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7 March 2023

Dear Dr Chakravarty

Re: Notice of Appeal – molnupiravir for the treatment of people with COVID-19 [ID 4038]

Merck Sharp & Dohme (UK) Limited ("MSD") wishes to appeal against the Final Draft Guidance ("FDG") for ID4038 – *Therapeutics for people with COVID-19*. MSD is the UK marketing authorisation holder for Lagevrio (molnupiravir), which is one of the technologies under review in this multiple technology appraisal ("MTA"). MSD's appeal specifically concerns the assessment of molnupiravir.

The decision to appeal is not one MSD takes lightly. We recognise the exceptional nature of the disease area and the importance of providing timely advice about COVID-19 therapeutics to the NHS. We are especially conscious of avoiding unnecessary or unjustified delays in publishing this guidance. None of this, however, should compromise NICE's duties to act fairly and conduct an appraisal rationally given the evidence before it and with due thoroughness. In principle, MSD supports proportionate and pragmatic approaches to improve access to medicines. However, we have deep concerns that in this case NICE's deviation from established procedures has cut corners inappropriately and led to unfair assumptions materially affecting the assessment. By law, a technology appraisal must follow NICE's published methods and processes. To have done otherwise undermines the purpose and legal effect of an MTA, and the validity of the conclusions reached.

The NHS has already procured and currently holds a stock of molnupiravir, which NHS clinicians could employ without making additional purchases from MSD. Therefore, this appeal is not motivated by the prospect of immediate commercial gain. Rather, our aim is to highlight and seek to remedy the Appraisal Committee's unfair and unreasonable appraisal of molnupiravir.

The Appraisal Committee only reaches the conclusion to not recommend molnupiravir by relying on unsound and incomplete evidence, not considering all available and relevant evidence, and failing to eliminate or adjust for bias. As a direct consequence, the Appraisal Committee concludes that molnupiravir has "limited effectiveness" in the treatment of mild COVID-19.

This MTA followed a non-standard, *ad hoc*, and often-changing process. At critical points in the evaluation, the Appraisal Committee took procedural decisions that created biases specifically against molnupiravir. Molnupiravir faced a disproportionately negative assessment compared to the other technologies being appraised.

MSD is confident that molnupiravir is a clinically effective treatment option in the relevant treatment population that falls within NICE's cost-effectiveness criteria. It has helped numerous NHS patients already. It can, and

should, be part of a range of treatments available to the NHS going forwards – not least because of its ease of use for the NHS, which can be critical at a time when the health service is under enormous pressure.

The product is uniquely well-suited to treating COVID-19 in the endemic phase. It is an oral therapy that is straightforward to administer at low cost in community settings. Unlike other treatments, molnupiravir is associated with no known drug-drug interactions ("DDIs"), reducing NHS resource burden and the risk of inequality between patient groups. Had NICE conducted a fair and robust procedure and appropriately reviewed and analysed all available evidence, the recommendation may well have been positive. Instead, the negative recommendation will deprive patients and NHS clinicians of a high-quality treatment option entirely because of an unbalanced and selective review of the evidence.

As the Appraisal Committee and the FDG repeatedly acknowledge, the clinical evidence for COVID-19 therapeutics was, and remains, highly uncertain. The disease, its variants, treatment pathways and population immunity were continuously evolving during the pandemic (when much of the clinical evidence was generated), and will evolve during the endemic phase. In such a context, the relevance and generalisability of evidence are key issues for all treatments under assessment, not only molnupiravir. The need to be thorough, circumspect, to examine all available evidence, and to scrutinise rigorously its relevance is also critically important. Yet in its assessment of molnupiravir, NICE's methodology ran entirely in the opposite direction: relevant evidence was omitted from the review and the evidence available was not adequately critiqued. Sadly, the Appraisal Committee's laudable aim to be pragmatic and responsive has in reality resulted in a flawed assessment of molnupiravir and an unreasonable and irrational outcome.

That outcome removes a potential treatment option for patients for whom nirmatrelvir plus ritonavir is contra-indicated – who are often the most vulnerable in society and have legally protected characteristics. The recommended alternative – sotrovimab – has very different characteristics to an antiviral and places significant and unequitable hurdles before that vulnerable patient group. Access to molnupiravir would have significantly lowered those barriers, which makes the unsound and unfair assessment of molnupiravir both particularly concerning and potentially unlawful. More could and should have been done to appraise molnupiravir in a focused and fair manner. Above all else, this is why we feel obliged to bring this appeal.

Background and Introduction

Molnupiravir

Molnupiravir is an oral antiviral prodrug used in the treatment of COVID-19. It is metabolised to the ribonucleoside analogue N-hydroxycytidine ("NHC"), which distributes into cells where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate ("NHC-TP"). NHC-TP acts by a mechanism known as viral error catastrophe. NHC-TP incorporation into viral RNA by the viral RNA polymerase results in an accumulation of errors in the viral genome leading to the inhibition of replication.[1]

Molnupiravir's unique mode of action means it is not vulnerable to a loss of efficacy through the appearance of new variants. This contrasts with various monoclonal antibodies that were approved and subsequently had their licenses revoked or were deemed unsuitable for use against the Omicron variant.

Molnupiravir has no contraindications or known DDIs, so it can be prescribed and dispensed in a timely-manner and at scale. As an oral treatment, it is easy to administer and suitable for treatment in the primary care setting. These factors allow for efficient treatment of COVID-19 in the community and set molnupiravir apart from the treatments recommended by NICE (nirmatrelvir plus ritonavir and sotrovimab), which either exclude certain vulnerable patients due to DDIs or require more costly and resource and time intensive intravenous ("IV") infusion. Molnupiravir offers a reduced likelihood of face-to-face contact with healthcare professionals, alongside a lower cost of administration and patient-friendly treatment.

MTA Process

ID4038 did not follow NICE's established MTA procedure, instead it followed a re-sequenced process with shortened timelines. NICE gave assurances that despite these changes, its underlying methodology and standard

[1] Summary of Product Characteristics for Lagevrio (last updated 19 December 2022), hiips://www.gov.uk/government/publications/regulatory-approval-of-lagevrio-molnupiravir/summary-of-product-characteristics-for-lagevrio

of review would be the same as under a conventional MTA. A central theme in this appeal is that, in hindsight, the procedural changes did materially and negatively affect the standard and rigour of the appraisal, disproportionately so for molnupiravir.

Summary of Grounds

ID4038 did not follow NICE's conventional procedure for MTAs. The core of this appeal is that the process that NICE *did* follow fell far short of the standards required of an MTA, and further was inappropriate, unfair and unfit for purpose. NICE has published procedures to ensure appraisals are carried out with necessary rigour and thoroughness. They exist for a good reason. They safeguard the validity of the recommendations NICE makes at the conclusion of an appraisal. In ID4038, the key procedural decisions that the EAG and Appraisal Committee took departed materially from the norm and contributed step-by-step to an incomplete and partially sighted review of the evidence. Ultimately, these procedural steps led to bias against molnupiravir, and were the driving force behind its negative recommendation.

The first seven appeal grounds stem from this core issue, addressing the fairness and validity of the appraisal process: Grounds 1a.1, 1a.2, 1a.3, 1a.4, 1a.5, 1a.6 and 1a.7. Grounds 1a.1 and 1a.2 concern the process as a whole; the remainder concerns specific procedural steps or decisions. Grounds 1a.3 to 1a.7 also contain elements that go to reasonableness. For succinctness, we have not duplicated these points under Ground 2, but could do so if the Chair or Scrutineer considered this helpful. Ground 1b.1 relates to NICE's failure to uphold its human rights and equality obligations, by failing to pay proper regard to molnupiravir and in doing so (avoidably) leaving vulnerable patients with limited options.

Ground 1a.1: NICE has followed an *ad hoc* process and departed significantly from established procedures for MTAs. NICE intended for ID4038 to "follow all the steps of an MTA" albeit in a different order and in a shortened timeline, but without affecting an MTA's core methods or structured decision making. In actuality, the process departed so substantially from established procedures and safeguards that ID4038 is essentially an *ad hoc* assessment with obvious deficiencies in the scope and standard of evidence review.

Ground 1a.2: The *ad hoc* process that NICE followed was inconsistent, unfair and unfit for purpose. Leaving aside that ID4038 materially departed from a conventional MTA, NICE failed to ensure the process it ultimately followed was consistent, fair and fit for purpose. In particular, the Appraisal Committee inappropriately delegated key procedural choices to the EAG, whose subsequent decisions were obscure, undermined MSD's legitimate expectations, and did not adequately compare highly heterogeneous and incomplete evidence.

Ground 1a.3: The Appraisal Committee's closing its eyes entirely to relevant real-world evidence about molnupiravir proposed by MSD is procedurally unsound and led to an unfair assessment. MSD urged the Appraisal Committee to review a suite of highly relevant and much-needed real-world evidence ("RWE"). This RWE appears to have been set aside by default, without the Appraisal Committee considering its merits or potential relevance.

