reference in any published NICE procedure to the adoption of a so-called "Process Statement" either during or after the scoping phase of an MTA. The Process Statement appears to be a new concept conceived specifically for this particular appraisal, and has come into existence because NICE felt it could not follow the Guidance Manual in this case. The Process Statement is therefore simply an *ad hoc* expression of the procedure NICE decided to follow in this particular appraisal, because it felt the need to deviate from established procedures. It is therefore not a procedure that NICE is *legally bound* to follow in all appraisals, but rather something that NICE has *chosen* to follow because of the peculiarities of this particular appraisal. In those circumstances, MSD cannot see any reason why the Process Statement should be immune from challenge in an appeal. Certainly the reasoning which we understand applies to the Guidance Manual does not apply to the Process Statement. To suggest it has some special immunity is a novel position being adopted for the first time and risks arriving at a perverse outcome where an appraisal committee could unilaterally deviate as much as it wishes from the Guidance Manual, without even the supervision of an appeal process. Any changes to NICE's published processes in the Guidance Manual (which is adopted after mandatory consultation, as you will know) – no matter how procedurally unfair they might be – would then apparently be beyond the scope of an appeal and only challengeable by way of a judicial review. We respectfully suggest that cannot be right.

d) In case further background assists, MSD understands NICE issued the original version of the Process Statement (minus the September Addendum) in April 2022, after it had completed its consultation on the draft Scope. In that respect, it is a post-Scoping document that NICE developed unilaterally and without consultation to address issues raised in Scoping and to mitigate the challenges NICE faced when considering the exceptional nature of the disease area.[2] Excerpts from Slide 5 of the Stakeholder Information Meeting presentation confirm NICE's decision to deviate from its processes:

> "*Outcome of the scoping workshop*
>
> *NICE's consideration of comments*
>
> - *Acknowledge the concerns around timing* […]
> - *NICE would not be able to respond quickly using its standard MTA approach if it becomes clear that guidance is required.*
> - *Taking this all into account, we will be resequencing the steps of an MTA* […]
> - *Developing and validating an economic model first will enable us to be much more responsive and undertake the evaluation stage and produce recommendations in a shorter time frame.*"[3]

Given the above, the suggestion that a new type of document emerging from the Scoping process, and developed to address a particular logistical concern arising in the context of a specific appraisal, is the same species of document as the Guidance Manual (and benefits from the same protection) seems illogical, and must surely be incorrect.

e) It seems to have been NICE's intention to re-order and shorten an otherwise conventional MTA. The Stakeholder Information Meeting Slides state under "Governance" (Slide 8):

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process has not been followed may appeal on [Ground 1a]" may be a hangover from earlier grounds of appeal which were worded differently to the present grounds. Be that as it may, the appeal guide must be applied within the powers established by the Regulations, which is to say with the words "*because the published process has not been followed*" either ignored or treated as only one example of how unfairness might arise.

[2] Paragraph 2 of the Process Statement

[3] Stakeholder Information Meeting Presentation (14 April 2022), slide 5

"• *This MTA will follow all the steps in* [the NICE health technology evaluations guidance development manual], *but re-sequenced and with shortened timelines because of the exceptional nature of the disease area* [...]

• *Changes* [will] ***only relate to process, not methods or committee structured decision-making***" (emphasis added).[4]

However, the Process Statement did not reflect that intention. As noted in the Appeal Letter, the re-ordering of Phases 1 and 2 meant that the External Assessment Group ("EAG") developed its analysis and modelling by selecting what evidence to review, without the benefit of evidence submissions from manufacturers. Manufacturers were not able to make full evidence submissions, and there was no proper mechanism to consider manufacturer-submitted evidence. The Process Statement says that once the EAG has completed its report, NICE will "[issue] *an invitation for stakeholders to submit evidence*" and this should be "*evidence that is not included in the external assessment report*."[5] The Appraisal Committee would then consider these submissions by following "*the steps outlined in sections 5.7.2 to 5.7.22 of the guidance development manual*."[6]

It is striking that sections 5.7.2 to 5.7.22 of the guidance development manual set out arrangements for Appraisal Committee Meetings. They do not concern whether or how the Appraisal Committee or EAG would consider evidence, and one must surely question how the Committee could have expected to review various stakeholders' raw evidence submissions properly, and in a limited timeframe, while at the same time drawing the evaluation phase to a conclusion during a meeting with stakeholders.