Ground 1a.4: The approach to real world evidence in this appraisal is inconsistent and runs contrary to the Guidance Manual and NICE's obligation to carry out a fair and rational process. ID4038 rejected MSD's proposed suite of RWE, but (i) did selectively and inconsistently review other RWE; and (ii) failed to comply with the Guidance Manual, which positively requires considering all available evidence, including RWE – particularly where (as in this case) the randomised-controlled trial ("RCT") evidence is uncertain.

Ground 1a.5: The Appraisal Committee's over-reliance on the PANORAMIC data to estimate the treatment benefit of molnupiravir and its approach to evidence synthesis were procedurally unfair. The PANORAMIC study was uniquely, such that its output data could not directly be generalised to this appraisal. Despite the Appraisal Committee acknowledging this issue, the EAG and Appraisal Committee took the PANORAMIC study data at face value; the influence of these data in the synthesised evidence led to molnupiravir's negative recommendation.

Ground 1a.6: **The Appraisal Committee's blanket capping of the efficacy levels of all treatments, without due consideration of each individual case, resulted in considerable bias and unfairness against molnupiravir.** To account for the RCT evidence being in a pandemic setting, the Committee applied a blanket efficacy cap at the mean efficacy scenario for all technologies in this appraisal. However, the PANORAMIC study data, which only affected molnupiravir, were from a later disease phase. To have applied this cap to molnupiravir essentially "double counts" a downward adjustment and is illogical and unfair.

Ground 1a.7: NICE unduly focused on mortality and hospitalisation rates to assess clinical benefit rates and failed to give due consideration to other outcome measures, thereby creating bias against molnupiravir. In contradiction of the Final Scope, the Appraisal Committee based its recommendations on only two outcome measures – hospitalisation and mortality rates – to the exclusion of outcome measures more relevant to the endemic setting.

Ground 1b.1: NICE has breached its legal obligations under human rights and equalities laws. The recommendation of sotrovimab as an alternative for patients who are contraindicated nirmatrelvir plus ritonavir, who are likely to be vulnerable and have protected characteristics, in effect creates additional access and treatment barriers for those patients. NICE's failure to give proper consideration to molnupiravir as a less burdensome and better alternative breaches NICE's obligations under human rights and equalities laws.

Ground 2.1: By evaluating evidence selectively, inappropriately, and in a methodologically unsound and unfair manner, the Appraisal Committee's conclusions in respect of molnupiravir are necessarily unreasonable in light of the available evidence. The Appraisal Committee's conclusions were necessarily unreasonable in light of the deeply unsound process it followed.

Ground 2.2: The Appraisal Committee's administration cost assumptions for molnupiravir and nirmatrelvir plus ritonavir are unreasonable. This is a cost-effectiveness related ground, and subject to the Panel's assessment of the other grounds in this appeal.

Grounds of Appeal

Ground 1a: In making the assessment that preceded the recommendation, NICE has failed to act fairly

Ground 1a.1 – In this appraisal, NICE has followed an *ad hoc* process and departed significantly from established procedures for MTAs

Although the Final Scope did not indicate that the assessment would not be handled as a standard MTA, NICE refers to ID4038 as a "re-sequenced" MTA. NICE explained this concept to consultees at the outset of the process, at a stakeholder meeting in April 2022. At the meeting, NICE indicated that ID4038 would "follow all the steps" of an MTA but in a different order and in shorter time. These changes would not affect NICE's usual MTA "*methods…or structured decision-making.*"[2] This is also reflected in the Process Statement NICE issued on 28 September 2022, which stated that "*This multiple technology appraisal* ***will follow all the steps in [the MTA process]****, but re-sequenced and with shortened timelines. This is described below, with cross-references to the relevant sections of the manual*" (emphasis added).

In reality, and with the benefit of hindsight, ID4038 has not simply been a "re-sequenced" MTA (without conceding that it is open to NICE to re-sequence an MTA), but rather has followed an *ad hoc*, light touch programme which departs so significantly from the established procedures for technology appraisals under the NICE Health Technology Evaluations Manual (the "Guidance Manual") that it cannot in truth be called an MTA at all.

Most worryingly, it is clear that the *ad hoc* process followed has led to the Appraisal Committee and the External Assessment Group ("EAG") applying a less rigorous standard and methodology of review than is required under a conventional MTA. Examples of these lower standards pervade through each of the remaining appeal grounds.

Notably:

- The EAG reported without receiving any evidence submissions from consultees. There followed a short window for consultees to submit only "targeted" evidence. This approach severely restricted manufacturer input, far short of the evidence submissions manufacturers would expect (and have the right) to make in a conventional MTA.

- There was no systematic gathering or review of evidence. The EAG makes clear that its research is "*not aligned with a typical NICE multiple technology appraisal ("MTA")*" and it will need to adjust its

[2] *Therapeutics for people with COVID-19*, Stakeholder Information Slides (14 April 2022)

approach to meet shortened timescales and will notify NICE of these shortcuts.[3] The EAG then selected what evidence to look into and determined the scope of any further explorations. Consultees had limited input, if any, in this process. This is far from the "systematic" evidence review required for MTAs in the Guidance Manual.

- NICE and the EAG took a "pragmatic" approach to evidence review; the precise meaning of which is unclear. However, as discussed in the following appeal grounds, "pragmatism" in this case appears to have entailed (i) drawing firm conclusions from uncertain evidence; (ii) limited efforts at removing bias in the evidence base; and (iii) foreclosing the possibility of reviewing key RWE.

In addition, notwithstanding NICE's commitment to follow "all the steps" of an MTA, the Process Statement issued on 28 September 2022 illustrates some key gaps:

- Paragraph 7 of the Process Statement states that the EAG's assessment "w*ill be based on a synthesis of all the publicly available evidence.*" It does not suggest that the EAG would select some publicly available evidence and refuse to consider other published data. Paragraphs 10 and 12 go on to state that NICE would then invite stakeholders to submit evidence that is not included in the EAG's report. In reality the evidence request from stakeholders was narrower, and in effect asked consultees to highlight any unpublished clinical data. This approach would not capture RWE that the EAG had not already taken into account. In the Protocol, the EAG appears to acknowledge that it has resorted to a less than systematic evidence gathering approach: "*Due to the limited timelines of the projects, we will undertake a pragmatic review approach in identifying and reviewing relevant evidence from these sources."*[4]

- Paragraphs 10 and 12 also suggest that, following consultee submissions, the Appraisal Committee would follow paragraphs 5.7.2 – 5.7.22 of the Guidance Manual. In fact, paragraphs 5.7.2 – 5.7.22 of the Guidance Manual set out the process for committee meetings; they do not provide a methodology for evaluating evidence submitted by stakeholders. If anything, this stakeholder-submitted evidence simply fell into a procedural vacuum, and the "publicly available" evidence selected by the EAG held primacy. Any in-built biases in the EAG's evidence base were in effect reinforced. Despite the commitment to follow "*all the steps*" of an MTA, the evidence review methodology does not contain the same safeguards as a conventional MTA.

- Notwithstanding the commitment to follow "all of the steps" of an MTA, the Process Statement appears to omit much of Paragraph 5.6 of the Guidance Manual, skipping to Paragraph 5.6.15, which includes the following steps:

    - "*For multiple technology evaluations in technology appraisals and highly specialised technologies, the companies are invited to provide an evidence submission but are not formally required to do so.*

    - *The EAG does an assessment of the clinical outcomes and cost effectiveness of the technologies, and diagnostic test accuracy where relevant.* ***The assessment is based on systematic reviews of the literature, data provided by the companies, information from the experts or specialist committee members, and modelling of patient outcomes, costs and cost effectiveness.***

    - *The EAG's assessment highlights the uncertainties in the evidence and may include an analysis of the value of reducing those uncertainties*" (emphasis added).

The Process Statement for ID4038 required committed the EAG to carrying out a systematic evidence review, in accordance with the Guidance Manual. In practice, the process for gathering and reviewing was selective and any additional evidence submitted by consultees did not receive proper attention or review at different appraisal stages that could have facilitated engagement between companies and NICE.

[3] Paragraph 1.7 of the MTA Final Protocol

[4] Paragraph 2 of the MTA Final Protocol

Please also refer to the table attached at Appendix 1 to this appeal letter for a summary of further departures from NICE's usual MTA process.

MSD has been, and remains, very supportive of NICE's efforts to carry out proportionate and efficient technology appraisals. In our view, this flexibility contributes to NICE being a world-leader in its field. Nonetheless, there is a marked difference between a welcome degree of pragmatism within the safeguards of an established process; and devising a new process entirely, whose parameters evolve as the review proceeds, and where the output falls far short of requisite standards.

Proceeding in line with established processes is especially important in an MTA, where there is a particular need to be fair between potentially competing manufacturers and technologies (this is absent in an STA). Being clear as to what the process is and ensuring it is followed properly are key elements of a properly-conducted MTA. Similarly, in an MTA, the EAG carries significant responsibility for the scope and standard of evidence review. For the process to be fair, and seen to be fair, the EAG's parameters must be clear from the outset – if there is flexibility and discretion, then this must be within the parameters provided by NICE's published MTA procedures.

Statute defines a technology appraisal recommendation as:

> "*a recommendation made by NICE following an appraisal of the benefits and costs of a health technology* ***conducted by NICE in accordance with NICE's published methods and processes for appraisal of health technologies*** *that results in a positive assessment*" (emphasis added).[5]

It follows that the output of an appraisal process that does not follow published procedures cannot deliver a "technology appraisal recommendation" under law and would not carry the same legal effect as such. One must question what the legal effect of ID4038 is and whether it should be promulgated as an "MTA."

This is not merely a dry, formalistic point. The Guidance Manual contains important procedural rules that safeguard the recommendations NICE issues. Deciding to ignore or skip over these safeguards fundamentally undermines the output.

NICE has not explained why it chose the MTA format but then so markedly departed from the MTA procedures in following an *ad hoc* process. If the Department of Health and Social Care needed rapid advice in this area, NICE could in principle have delivered it under its broad statutory remit and not as a formal MTA. However, if an MTA is the chosen format, then MSD submits that "*all the steps*" in the MTA process ought to have been respected in full, as NICE had suggested they would at the outset.

MSD further questions at what point NICE reviewed and approved the departures from the conventional MTA process; whether this was consulted upon and formalised; and what safeguards it put in place to ensure that the methodology and standard of review remained unaffected.

Ground 1a.2 – The *ad hoc* process that NICE followed was inconsistent, unfair and unfit for purpose

Leaving aside the departure from the MTA process, the Institute must ensure that whatever process it follows is rational, fair, consistent and fit for purpose. These are fundamental principles and part of NICE's core legal obligations. MSD submits that ID4038 falls far short.

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.

For example, it is the role of the Final Scope to *"*[provide] […] *the framework for the evaluation. It defines the issues for consideration (for example, population, comparators, care pathway, and outcome measures) and sets the boundaries for the work to be done by the external assessment group, and any evidence submissions for the evaluation.*"[6]

[5] Regulation 2 of the National Institute for Health and Care Excellence (Constitution and Functions) and NHS England (Information Functions) Regulations 2013/259

[6] Paragraph 2.1.1 of the Guidance Manual

In ID4038, the Final Scope is constructed to follow the course of an MTA (the Draft Scope expressly uses the words "multiple technology appraisal" and this is implicit in the Final Scope). The Final Scope goes on to say:

- The comparators would be:
    - Established clinical management with or without corticosteroids and appropriate respiratory support; and
    - The interventions will be compared to each other.
- The outcome measures to be considered include:
    - mortality;
    - requirement for respiratory support;
    - time to recovery;
    - hospitalisation (requirement and duration);
    - time to return to normal activities;
    - virological outcomes (viral shedding and viral load);
    - symptoms of post-COVID-19 syndrome;
    - adverse effects of treatment; and
    - health-related quality of life.
- "*Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator*."[7]

Despite the fact that the Final Scope was extensively consulted upon and was bespoke to this appraisal, the Protocol published contemporaneously gives a jarringly inconsistent message.

The Protocol states:

> "*This **research is not aligned with a typical NICE multiple technology appraisal** (MTA) primarily due to the **shortened timescales which will require the EAG to pragmatically assess where time savings can be made without impacting on the main conclusions**. NICE will be kept informed of such decisions"* (emphasis added). [8]

The suggestion is that – notwithstanding what is set out in the Final Scope – the EAG was in a position to adjust the parameters of the review howsoever it saw fit in order to derive time savings. How it could do so "*without impacting on the main conclusions*" is unclear and counterintuitive (for instance, how could the EAG reject evidence without first assessing its potential relevance – put in plain English; how was the EAG to know what it had done had not impacted on the main conclusions? Further, how were consultees and commentators to know whether there was an impact or not?). This is procedurally improper on at least two counts.

- First, the Appraisal Committee has over-delegated responsibilities that it must retain. It is NICE's (and therefore the Appraisal Committee's) responsibility to ensure the appraisal follows a fair and robust process – this is not the EAG's role; nor is the EAG expert in these matters. To give the EAG free rein as to the scope of admissible evidence, how to scrutinise it, what to reject, and to take other shortcuts to improve efficiency is wrong.

- Second, leaving the EAG to make procedural and methodological changes and simply notify these to NICE leaves consultees entirely in the dark. How could companies and others meaningfully

[7] MTA Final Scope

[8] Paragraph 1.7 of the MTA Final Protocol

> follow and contribute to an evidence review process without knowing what would and would not be reviewed, when, and to what standard?

Further, the Protocol states that:

> *"*[i]*t is anticipated that re-running of models may be required as new evidence emerges, for example if studies reporting new data on the efficacy of interventions, potentially to new variants of SARS-CoV-2, are published, however, this will be dependent on when the MTA is taken to a NICE Appraisal Committee."*[9]

This suggests that the procedure would be open to considering new data as and when it emerged, which led to a legitimate expectation that all new data would be considered (or, possibly, only data whose exclusion would impact on the main conclusions. The confusion here, and the difficulty of being sure what will or will not impact on the main conclusions, highlights how unfair this process was).

Paradoxically, it also suggests that evidence synthesis would hinge on when the appraisal had to go to Committee, rather than the other (and we say proper) way round of going to Committee when sufficient high quality evidence was available. NICE started with a need for speed, and allowed that to dictate the evidence looked at, rather than starting with the evidence, and allowing that to dictate how quickly the appraisal can progress. Thus in reality, the EAG and Appraisal Committee adopted a selective approach to its evidence review, particularly relating to newly emerging RWE, as discussed at Grounds 1a.3 and 1a.4 below. The EAG did not carry out a systematic literature review. No attempt was made to capture all available and relevant evidence. The evidence collected from consultees was "targeted" and therefore highly limited. The process did not provide consultees with a defined and dedicated opportunity to submit further evidence they considered relevant. Consultees such as MSD tried on their own initiative to point to particularly important "missed" evidence during the Appraisal Consultation Document ("ACD") consultations, but it is unclear whether or how such was reviewed for inclusion in the process.

The Protocol also set out the following:

> "*Comparators for these interventions are: (i) other interventions when used in the same position, and (ii) standard of care (SoC) excluding the interventions, which would be dependent on the severity of the patient.* ***SoC is defined as any treatment widely accepted by the NHS as standard of care, which is routinely funded by the NHS with no strong rationale to appraise it,*** *for example supplemental oxygen and dexamethasone.* ***The EAG are aware that the SoC has been an evolving area, and that SoC for earlier clinical trials differs from recent ones. In this regard, the EAG is limited by the available evidence of relative treatment effect as discussed in Section 2, and acknowledge that not adjusting for the variation in the SoC across trials is not ideal.*** *However,* ***the EAG believes the results from the MTA could still be informative particularly for comparisons among treatments whose clinical trials were conducted recently.*** *Sensitivity analyses related to SoC will be performed if feasible within the timescales of the project*" (emphasis added).[10]

The Protocol acknowledges that the standard of care would vary between clinical trials used as data sources, and that this was "not ideal." However, a comparison between treatments may still be "informative", particularly using data from more recent studies. The EAG does not explain this any further, and the uncertainty created is another notable component of this appeal. It is common ground that the evidence base was highly heterogeneous and often subject to significant uncertainty. Determining what types of comparisons could be "informative" was crucial to the outcome, and yet this key step is obscure and referenced virtually in passing.

Although this is a single set of examples, it demonstrates a central flaw and unfairness of approach. NICE departed from its set procedures, replacing these with an *ad hoc* approach that created gaps, inconsistencies, and unsound comparisons.

We note that the recent announcement that NICE will be consulting on a rapid update process of COVID-19 treatments appears to underline the fact that the process followed in ID4038 was unfit for purpose and that a better way of doing things is required.

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[9] Paragraph 1.7 of the MTA Final Protocol

[10] Paragraph 1.5 of the MTA Final Protocol

Ground 1a.3 – the Appraisal Committee closing its eyes entirely to relevant real-world evidence about molnupiravir proposed by MSD is procedurally unsound and led to an unfair assessment

The pivotal Phase 3 trial, MOVe-OUT, showed that molnupiravir was effective in high-risk, unvaccinated non-hospitalised patients infected with early variants of COVID-19. Given the rapidly-changing epidemiology of the disease, MSD believed it was important to review available non-randomised observational RWE to support the findings in MOVe-OUT. RWE could correspond more effectively to the status of COVID-19 under review than some of the clinical evidence, particularly in respect of the prevalence of Omicron, as well as the risk and vaccination status of patients.