The obvious concern is that despite the best intentions not to alter the methods of review and structured decision-making, the process has changed so significantly that its steps are fundamentally compromised or leave major gaps – in particular that there was an inadequate review of the evidence submitted in what the Process Statement describes as Phase 2. As a result, the quality, scope, thoroughness, rigour and methodology of stakeholder evidence review did change negatively, and structured decision-making did not take place. A key driver in this is the Process Statement, which failed to execute the plan NICE had intended to follow and the reassurances NICE gave to stakeholders.

In our view, it is inconceivable for the Process Statement to be outside the scope of the appeal.

f) With respect to the Process Statement, our appeal therefore asks **two** distinct questions:

i. whether the Process Statement is consistent with the Guidance Manual and upholds the procedural safeguards in the Guidance Manual; and

ii. separately, whether the Appraisal Committee did in fact follow the Process Statement in this appraisal.

MSD submits that both issues are within the scope of the appeal (rather than only the second point), and further that this appraisal fell short on both counts.

g) For the sake of completeness, to address a point you raise, the re-sequencing and shortening of the timescales in this appraisal cannot be outside the scope of this appeal. The re-sequencing and shortening of the MTA process is a deviation from established methods and procedures contained in the Guidance Manual, and is the aim of the Process Statement. As indicated above, use of a "Process Statement" as what could be described as a "loophole" to avoid procedural safeguards in NICE's published procedures is clearly unjustified on public law procedural fairness grounds.

h) With respect to your points numbered 1 – 5 (which we address in the same order):

[4] Stakeholder Information Meeting Presentation (14 April 2022), slide 8

[5] Paragraph 10 of the Process Statement

[6] Paragraph 12 of the Process Statement

Point 1: We agree that the overall contention here is that the process followed in ID4038 did not align with the established procedure for an MTA, as set out in the Guidance Manual. We believe this is consistent with the appeal point you consider admissible, and should rightly be addressed as part of that point. We see no reason to strike these points from the appeal (appreciating that is not necessarily what you propose).

"Re-sequencing" implies re-ordering steps in the Guidance Manual (assuming that it was open to NICE to do this). It cannot justify *omitting* steps, rendering them ineffective, or overriding key procedural safeguards (which we submit has taken place). Re-sequencing – if it can happen at all – presupposes that the new order of the steps is logical and preserves the rigour, fairness and accountability of a technology appraisal. Our point is that all this fell by the wayside and that these critical safeguards were not preserved.

Our observation that any appraisal that fails to adhere to the Guidance Manual may not have the legal effect of an MTA (despite being called an "MTA") seems to be self-evident based on statute. We appreciate that this is a legal point that the Appeal Panel may not wish to opine upon, although we note that the Appeal Panel does benefit from the services of a legal advisor before during and after its hearings. Nonetheless, the observation remains pertinent as it informs the argument being advanced and puts the point into context. Vital though fairness is, what has gone wrong here goes even further than that.

Point 2: We note your comments. To clarify the point being made at the top of page 5 of the Appeal Letter (the third bullet), to which you refer: this is simply to say that the drive to be "pragmatic" left a number of procedural steps open and subject to change. The argument is a general one, as it goes hand in hand with not being clear about what "pragmatism" meant and what this enabled the EAG to do or not do.

Points 3 – 5: We note your observations, but ask that in respect of the Process Statement you refer to our comments above. We consider that a challenge to the Process Statement as characterised above and in the letter is firmly within the scope of an appeal.

Appeal point 1a.2

We appreciate your highlighting two key issues in this appeal point, namely:

> "[…] *that NICE acted unfairly because it departed from published process by (1) allowing EAG to take decisions that should have remained with the Committee and (2) by allowing the EAG to make procedural and methodological changes without prior warning*."[7]

We address these at the bottom of page 7 and the top of page 8 of our Appeal Letter.