Given that this is an area of continued scientific development, the EAG ought to have conducted systematic literature reviews to identify all the evidence and present it to the Appraisal Committee for consideration.

This duty is fundamental to conducting a proper technology appraisal. The Guidance Manual provides as follows:

- The evidence considered by the Appraisal Committee must be "[**r]elevant to the evaluation**" and "[a]*nalysed in a way that is* ***methodologically sound***" and "**minimises any bias**" (emphasis added).[11]

- There must be a "systematic review" that "*attempts to assemble* ***all available relevant evidence*** […] *in a way that minimises the risk of biased selection of studies*" (emphasis added).[12]

- "*Evidence on outcomes should come from a systematic review, defined as systematically locating, including, appraising and synthesising the evidence to give a reliable and valid overview of the data related to a clearly formulated question.*"[13]

- *"It is essential that* ***limitations in the evidence are fully described and the impact on bias and uncertainty fully characterised and ideally quantified***" (emphasis added).[14]

Carrying out a systematic review is central to understanding whether there is bias in the evidence available. It is also important to understanding whether there are currently unknown or unquantified biases to consider.

The EAG undertook no such systematic reviews.

MSD conducted a literature survey of RWE studies that include molnupiravir and urged the EAG and Appraisal Committee to consider this additional evidence. Neither did so.

MSD understands this was "due to time constraints." MSD submits that time constraints cannot be a valid reason not to consider otherwise relevant material (particularly where the underlying material suffered from significant uncertainty)..

In further support of its approach, the Appraisal Committee cautioned against "*solely relying on non-randomised evidence when making decisions on treatment effect*" noting potential concerns "*when* […][the outcomes of RWE] *contradict the outcomes from a randomised controlled trial*."[15] Respectfully, this appears illogical. MSD encouraged the Appraisal Committee to consider RWE *alongside* the RCT data, not in place of it. If the two were in fact contradictory (MSD submits this was not the case), then further exploration would be necessary to understand why and rule out bias. Instead, the EAG appears to have rejected the MSD RWE because (i) it is RWE; and (ii) it does not support the EAG's (incorrect) synthesis of RCT evidence. If anything, this compounds rather than reduces confirmation bias.

[11] Paragraph 3.2.1 of the Guidance Manual

[12] Paragraph 3.3.4 of the Guidance Manual

[13] Paragraph 3.4.2 of the Guidance Manual

[14] Paragraph 3.2.2 of the Guidance Manual

[15] Paragraph 3.11 of the FDG

In respect of molnupiravir, the EAG and Appraisal Committee therefore limited their review to:

- two network meta-analyses ("NMAs") of clinical trials: Covid-NMA and metaEvidence;
- evidence synthesised using these data from the NMAs and the results of the PANORAMIC study; and
- data from OpenSAFELY (consisting of non-randomised observational RWE from English GP practices).

In the context of this appraisal, the failure to search for and review other evidence was procedurally unsound.

Challenges with Available Clinical Evidence

This procedural error is especially pronounced given the limitations in the evidence that the EAG selected to review. The Appraisal Committee recognises these limitations, but fails to recognise that the absence of a systematic review may be the root cause.

At paragraph 3.10 of the FDG, the Appraisal Committee notes the "significant limitations" of the clinical evidence used in the appraisal. In particular:

- *"Each trial included in the analysis was done at a different time in the pandemic."*
- *"Most trials compared an individual treatment against the standard care at the time. Standard care has evolved in response to better understanding of the disease course, changes to respiratory support and use of dexamethasone."*
- *"The context of the disease also changed with different circulating variants of concern, and changes in protection through vaccinations and natural immunity over time."*
- *"Each of these limitations were compounded by significant differences in trial design, baseline characteristics and geographical locations."*
- *"*[T]*he analysis assumed any relative effect of treatment is transferable to current clinical management."*
- *"*[T]*he weighting of each trial in a meta-analysis may not consider the relevance of the context of each trial within the analysis, for example, with different variants."*[16]

As a result: "[t]*he committee recognised the high levels of uncertainty with each treatment effect and the context-specific nature of the evidence.*"[17]

While the Appraisal Committee acknowledged this limitation, it made no attempt to adapt its approach to cast its net wider or appreciate the existence of other sources of evidence that may help.

These Challenges Directly Influenced the Negative Appraisal of Molnupiravir

When addressing the relative treatment effect of molnupiravir, the FDG states:

> "[t]*he committee concluded that it could not be certain of molnupiravir's clinical efficacy in terms of hospitalisation and mortality rates when the potential benefit is minimal.*"[18]

[16] Paragraph 3.10 of the FDG

[17] Paragraph 3.10 of the FDG

[18] Paragraph 3.19 of the FDG

And further:

> *"*[…] *stronger clinical evidence is needed to justify a relative difference in clinical effects*."[19]

The statement that the treatment benefit of molnupiravir is "minimal" is a direct result of the uncertainty of the evidence base. The FDG acknowledges this:

> "*the mean-efficacy estimates in the evidence synthesis (pooling the PANORAMIC results with earlier trials) were uncertain because of population differences*." [20]

As discussed at Ground 1a.5 below, the Appraisal Committee also acknowledged that PANORAMIC (a study that would have materially affected the evidence synthesis) was not powered to show these benefits due to the exclusion of the groups of people at highest risk of progression.[21]

In effect, the Appraisal Committee acknowledged that, intentionally and in the interests of speed, it persevered with uncertain and limited evidence that drove the negative recommendation for molnupiravir.

Particular Relevance of the RWE that MSD Urged NICE to Consider

To address clear deficiencies in the evidence, MSD submitted an extensive list of RWE studies on molnupiravir at Appendix 3 of its response of 6 December 2022 to the ACD. MSD highlighted the particular significance of certain key observational study data:

- Molnupiravir was shown to be associated with a reduced risk of hospitalisation or death in high-risk patients with COVID-19 who were aged 65 years and older in an observational, retrospective assessment of data collected in Israel (Arbel *et al.* 2022).[22] This study therefore provides positive data for molnupiravir in relation to NICE's two primary outcome measures: hospitalisation and mortality rates. Most patients (92%) in this study had previous COVID-19 immunity (*i.e.*, by vaccination, prior COVID-19 infection, or both) and received molnupiravir during the Omicron wave.[23]

- In an observational, retrospective cohort study conducted in Hong Kong by Wong *et al.*, non-hospitalised patients with an officially registered diagnosis of SARS-CoV-2 (4,983 of whom received molnupiravir, alongside 49,234 matched controls) were analysed during a period in which the Omicron variant was dominant. After propensity score matching, the mean age of participants treated with molnupiravir was 71.4 years. Molnupiravir use was associated with lower risks of all-cause mortality (crude incidence rate of 17.9 vs. 22.1 per 100,000 person-days, respectively: HR 0.76 [95% CI 0.61 to 0.95]) and in-hospital disease progression compared with matched controls,[24] again rendering this data highly relevant to NICE's assessment. The study vaccination rate was ~17%.

- Similarly, an evaluation of the clinical effectiveness of molnupiravir (by the same authors) in patients in Hong Kong who were hospitalised due to their high risk of progression to severe disease showed that molnupiravir was associated with a lower risk of death compared with matched controls (HR: 0.48 [95%

[19] Paragraph 3.19 of the FDG

[20] Paragraph 3.19 of the FDG

[21] Paragraph 3.19 of the FDG

[22] Arbel R, Sagy YW, Battat E, et al. *Molnupiravir Use and Severe Covid-19 Outcomes During the Omicron Surge*. Research Square. 2022 2022;doi:10.21203/rs.3 rs-2115769/v1

[23] Arbel R, Sagy YW, Battat E, et al. *Molnupiravir Use and Severe Covid-19 Outcomes During the Omicron Surge*. Research Square. 2022 2022;doi:10.21203/rs.3 rs-2115769/v1

[24] Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. *Real-world effectiveness of molnupiravir and nirmatrelvir/ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory COVID-19 patients during the BA.2.2 wave in Hong Kong: an observational study*. medRxiv. 2022-01-01 2022:2022.05.26.22275631. doi:10.1101/2022.05.26.22275631

CI 0.40 to 0.59]).[25] Notably, the mean age after propensity score matching in the molnupiravir arm was 80.7 years, further demonstrating molnupiravir's effectiveness in tackling the two outcomes NICE predominantly focused on in this MTA among the elderly population in particular.

- In a retrospective cohort study conducted by Bruno *et al*. in southern Italy, 719 high-risk patients received treatment for COVID-19 during a period when Omicron and sub-variants were dominant. Of the trial population, 554 patients received molnupiravir (with a mean age of 73 years) whereas 165 patients received nirmatrelvir plus ritonavir (with a mean age of 62 years), and 93% of the total trial population was fully vaccinated. No differences between the two antivirals were observed and both helped to limit hospitalisation and deaths at 30 days among patients who were at high-risk of disease progression, in a period when Omicron was dominant and most of the population was vaccinated. Such a setting is more similar to the endemic phase scenario with which UK healthcare services are currently faced.[26]

- Sub-group analyses in another retrospective study conducted in Israel by Najjar-Debbiny *et al.* in 2022 found that molnupiravir was associated with a significant decrease in the risk of progression to severe COVID-19 or COVID-19 specific mortality in older patients (HR: 0.54 [95% CI, 0.34 to 0.86]), females (HR: 0.41 [95% CI, 0.22 to 0.77]), and in patients with inadequate COVID-19 vaccination (HR: 0.45 [95% CI:0.25 to 0.82]).[27] The vaccination status in the study was ~77%. Authors report that adequate vaccination was associated with a significant decrease in the number of events for all examined outcomes.

- A retrospective study, conducted by Flisiak *et al.* in 2022, assessed the efficacy of molnupiravir in patients hospitalised for COVID-19 in a real-world clinical practice during the wave of Omicron infections. This study showed a reduction in 28-day mortality, particularly in the population of patients over 80 years of age treated in the first 5 days of the disease (14.6% vs 35.2%, p=0.016).[28] Data on the vaccination status of participants included in the study are not available.

- In addition, MSD highlighted a study involving over 27,000 individuals from Victoria, Australia, the data from which is set to provide a valuable source of evidence for the use of molnupiravir in the real-world setting when published. Top-line results reported by the authors note that the risk of hospitalisation reduced by 26% and the risk of death reduced by 54% for molnupiravir-treated patients over 70 years of age.[29]

These real-world studies consistently report the ongoing effectiveness of molnupiravir versus standard of care with evidence of benefit in higher risk populations (including older ages and unvaccinated patients). The RWE presented by MSD has particular significance given the treatment setting for which this MTA is designed. The RWE reinforces the benefits of molnupiravir for older, more vulnerable individuals. Molnupiravir is also straightforward to prescribe, is not associated with any known DDIs, and can easily be deployed in a primary care setting. The combination of these factors leads to significant utility for patients who cannot receive alternative recommended oral treatment options in the community due to contraindications, or for whom geography may act as a barrier preventing or delaying them from gaining access to alternative recommended community treatment options.

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[25] Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. *Real-world effectiveness of early molnupiravir or nirmatrelvir–ritonavir in hospitalised patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2 wave: a retrospective cohort study*. The Lancet Infectious Diseases. doi:10.1016/S1473-3099(22)00507-2

[26] Bruno G, Giotta M, Perelli S, De Vita G, Bartolomeo N, Buccoliero GB. *Early Access to Oral Antivirals in High-Risk Outpatients: Good Weapons to Fight COVID-19*. Viruses. 2022 2022;14(11):2514. doi:10.3390/v14112514

[27] Najjar-Debbiny R, Gronich N, Weber G, et al. *Effectiveness of Molnupiravir in High-Risk Patients: A Propensity Score Matched Analysis*. Clinical Infectious Diseases. 2022-09-20 2022:ciac781. doi:10.1093/cid/ciac781

[28] Flisiak R., Zarębska-Michaluk D, Rogalska M, et al. *Real-world experience with molnupiravir during the period of SARS-CoV-2 Omicron variant dominance*. Pharmacological Reports. 2022-08-24 2022;doi:10.1007/s43440-022-00408-6

[29] 'Paxlovid is Australia's first-line COVID antiviral but Lagevrio also prevents severe disease in over-70s', *The Conversation*, 2022. Accessed 6 Dec 2022. hiips://theconversation.com/paxlovid-is-australias-first-line-covid-antiviral-but-lagevrio-also-prevents-severe-disease-in-over-70s-195349

The RWE covers a period in which Omicron was prevalent in a highly vaccinated population, where vaccines used were similar to those used by the NHS in the UK and in similar populations. This renders these datasets relevant for a thorough and fair appraisal of molnupiravir within this MTA. The RWE could also have provided alternative and justified means of adjusting the pivotal RCT data for molnupiravir and other comparators in a manner more robust and reflective of the clinical reality in the endemic phase.

Given the above, the following points ought to have been clear (and were made clear by MSD) to the Appraisal Committee:

1. the RWE collected by the company had merit and could have been valuable to this MTA;

2. the RWE could materially alter its existing assumptions about the treatment benefit of molnupiravir; and

3. the rapid evolution of the COVID-19 pandemic and its effects on clinical data mean that a proper assessment of benefit can only occur by considering RCT and RWE data.

MSD's RWE was self-evidently relevant and material to this appraisal and could have addressed deficiencies and limitations that the Appraisal Committee had recognised as issues. It was improper and unfair for the Committee to close its eyes entirely to the RWE that MSD flagged as relevant and valuable.

Ground 1a.4 – The Appraisal Committee's approach to real world evidence in this appraisal is inconsistent and runs contrary to the Guidance Manual and NICE's obligation to carry out a fair and rational process

Ground 1a.3 above focused on the unfairness of rejecting MSD's RWE submission outright and without examining its merits. This appeal ground concerns the Appraisal Committee's broader approach to RWE in this appraisal.

NICE's Approach to RWE Runs Contrary to the Guidance Manual

The Guidance Manual does not justify the outright rejection of material RWE, particularly where the available RCT evidence is uncertain.

The Guidance Manual explains as follows:

- "*There are some **key limitations of RCTs**:*

    - *For some indications or technologies, RCTs may not provide enough evidence to quantify the effect of treatment over the course of the condition* […]

    - *For some evaluations the results **may not be generalisable to the population of interest**, either because of the relevance of comparator or the relevance of the population, setting and treatment pathway in which it was used* [...]" (emphasis added).[30]

- *"**The need to search beyond RCTs for treatment effects should be informed by the residual uncertainties**, the **likelihood of this uncertainty being resolved through non-randomised evidence**, and the **practicalities of the evidence search***" (emphasis added).[31]

- "[N]*on-randomised studies may **complement RCTs when evidence is limited***" (emphasis added).[32]

NICE is under a clear obligation to assemble all available relevant evidence, and to describe, assess and minimise the risk of bias. The Guidance Manual acknowledges the potential limitations of RCT evidence. Where the RCT evidence is limited, and there is a high degree of uncertainty (as was the case here), the Appraisal Committee is

[30] Paragraph 3.3.8 of the Guidance Manual

[31] Paragraph 3.3.3 of the Guidance Manual

[32] Paragraph 3.3.2 of the Guidance Manual

under a positive obligation to look for other sources of evidence to estimate treatment effect. In particular, it is empowered to consider RWE.

With respect to RWE, the Guidance Manual provides that:

- "*Evidence from non-randomised studies may be* ***beneficial in supplementing and supporting RCT data, or substituting for RCT data if there is none.***

- *Non-randomised data may also be used to* ***contextualise results from RCTs by, for instance, understanding differences in patient populations, treatment patterns, or outcomes***[…].

- *Non-randomised evidence may be used to:*

    - ***assess the generalisability of results from RCTs***[…]

    - *describe the characteristics of real-world populations of interest*

    - *understand differences in treatment patterns or outcomes* […]" (emphasis added).[33]

Apart from the OpenSAFELY study, the Appraisal Committee did not seek to supplement or contextualize findings from RCT evidence using RWE, or to assess whether the RCT results can be generalised to the subject of the assessment.

This was clearly not a conventional MTA, where the RCT evidence was aligned to the decision problem. The available RCT evidence suffered from significant limitations and uncertainties – more so than in most conventional MTAs due to the nature of COVID-19 itself. By contrast, the RWE (which is ordinarily associated with greater uncertainty) offered unique perspectives that could have mitigated against the limitations in RCT evidence.

Given the obvious limitations in the RCT evidence, the Guidance Manual positively required the Appraisal Committee to examine what other contextualizing evidence was available and use that to inform the appraisal and minimise the risk of potential bias. In failing to do so, the Committee has not adhered to the Guidance Manual, and the important safeguards it puts in place.

NICE's Public Law Obligations

As a public body, NICE must take reasonable steps to acquaint itself with all relevant evidence, and carry out a rational and fair assessment of the level of weight to attach to such. According to case law:

- A public decision-maker must ensure that it has "*(i) taken adequate steps to inform* [itself] *of the position* […] *(ii) properly considered the information which is available to* [it] *and (iii) come to a decision which is consistent with that information recognising that it is* [its] *responsibility to evaluate the material which is available to* [it]";[34]

- "*The Court may interfere if the* [decision-maker] […] *has failed to take into account a relevant consideration*";[35] and

- "*Courts* […] *have been willing to strike down as unreasonable decisions where manifestly excessive or manifestly inadequate weight has been accorded to a relevant consideration.*"[36]

[33] Paragraph 3.3.11 of the Guidance Manual

[34] *R v Secretary of State for the Home Department, ex p Iyadurai* [1998] Imm AR 470, 475

[35] *R v Director General of Telecommunications, ex parte Cellcom Ltd* [1999] COD 105 [27]

[36] *R v SoS for Trade and Industry, ex parte BT3G Ltd* [2001] EuLR 325

The failure even to consider the RWE submitted in this MTA amounts to the outright rejection of relevant evidence. It also leads to manifestly excessive weight being accorded to flaws and shortcomings associated with the RCT data under review.