While these are two of the key issues, the appeal point is somewhat broader and should not be limited to these two points alone. Specifically:

a. For the reasons set out above, we disagree with your observation that "*if an appellant wishes to challenge the processes set out in the* […] *Process Statement (i.e. the* […] *sequencing and timing set out in the Process Statement), as opposed to the committee's compliance with those processes, then it seems to me that is outside of the scope of the appeals process and would be a matter for NICE*."[8]

b. There are certain other aspects to this appeal point, which we are concerned would be discarded by the narrowing you propose.

    i. In the second paragraph under Ground 1a.2, the Appeal Letter states:

[7] Initial Scrutiny Letter, dated 14 March 2023, p.3

[8] Initial Scrutiny Letter, dated 14 March 2023, p.4

> "*The process and how this affects the appraisal methodology were not clear from the outset, changed as the appraisal moved forwards, and often left key procedural decisions in the hands of the EAG*."[9]

While you acknowledge these points individually, the sentence is deliberately sequential.

The wider point here is that the unfairness of the process comprises individual examples as well as their cumulative effect. Taken in isolation, certain issues raised may seem innocuous, low impact, or within a margin of discretion (although we make no such concession). However, our intention here is also to argue that the Appeal Panel must step back and examine the appraisal of molnupiravir holistically, taking into account each case where the Appraisal Committee exercised its discretion negatively for molnupiravir (often disproportionately or inconsistently, relative to other treatments under review), including those cases where the Appeal Panel judges that the Appraisal Committee's action looked at in isolation was not unfair..

This cumulative effect argument falls within the scope of an unfairness appeal ground, and risks being overridden by narrowing this ground in the manner proposed. We ask you to refer the appeal point in its entirety to the Appeal Panel.

ii. Over pages 6 and 7 of the Appeal Letter, we discuss inconsistency between the Protocol and Final Scope (and a failure to follow the Final Scope more generally). We believe the Appeal Panel must be able to hear these arguments.

iii. The latter half of page 8 of the Appeal Letter notes that in the Protocol the EAG recognised a key methodological issue (namely the significant heterogeneity in standard of care across trials, and not adjusting for that variation). MSD's argument here is that this was an acknowledged shortcoming, exacerbated by the re-sequenced process and shortened timelines. While the EAG raised this as an issue, the Appraisal Committee appeared to brush it under the carpet without resolution. The issue pervaded the appraisal and remained outstanding in the Final Draft Guidance ("FDG"). A decision-making process cannot hold itself out to be sound and fair, if the decision-maker is told of a material shortcoming and either fails to deal with it or fails to explain how it has dealt with it. Both are in our view issues for the Appeal Panel to consider.

Notwithstanding this, the EAG states that "*the results from the MTA could still be informative.*"[10] To clarify, the intention in the Appeal Letter is to call into question what "informative" means; who decides what it means; and whether "informative" is the correct standard under as rigorous a process as a technology appraisal that has direct legal effects on the NHS budget. The analysis under an MTA should correctly be "rigorous" and "robust", rather than merely "informative."

To leave the point open-ended, unspecified, and open to change, is a procedural fairness issue in its own right.

c. We also note your comments at numbered point (3) on page 4 of the Initial Scrutiny Letter, but submit that our legitimate expectation argument should not be discarded. We consider it falls within the broader point that the EAG took decisions inconsistently, inappropriately, and without proper warning or consultation (*i.e.*, within the remit of what you consider admissible).

We appreciate that there is some commonality between the two points you highlight that relate to the EAG (namely that the Appraisal Committee allowed the EAG to take decisions that ought to have remained with the Committee and that the EAG made procedural and methodological changes without warning).