Inconsistent Treatment of RWE

While the Appraisal Committee rejected MSD's proposed RWE, it did consider data from the non-randomised, observational OpenSAFELY study. It did so relatively late in the process, giving little opportunity for comment. The Appraisal Committee failed to justify its decision to include one piece of RWE, but reject other relevant studies that MSD highlighted earlier in the MTA process. The inconsistency of approach without appropriate justification (indeed without *even considering* whether the RWE proposed *could be assistive and may warrant inclusion*) is indicative of an unfair and potentially arbitrary process.

As OpenSAFELY supported the Appraisal Committee's position, one might also ask whether the Committee adequately guarded against confirmation bias by including OpenSAFELY and rejecting other RWE.

Additional Considerations

Connected to the above, MSD highlights the following additional instances of procedural impropriety with respect to RWE:

- Paragraph 3.3.25 of the Guidance Manual states that "[t]*o ensure that the evaluation does not miss important relevant evidence, it is important that attempts are made to identify evidence that is not in the public domain*." [37] As noted above, MSD highlighted that the unpublished dataset from Australia's Victoria Government could be a key source of evidence for molnupiravir. Published top-line results – from a large and relevant dataset – suggested that the risk of hospitalisation reduced by 26% and the risk of death reduced by 54% for molnupiravir-treated patients in patients over 70 years of age. MSD understood that the researchers were prepared to share unpublished data with NICE for the purposes of this MTA. In December 2022, MSD requested that NICE contact the researchers to obtain these data for the Appraisal Committee's consideration, just as the Appraisal Committee had done in respect of the PANORAMIC data. In January 2023, the responsible Associate Director of Technology Appraisals responded that "*the onus is on companies to source relevant data if they would like the committee to consider it*," but also stated that he had been in touch with the authors of the Victoria Government study. As far as MSD is aware, this was not pursued further. The failure to pursue this opportunity to gather key evidence sharply contrasts with the approach taken to the PANORAMIC data. While it was unpublished, NICE proactively contacted the relevant research team to ask for a pre-print from that study. This exemplifies selectivity and inequality. In some cases, NICE took proactive steps to meet its obligations under Paragraph 3.3.25 of the Guidance Manual; in other cases it either did not follow-up or de-prioritised the search. This is unfair and prejudiced against molnupiravir.

- In relation to its draft guidance in TA1102, NICE's director of medicines evaluation, Helen Knight, acknowledged that NICE "*need*[s] *to have a way of establishing the cost effectiveness of existing medicines against current variants in an agile way*" which entails "*developing a process to monitor real world data and re-evaluate the medicines as needed against that data in a faster way than we currently do for other drugs*."[38] Although this process remains in development, the approach contradicts the position adopted in the MTA for molnupiravir (*i.e.*, that the RWE highlighted by MSD should not be included in the assessment). Further, the Appraisal Committee did not need to await the development of such a process in this instance, as the RWE had already been identified by MSD. Given that NICE appears to be committed to collating RWE for COVID-19 and assessing this rapidly, it is unclear why the extensive RWE presented by MSD was not considered. The implication of the comments above is that had NICE conducted this MTA in less haste, a fuller evaluation of relevant RWE could and arguably should have been undertaken in ID4038.

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[37] Paragraph 3.3.25 of the Guidance Manual

[38] 'NICE says evidence that COVID-19 treatment Evusheld is effective in protecting vulnerable adults against current variants is lacking as it announces new rapid update process for COVID-19 medicines', *NICE*, 16 February 2023, hiips://www nice.org.uk/news/article/nice-says-no-evidence-that-covid-19-treatment-evusheld-is-effective-in-protecting-vulnerable-adults-against-current-variants-as-it-announces-new-rapid-update-process-for-covid-19-medicines

Ground 1a.5 – the Appraisal Committee's over-reliance on the PANORAMIC data to estimate the treatment benefit of molnupiravir and its approach to evidence synthesis were procedurally unfair

The PANORAMIC data were influential in NICE's assessment of molnupiravir and contributed significantly to the negative recommendation. In its summary of recommendations, the FDG points to one clear reason why molnupiravir was not recommended: "*published PANORAMIC results (Butler et al. 2022) showed no significant difference between molnupiravir and standard care on hospitalisation or death in a high-risk population*."[39]

Moreover, due to the size of the study, the PANORAMIC data significantly affected the evidence synthesis exercise, disproportionately negatively adjusting molnupiravir's true clinical benefit. To invest the results of the PANORAMIC study with such significant weight and pool them together in an unadjusted manner with disparate other data sources led to substantial procedural unfairness.

The inclusion of PANORAMIC data in the pool acts as a lead weight exclusively for molnupiravir – the one technology for which data from that study are currently available. In effect, the treatment effect of molnupiravir is unfairly "adjusted" downwards relative to the other therapies. MSD raised this issue during consultation. However, MSD understands that neither the Appraisal Committee nor the EAG even acknowledged, let alone accounted for, the obvious methodological inequality and the risk of bias. The rule against bias is one of the "*essential characteristics of what is often called natural justice.*"[40] The Appraisal Committee's failure to mitigate against the risk of bias against molnupiravir breaches the Guidance Manual and is procedurally unfair.

PANORAMIC's Limitations

While PANORAMIC is a well-designed and well-conducted study, the patient population it enrolled had fundamental differences to those that are the focus of the MTA:

- The relevant patient population for molnupiravir in this MTA is "*people with mild COVID-19 at high risk of progressing to severe COVID-19.*"[41] The Committee's preferred definition of "high risk" corresponds to that in the McInnes study.[42] The Committee further concluded that PANORAMIC included patients with a lower risk of severe COVID compared to the McInnes definition.[43] This is also a lower risk patient population compared with the population in the MOVe-OUT RCT (which formed the basis for the marketing authorisation for molnupiravir).[44] The inclusion criteria in PANORAMIC contained a broad and subjective criterion, namely that the recruiting healthcare professional considered that a patient **might** be clinically vulnerable.[45] PANORAMIC therefore included patients who may have been at lower risk of developing severe disease than those of relevance to this MTA.

- Further, evidence from clinical experts indicated that the patients at highest risk of disease progression were triaged to receive treatment *via* the established COVID Medicines Delivery Units ("CMDUs") and were not routed to PANORAMIC. The highest risk patients (those of particular relevance to this MTA, given the McInnes definition) were therefore likely to be underrepresented in PANORAMIC.

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[39] Paragraph 3.19 of the FDG

[40] *Kanda v Government of Malaya* [1962] AC 322, 337

[41] MTA Final Scope, *Populations*, p.3

[42] Paragraph 3.8 of the FDG

[43] Paragraph 3.4 of the FDG

[44] Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. *Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients*. The New England journal of medicine. 2022-02-10 2022;386(6):509-520. doi:10.1056/NEJMoa2116044. For a summary of the inclusion criteria for MOVe-Out, please see Appendix 1 of MSD's comments on the ACD.

[45] Butler et al. C. *Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): preliminary analysis from the United Kingdom randomised, controlled open-label, platform adaptive trial*. 2022. For a summary of the inclusion criteria for PANORAMIC, please see Appendix 1 of MSD's comments on the ACD.

- Patients treated with molnupiravir in PANORAMIC were a highly heterogeneous group: not only were they potentially at lower risk, but also the highest risk patients may not have been included.

  The baseline hospitalisation rate in PANORAMIC was 0.77%. The Appraisal Committee eventually agreed that this likely underestimates the hospitalisation rate for genuinely high-risk patients (*i.e.*, under the McInnes definition of high-risk, which was the standard in this MTA).[46] The Committee concluded that the hospitalisation rate for the McInnes high risk group is between 2.41% and 2.82%, and for patients contraindicated to nirmatrelvir plus ritonavir, the baseline rate is 4%. The difference in baseline hospitalisation between PANORAMIC (0.77%) and the patient group who would likely benefit the most from molnupiravir (4%) exemplifies the obvious flaws in using data from that study to estimate clinical effectiveness in the true high-risk population. Therefore, patients enrolled into PANORAMIC were generally less likely to be hospitalised to begin with.

  Estimating the treatment effect of an intervention in higher risk patients from this study is inherently unsound and unstable.

- Additionally, people randomised to standard care in PANORAMIC were able to obtain molnupiravir and other treatments through the NHS, outside of the study, which confounds the estimates of effect from the standard care group in PANORAMIC, and results in lower rates of hospitalisation and death, both of which contribute to the underestimation of the comparative clinical effectiveness of molnupiravir.

Given the Appraisal Committee's focus on hospitalisation and mortality rates as key outcome measures, the relevance of data from PANORAMIC to the appraisal of molnupiravir is both questionable and profoundly limited. The Committee noted as much (at paragraph 3.19 of the FDG):

> "*PANORAMIC may have excluded some of the highest risk groups that could have powered the study to see benefits in hospitalisation or mortality*."

MSD submits that there is an internal inconsistency here. Given acknowledged limitations in the generalisability of the PANORAMIC study, why were its data relied upon so significantly for the negative recommendation for molnupiravir? This inconsistency, and subsequent procedural unfairness. is one of the key issues for this appeal.

NICE's Duties Under the Guidance Manual and Public Law

Understanding the relevance of clinical evidence, and the removal of bias created by irrelevant data sources, are central to the NICE process.

As noted above, according to the Guidance Manual, the evidence considered by the Appraisal Committee must be:

- "[r]*elevant to the evaluation in terms of patient groups*[…][and] *outcomes*[; and]
- [a]*nalysed in a way that is methodologically sound and, in particular, minimises any bias*."[47]

As a matter of public law, basing a decision on evidence that has been given excessive weight despite its questionable relevance may render the decision itself invalid. Case law suggests "[t]*he Court may interfere if the* [decision-maker] *has taken into account an irrelevant consideration*."[48] A key legal test is whether the potentially irrelevant feature "*played a significant role in the decision-making,*"[49] or was dealt with appropriately.

The PANORAMIC data clearly played a significant role in the assessment of molnupiravir. The EAG included PANORAMIC data in its synthesis of clinical evidence using a random effects model. Given the number of

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[46] Paragraph 3.22 of the FDG

[47] Paragraph 3.2.1 of the Guidance Manual

[48] *R v Director General of Telecommunications, ex parte Cellcom Ltd* [1999] COD 105 [27]

[49] *R (FDA) v Secretary of State for Work and Pensions* [2012] EWCA Civ 332

patients in PANORAMIC relative to the other studies under review, the weight attached to the PANORAMIC results was material to – and therefore likely skewed – the outcome.

As noted above, the Appraisal Committee acknowledged that PANORAMIC was unlikely to have been powered to show benefits in hospitalisation or mortality in those at high-risk of progression to severe disease.[50] MSD highlighted these limitations in the ACD response, calling for the data to be adjusted or excluded. Despite acknowledging a substantial flaw in what the Appraisal Committee held to be key evidence, the FDG neither explains nor justifies the inclusion of the PANORAMIC data, or why these data were considered a valid basis to conclude that molnupiravir was not clinically beneficial. Moreover, the FDG fails even to acknowledge that standard care patients in PANORAMIC might also have received molnupiravir, and that this could have artificially narrowed differences in the two arms, underestimating the true clinical effect of molnupiravir in the study.

MSD submits that (a) the relevance of PANORAMIC to the assessment of molnupiravir is limited; (b) the PANORAMIC data played an unduly significant role in the assessment of molnupiravir; and (c) the data were not appropriately scrutinised or handled. This contravenes both the Guidance Manual and public law principles, and is clearly procedurally unfair.

Evidence Synthesis Using PANORAMIC Data

As a result of the above limitations with the PANORAMIC data, the Appraisal Committee's approach to evidence synthesis is methodologically unsound and leads to unjustifiable bias against molnupiravir relative to the other technologies under review.

The Guidance Manual requires that:

> "[e]*vidence synthesis methods should be appropriate to the evaluation context. The underlying assumptions, purpose and strengths and limitations of the chosen method should be described and justified*."[51]

The Guidance Manual also acknowledges that:

> "*there are likely to be many sources of heterogeneity across test results, arising from differences in setting, patient population* […,]"

and in that light:

> "[t]*he appropriate choice of method depends on the data available and should be justified*."[52]

A critical factor in an MTA is assessing and reducing the risk of bias, particularly in RCT data. The Guidance Manual provides as follows:

- "*The aim of clinical-effectiveness analysis is to get precise, relevant and unbiased estimates of the mean clinical effectiveness of the technologies being compared*."[53]

- Valid synthesis hinges on a systematic review of all available evidence: "*Identify and quantify all health effects, and clearly describe all data sources. Evidence on outcomes should come from a systematic review, defined as systematically locating, including, appraising and synthesising the evidence to give a reliable and valid overview of the data*."[54]

[50] Paragraph 3.19 of the FDG

[51] Paragraph 3.4.22 of the Guidance Manual

[52] Paragraph 3.4.23 of the Guidance Manual

[53] Paragraph 3.4.1 of the Guidance Manual

[54] Paragraph 3.4.2 of the Guidance Manual

- "*The quality of a study's overall design, its execution, and the validity of its results determines its relevance to the decision problem. Critically appraise each study that meets the criteria for inclusion.*"[55]

- "*Accompany statistical pooling of study results with an assessment of heterogeneity (that is, any variability in addition to that accounted for by chance)* [...] *the degree of heterogeneity and the reasons for this should be explored as fully as possible.*"[56]

- "*When there is doubt about the relevance of a particular study, a sensitivity analysis should exclude that study. If the risk of an event differs substantially between the control groups of the studies in a meta-analysis, assess whether the measure of relative effectiveness is constant over different baseline risks.*"[57]

- For NMAs: "*Bias adjustments should be considered if there are concerns about methodological quality or size of included studies in a network meta-analysis.*"[58]

MSD submits that the Appraisal Committee did not adhere to the procedural safeguards in the Guidance Manual, resulting in an evidence synthesis that is biased.

The EAG did not carry out a comprehensive systematic literature review. It collected evidence selectively and key evidence was not included (RWE), as discussed at Grounds 1a.3 and 1a.4. The EAG did not adequately take into account the heterogeneity of the study data, in particular from the PANORAMIC study. This was clearly not explored "*as fully as possible*."

The vast majority of studies included in the evidence synthesis originated in the pandemic phase. These were conducted in a largely unvaccinated population, pre-Omicron, in a particular treatment setting. This presents fundamental challenges for generalisability.

Further complexities arise for PANORAMIC. Taking place more recently, PANORAMIC differed in baseline characteristics, enrolling largely vaccinated patients at a time when the incidence of Omicron was higher. As noted above, PANORAMIC likely enrolled patients at lower risk, may not have included patients at the highest risk, and some patients in the standard care arm may have received treatment from other agents undergoing assessment in this appraisal that are or were available *via* the CMDU, including molnupiravir.

The RCTs were highly heterogeneous and PANORAMIC stood yet further apart. Notwithstanding this, in the case of molnupiravir, the evidence synthesis pooled data from the NMAs and PANORAMIC as if directly comparable, giving rise to considerable bias against molnupiravir.

Ground 1a.6 – The Appraisal Committee's blanket capping of the efficacy levels of all treatments, without due consideration of each individual case, resulted in considerable bias and unfairness against molnupiravir

When discussing the generalisability of the RCT evidence to the endemic context, at paragraph 3.12 of the FDG, the Appraisal Committee concluded that:

- "*changes in best supportive care and higher vaccination rates mean that* ***any limited relative treatment effects seen during the pandemic setting would have less effect in an endemic setting***"; and as such,

- the "***mean-efficacy scenarios*** *from* [RCTs] *likely reflect the* ***highest clinical effectiveness*** *or 'ceiling efficacy' of the treatment.*"[59] (emphasis added).

[55] Paragraph 3.4.6 of the Guidance Manual

[56] Paragraph 3.4.10 of the Guidance Manual

[57] Paragraph 3.4.10 of the Guidance Manual

[58] Paragraph 3.4.21 of the Guidance Manual

[59] Paragraph 3.12 of the FDG

The EAG defined the mean efficacy of a treatment as "*the efficacy expected if the conditions were exactly the same as during the studies contained in COVID-NMA and metaEvidence*,"[60] to explain their preference for the low-efficacy scenario.

These are sweeping conclusions, applied universally to all technologies being appraised. While these general rules may rightly apply to the other technologies, it was manifestly unreasonable to apply them to molnupiravir.

The Appraisal Committee noted that various treatments would have seen their highest levels of clinical benefit earlier in the pandemic, when the studies in the NMAs took place in a largely unvaccinated population. Now that the population was largely vaccinated, the Appraisal Committee considered it right to cap efficacy at the mean from all studies. Applying the same "ceiling efficacy" to molnupiravir lacks clear justification and is manifestly unsound given the differences in evidence base.

For molnupiravir, the Appraisal Committee used evidence from the NMAs synthesised with the more recent PANORAMIC data. As discussed under Ground 1a.5 above, PANORAMIC is a more recent study, conducted in a time of **higher vaccination rates and incidence of Omicron than the other RCTs** and with a lower risk patient population. PANORAMIC was therefore unlike other RCT evidence in the NMAs, and received significant weight in the evidence synthesis.