On reflection, that commonality may best be characterised by an additional appeal ground under Ground 1b, that NICE has acted *ultra vires* by wrongly delegating its powers. This ground could then sit alongside and

[9] MSD's Appeal Letter, dated 7 March 2023, p.6

[10] Paragraph 1.5 of the MTA Final Protocol

complement appeal point 1a.2, which would relate to unfairness (and also include the EAG points, as unfairness arguments).

We believe this may help keep matters clearer for the Appeal Panel, and invite you to consider this as an option.

Appeal points 1a.3 and 1a.4

We are comfortable with combining the two points. We had originally kept them separate simply to assist with clarity and focus.

Respectfully, we believe a correction is necessary in your summary of the combined points (at numbered point (1) at the top of page 5 of the Initial Scrutiny Letter):

Where you state "[Whether the Committee] *failed to take adequate steps to identify evidence outside the public domain*,"[11] we ask you to replace the words "*evidence outside the public domain*" with "relevant evidence."

Much of the evidence MSD highlighted to the Appraisal Committee, and that the Appraisal Committee failed to consider, was in the public domain and published. It is therefore incorrect to say MSD is appealing against the decision not to identify unpublished evidence – the failure is broader and affects a suite of published and unpublished evidence.

Appeal point 1a.5

MSD strongly but respectfully disagrees. In our view, there is a clearly arguable and indeed compelling procedural unfairness point here.

It is common ground that the PANORAMIC data were materially different to the other datasets considered in this appraisal. It is also common ground that the patient population in PANORAMIC differed significantly to those who fall within the scope of ID4038. Further, it is established that the inclusion of the PANORAMIC data played a major role in the negative recommendation for molnupiravir.

The plain procedural point is whether the PANORAMIC data were critically assessed and these limitations, differences and biases accounted for. To admit a materially different, potentially biased, and severely limited data source – without any adjustment, allowance or accommodation – into an evidence synthesis exercise is self-evidently a question of methodological soundness and procedural fairness. We struggle to view this otherwise. It is correct that the weight to be given to a piece of evidence is a matter for the Appraisal Committee (subject only to that weight being reasonable), but consideration of the factors that go into forming a view on weight is a question of procedural fairness as it relates to whether all relevant factors have been considered. For example, when considering whether to accept a *post hoc* subgroup analysis, we would say an Appraisal Committee is obliged as a matter of fairness to ask itself questions as to whether any of the well-known limitations of such analyses apply to the particular analysis in question. Only if it does so correctly is the Committee then free to decide what weight to put on the analysis. Failure to carry out this first, procedural step means the Committee is proceeding not on the basis of a proper weighing of the actual evidence before it but instead on generic assumptions such as "*randomised-controlled trials are strong evidence*" or "*post hoc analyses are suspect*" which may well be correct globally but which may or may not hold true in any given case.

We would welcome further discussion or engagement on this point, as the precise counterargument is unclear in your letter.

Alternatively, to improve clarity, you may wish only to refer the evidence synthesis point to the Appeal Panel, the remainder being reference material.

In addition, or further in the alternative, is the point in your letter that this is more about the Committee's evaluation of the evidence rather than the process followed? If so, this may go to a relatively subtle distinction. That would require referring this point to the Appeal Panel under Ground 2 (unreasonableness); but not discarding

[11] Initial Scrutiny Letter, dated 14 March 2023, p.5

it outright. Notwithstanding our point above that this is a question of fairness we would be content to have it referred under Ground 2.

Point 1a.5 could also fall under Ground 2 as follows:

- The PANORAMIC study data had clear limitations in their relevance and generalisability, so making comparisons between, and synthesising, PANORAMIC data with data from other randomised-controlled trials considered in the appraisal was unsound, as established in the Appeal Letter.

- The Appraisal Committee itself acknowledged the limitations of the PANORAMIC study in its FDG.[12]

- Despite its awareness and acknowledgment of the lack of generalisability and limited relevance of the PANORAMIC data, the Appraisal Committee used these in a flawed evidence synthesis process and invested the results of such with unduly significant weight in its ultimate decision not to recommend molnupiravir.

- In light of the clear deficiencies in the evidence synthesis process using the PANORAMIC study that were presented to and acknowledged by the Appraisal Committee, its influential conclusions developed on such shaky foundations cannot reasonably be justified.

Appeal point 1a.6

We note your comments and appreciate your admitting this appeal point under Ground 2.

Appeal point 1a.7

We appreciate that you are minded to admit this appeal point, at least on the basis that the appraisal departed from the Final Scope by omitting virological outcomes from the consideration of outcome measures.

Separately, we appreciate that you are minded to admit our argument under point 1a.7(2) ("*The true benefits of molnupiravir were inadequately assessed in the MTA and omitted from the EAG's economic model*") as a valid Ground 2 point.

However, we respectfully disagree that the remainder of this appeal point is inadmissible under Ground 1a.

a) The Initial Scrutiny Letter (at the bottom of page 5) suggests that hospitalisation and mortality rates held primacy over other outcome measures because the Committee considered them to be "key drivers" for cost-effectiveness, and this was explained at paragraph 3.21 of the FDG. With respect, we consider that paragraph 3.21 of the FDG includes the following:

    - That hospitalisation and mortality were key drivers of the appraisal outcome because (we paraphrase) they indicate how many patients may experience the significant disbenefit as a result of COVID-19.

    - Because of the state of the disease, outcomes for these treatments are more nuanced than hospitalisation and mortality.

    - The model was therefore not sensitive to other benefits of treatment, such as faster resolution of symptoms.

    This goes as far as describing why hospitalisation and mortality were relevant outcome measures, but not why they held primacy, particularly so given the changing disease context and the list of other more relevant outcome measures under the Final Scope. MSD submits that in this respect, the approach is unexplained (or not adequately explained, in the alternative). We consider this remains a valid procedural fairness argument under Ground 1a. Put simply, the Appraisal Committee has to an extent explained

[12] For instance, at paragraphs 3.4 and 3.19 of the FDG

what it is doing, and why some of this is relevant, rather than (as it should) explain the significant decision step in full and with proper reasons.

b) The Initial Scrutiny Letter goes on to say that you "*do not see that this creates any procedural unfairness in the Committee deciding to apply greatest weight to the measures which they consider drive the cost effectiveness in this appraisal*."[13]

We do not in principle disagree. However, that is not quite the contention here. The Committee appears to have focused exclusively on these outcome measures, which are acknowledged to have serious limitations, at the expense of a systematic assessment of other relevant outcome measures.

This goes beyond the question of weighting, and is potentially closer to a rigid ideological stance (*i.e.*, that the modelling initially considered most relevant was beyond question, notwithstanding the increasing weight of evidence as to its limited relevancy). This does not align with the requirement for fairness.

For both the reasons above, we ask you to reconsider admitting Ground 1a.7 in its entirety (save for those aspects you have moved to consider under Ground 2).

Appeal point 1b.1

We appreciate that you are currently minded to refer this appeal point and broadly agree with your summary.

We acknowledge a factual connection between this appeal point and various others (particularly those under Ground 1a). However, we do not consider there to be complete overlap between this appeal point and Ground 1a. Although there is some factual nexus, they relate to separate and distinct issues.

Ground 1a concerns the fairness of the appraisal process, judged against NICE's established procedures and general public law requirements for a fair hearing. Ground 1b requires an examination of some of the same facts but under a very different lens, namely whether the Appraisal Committee properly and adequately considered and accounted for the special needs of a cohort of patients with protected characteristics who may have benefitted from access to molnupiravir. These are materially different issues, and require the Appeal Panel to ask materially different questions.

We disagree that the success of Appeal point 1b.1 is *inevitably* tied to success under one of the Ground 1a points. It might be said that they are correlated (possibly not strongly), rather than causatively connected. Arguments under Ground 1a could be unsuccessful at appeal while those under 1b.1 succeed on their own terms (or *vice versa*). That said, one can also see that NICE's duty to consider, and make reasonable adjustments for, the needs of patients with protected characteristics might bring its obligations to run a fair process and properly consider all relevant evidence into sharper focus.

It is entirely possible for the Appeal Panel to find that NICE's appraisal of molnupiravir was procedurally fair, but nonetheless failed adequately to consider, and make reasonable adjustments for, the needs of patients with protected characteristics who stand to be negatively affected. These are patients for whom nirmatrelvir plus ritonavir is contraindicated, who are likelier to have long term illnesses, be older and/or come from minority ethnic family backgrounds (in which population renal impairment may be more prevalent). The recommendations in the FDG leave these patients with a significantly more burdensome and potentially higher risk treatment option (sotrovimab) relative to the recommendation for other patients. Evaluating whether the Appraisal Committee did right by these disadvantaged patients, as required under human rights and equalities laws, is a separate question to whether the appraisal of molnupiravir was simply fair (albeit fairness might play a part in considering equalities questions). We caution against conflating the two appeal points or making the assumption that the success of one determines the success of the other.

There are various examples of adjustments that the Committee could have made to tackle equalities issues, which fall outside Ground 1a and do not directly relate to procedural fairness. In particular, once the Committee

[13] Initial Scrutiny Letter, dated 14 March 2023, p.6

recognised that equalities laws were engaged and there was a need to consider equitable alternatives to nirmatrelvir plus ritonavir, the Committee could (and in our view should) have:

- carried out further consultation with clinical experts and potentially other stakeholders as to the advantages and disadvantages of the other options;
- assessed the risks of creating further inequalities by recommending one alternative over another (particularly sotrovimab over molnupiravir); and
- considered the possibility of recommending more than one alternative.

Instead, the Committee took a second look at sotrovimab, flexing certain assessment criteria and assumptions (including applying higher hospitalisation rates for patients that were ineligible for nirmatrelvir plus ritonavir and halving the administration cost associated with the intravenous infusion sotrovimab (£820 to £410), which was assumed equal to that of oral treatments). The Committee did not give a second look to molnupiravir, nor show the same assessment flexibility. It is uncertain how a further review and additional flexibility may have affected the overall recommendation. However, the overarching point is that the second look and additional flexibility was not offered for molnupiravir, because the Appraisal Committee had probably already dismissed molnupiravir as an option without assessing the full impact of such a decision for vulnerable patients.

Appeal point 2.1

We respectfully disagree with your conclusions, but are concerned there may be a misunderstanding (for which we apologise).

MSD's submission is not that ***any*** recommendation made following alleged procedural errors must be unreasonable (as a general proposition). Rather, the particular recommendation for molnupiravir was subject to so many procedural errors, biases and inconsistencies, that the particular recommendation lacks a rational basis or foundation and simply does not add up.

As above, this is fundamentally a question of cumulative effect. The other appeal points highlight a number of errors, each of which results in a flawed or questionable decision being taken for molnupiravir. These errors lead to evaluative shortcomings (for example, the rejection of certain real-world evidence leads to incomplete and unrepresentative evidence being appraised, the failure to appraise highly pertinent evidence, and the wrong conclusion being reached). We say that each of those errors tends in the same direction, an unfavourable outcome for molnupiravir. (That will not always be the case, which is one reason why the general assertion that procedural errors must produce an unreasonable outcome is not advanced.)

This appeal point invites the Appeal Panel to step back and examine the combined effect of each flaw, error and shortcoming holistically and in the full context of the appraisal. When examined in this way, there is a clear and obvious reasonableness question that must be answered: in light of such a flawed review of the available evidence, does the Appraisal Committee's assessment "add up" or not? In our view, this is a critically important question for the Appeal Panel to answer, and one that is not covered under any other appeal point.

Appeal point 2.2

MSD acknowledges that as far as the FDG currently reads, the negative assessment for molnupiravir flows from the clinical assessment rather than cost. However, that does not mean that if NICE were to correct the errors relating to the clinical assessment, the appraisal would immediately be fair and reasonable. Administration costs would continue to be a material issue and valid appeal point. We submit the point should be admitted to the appeal, noting the assumption that the unfairness points relating to clinical efficacy must be resolved first.

With respect to your comments on our point (a) ("*Unreasonably high administration cost for molnupiravir*"), we apologise if our letter was unclear. We disagree that it is "*not arguable that it is unreasonable to use current administration costs to inform cost modelling*."[14] It would clearly offend the principle of reasonableness if the

[14] Initial Scrutiny Letter, dated 14 March 2023, p.7

current administration costs were shown to be wrong, or no longer relevant or appropriate for the treatment envisaged in the appraisal.

Evidence from various experts, consultees and commentators to the Appraisal Committee (including MSD) concurred that the administration costs currently modelled related to a very different disease context and would significantly overstate actual costs in the treatment setting covered by this appraisal.

Given that molnupiravir is an oral antiviral treatment with no known drug-drug interactions, it is quick and easy to administer in the community setting, so is significantly more cost effective than the overinflated administration cost adopted by the Appraisal Committee would suggest. MSD presented this to the Appraisal Committee in its response to the Appraisal Consultation Document.[15] This was also not a case of stakeholders putting forward vague, hypothetical figures. Indeed, the EAG noted that experts put forward concrete estimates of between £75 and £117.[16] It is obvious these estimates are of a far lower order than the figures taken in the model and preferred by the Appraisal Committee.

In that light, one must question whether the Appraisal Committee acted reasonably in failing to correct or look into this issue further. The question for the Appeal Panel is therefore whether the Appraisal Committee's decision to maintain administration costs at £410 for molnupiravir was reasonable in light of the weight of evidence available that this was a significant overestimation (by a multiple of three or four times).

Note further that the EAG gave the Appraisal Committee the option of reducing costs to a figure that more closely aligned with expert views, stating that "*if the Appraisal Committee decided that the true costs of providing oral treatment was £110, then the NMB of the treatment would be increased by £300; alternatively, incremental costs could be reduced by £300 and a new ICER calculated by the Appraisal Committee*."[17].

MSD submits there is a material overestimation by the Appraisal Committee here, and this goes squarely to the question of reasonableness.

With respect to your comments on our point (b) ("*Unreasonable underestimation of the administration cost of nirmatrelvir plus ritonavir*"), our observations are similar to those above. Given the Appraisal Committee's obligation to estimate administration costs rationally and reasonably across the board, the argument here is that the estimate for nirmatrelvir plus ritonavir must necessarily be higher than that for molnupiravir because of the significant additional steps that clinicians must carry out for nirmatrelvir plus ritonavir, including the time taken to assess patients for possible contraindications. The question of reasonableness relates to differentiating between the two treatments and their administration costs.

MSD also asks (in addition or in the alternative) whether there is also a 1a or 1b point here: that the Committee either unfairly or unlawfully ignored evidence from clinical experts and the EAG report, clinging dogmatically to its original cost assumptions. MSD asks you to consider re-directing this appeal point to Ground 1a or 1b, if you determine that reasonableness is not the correct basis for this appeal point.

Finally, if on final scrutiny, you maintain the position that the Process Statement itself is immune from challenge in an appeal process, or that any of our other suggested appeal points are inadmissible, MSD's only recourse would seem to be to maintain those arguments by way of judicial review, if so advised. In that event and to avoid the possibility of protective proceedings being needed or pre-action steps being truncated we would be grateful for your confirmation as part of final scrutiny that NICE would actively support an argument that the time for such a challenge only begins to run after the conclusion of this appeal process.

[15] Comment 6 of MSD's comments on the Appraisal Consultation Document, dated 6 December 2022

[16] Metry A, Pandor A, Ren S, Stevenson M, *Therapeutics for people with COVID-19. An economic evaluation: EAG additional analysis post NICE Appraisal Consultation Document*, 13 January 2023, paragraph 5.5

[17] Metry A, Pandor A, Ren S, Stevenson M, *Therapeutics for people with COVID-19. An economic evaluation: EAG additional analysis post NICE Appraisal Consultation Document*, 13 January 2023, paragraph 5.5

We thank you in advance for considering our responses to the Initial Scrutiny Letter and further observations, and look forward to hearing from you.

Yours sincerely