The true clinical benefit of molnupiravir (in terms of hospitalisation and mortality) was therefore already likely to be obscured or understated by virtue of the study's design. The patient population was likely more similar to the endemic setting than for the other RCTs under review.

Given these fundamental differences, the Appraisal Committee appears to have applied a blanket rule for efficacy caps to all technologies, without examining the merits of doing so in each case – particularly for molnupiravir where an effective downward adjustment was already in play due to PANORAMIC. Applying the same cap in these circumstances effectively "double counts" against molnupiravir. The PANORAMIC data already built-in various downward adjustments for molnupiravir; to which the other technologies were not subject. To apply the same cap results in molnupiravir being over-adjusted downwards. The fairer approach would have been to apply no cap for molnupiravir, or a higher cap, or to remove PANORAMIC data from the evidence synthesis. This would enable relative assessments on a more even footing.

In the alternative to this Ground 1a.6, MSD submits that applying the same efficacy cap was unreasonable in light of the evidence available to NICE about the timing and setting of the PANORAMIC study.

Ground 1a.7 – NICE unduly focused on mortality and hospitalisation rates to assess clinical benefit rates and failed to give due consideration to other outcome measures, thereby creating bias against molnupiravir

Grounds 1a.3 – 1a.4 and 1a.5 addressed, in turn, the rejection of highly relevant RWE and the relevance of, and weight given to, the PANORAMIC data. A more fundamental question is whether focusing on hospitalisation and mortality outcomes *is the correct basis for* assessment.

Paragraphs 3.21 to 3.31 of the FDG confirm that mortality and hospitalisation rates were the key drivers for assessing benefit in this MTA.

Mortality and hospitalisation were also the key drivers behind the negative recommendation for molnupiravir. The headline recommendation at Paragraph 1.4 of the FDG states:

> "*Clinical evidence suggests that* […] *molnupiravir has limited effectiveness at treating mild COVID-19 compared with standard care because it does not reduce hospitalisation and mortality rates*."[61]

The central issue in this appeal ground is whether hospitalisation and mortality ought to have held such primacy over other outcome measures.

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[60] 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 5.1

[61] Paragraph 1.4 of the FDG

The Appraisal Committee acknowledged that concentrating on mortality and hospitalisation in this MTA was potentially problematic, commenting at Paragraph 3.21 of the FDG that:

> "*The clinical experts commented that, because of changes to the disease, the outcomes for these treatments are now more nuanced than hospitalisation and mortality. The committee considered that relative treatment effect, and reduced hospitalisation and mortality rates are key drivers of benefit, but acknowledged that the model was not sensitive to other benefits of treatment like faster resolution of symptoms*."[62]

The FDG states at Paragraph 3.31:

> "*Clinical experts said hospitalisation and mortality rates are becoming less relevant clinical efficacy measures for COVID-19 treatments. They explained this was because of the changing COVID-19 landscape.*"

Notwithstanding these concerns:

> "[t]*he committee considered the model appropriate to capture the most important outcomes and appropriate for decision making given the available evidence base for COVID-19*,"[63] and further:

> "[t]*he committee concluded that it had not been presented with strong evidence that the health benefits of the technologies have been inadequately captured and may therefore misrepresent the health utility gained*."[64]

There is a fundamental paradox in the Appraisal Committee's statements and methods. On the one hand, it acknowledges that hospitalisation and mortality rates have increasingly limited relevance to the MTA. On the other, that the approach was nonetheless appropriate for decision making, and there was no strong evidence that the health benefits of the technologies had been inadequately captured in the appraisal.

MSD submits the Appraisal Committee's approach is irrational, procedurally unsound and leads to bias against molnupiravir. This is for the following four reasons.

1. Failure to strictly adhere to the Final Scope

As noted above:

> "*The scoping process aims to define what question the evaluation will answer and what will and will not be included. The scope provides the framework for the evaluation. It defines the issues for consideration (for example, population, comparators, care pathway, and outcome measures) and sets the boundaries for the work to be done by the external assessment group, and any evidence submissions for the evaluation*."[65]

Failure to strictly adhere to the Final Scope, without compelling reasons, is procedurally unsound and has been the subject of successful NICE appeals.[66]

The Final Scope in this appraisal provides that:

> "*The outcome measures to be considered* [in this MTA] *include:*

[62] Paragraph 3.21 of the FDG

[63] Paragraph 3.21 of the FDG

[64] Paragraph 3.31 of the FDG

[65] Paragraph 2.1.1 of the Guidance Manual

[66] NICE Appeal on TA282 (Advice on pirfenidone for treating idiopathic pulmonary fibrosis) (appeal date, 2 December 2016)

- *mortality*
- *requirement for respiratory support*
- *time to recovery*
- *hospitalisation (requirement and duration)*
- *time to return to normal activities*
- *virological outcomes (viral shedding and viral load)*
- *symptoms of post-COVID-19 syndrome*
- *adverse effects of treatment*
- *health-related quality of life.*"

The EAG stated that it considered eight of the nine outcome measures. Its model did not include virological outcomes as these "*would be of more relevance to decision problems that included transmission and the prioritisation of other endpoints given the limited time available*."[67] MSD understands that this in effect meant that virological outcomes were excluded as an outcome measure throughout this appraisal. This runs contrary to the requirement in the Final Scope.

Moreover, virological outcomes can be key when appraising treatments for highly-transmissible viral diseases. The ability of a treatment to reduce and eliminate infectious SARS-CoV-2 is an important consideration in the assessment of the treatment's effectiveness. A phase 2a clinical trial of molnupiravir in patients with COVID-19 showed that treatment with the drug was associated with an accelerated clearance of infectious virus, but the Appraisal Committee failed to consider such evidence of clinical benefit due to its limited focus on only two of the outcome measures set out in the Final Scope.[68]

In light of the above, it is clear that the Appraisal Committee and EAG departed from the Final Scope to narrow the outcome measures in a manner that materially skews the assessment of molnupiravir.

2. The true benefits of molnupiravir were inadequately assessed in the MTA and omitted from the EAG's economic model

The Final Scope specifically mentions time to recovery as an outcome measurement, and therefore this should form part of NICE's assessment criteria.

Although a secondary endpoint, results from the PANORAMIC study showed a significant improvement in the time to resolution of symptoms for patients treated with molnupiravir. The median time to first recovery was 9 days in molnupiravir and 15 days in usual care, resulting in an estimated benefit of 4.2 days with molnupiravir treatment.[69]

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[67] Metry A, Pandor A, Ren S, Shippam A, Clowes M, Dark P, McMullan R, Stevenson M, *Therapeutics for people with COVID-19. An economic evaluation*, 3 October 2022, Paragraph 1.4.4

[68] Fischer WA 2nd, Eron JJ Jr, Holman W, Cohen MS, Fang L, Szewczyk LJ, Sheahan TP, Baric R, Mollan KR, Wolfe CR, Duke ER, Azizad MM, Borroto-Esoda K, Wohl DA, Coombs RW, James Loftis A, Alabanza P, Lipansky F, Painter WP. *A phase 2a clinical trial of molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus*. Sci Transl Med. 2022 Jan 19;14(628):eabl7430. doi: 10.1126/scitranslmed.abl7430. Epub 2022 Jan 19. PMID: 34941423

[69] Butler CC, Hobbs FDR, Gbinigie OA, Rahman NM, Hayward G, Richards DB, Dorward J, Lowe DM, Standing JF, Breuer J, Khoo S, Petrou S, Hood K, Nguyen-Van-Tam JS, Patel MG, Saville BR, Marion J, Ogburn E, Allen J, Rutter H, Francis N, Thomas NPB, Evans P, Dobson M, Madden TA, Holmes J, Harris V, Png ME, Lown M, van Hecke O, Detry MA, Saunders CT, Fitzgerald M, Berry NS, Mwandigha L, Galal U, Mort S, Jani BD, Hart ND, Ahmed H, Butler D,
(continued…)

The FDG acknowledges "*a significant difference in the secondary endpoint of time to self-reported recovery*" for molnupiravir.[70] However, it is unclear how (if at all) this affected the Appraisal Committee's assessment of clinical benefit.

MSD understands that the EAG's modelling did not take time to recovery into account. This reflects a selective and unsound approach to PANORAMIC study data. The mortality and hospitalisation rates from PANORAMIC were picked out for consideration (to molnupiravir's detriment); whereas time to recovery was excluded. Although MSD appreciates time to recovery was not a primary endpoint in the study, its exclusion from further consideration is methodologically unsound.

3. Lack of justification

The Appraisal Committee's reasons for pursuing a narrow focus on hospitalisation and mortality in preference to other outcome measures is unexplained. To take such a significant procedural step required an intelligible and adequate explanation. Instead the Committee provides no explanation at all.

It is accepted by the courts that the Appraisal Committee is not under an obligation to explain each and every decision step. However, the failure by NICE to provide "intelligible and adequate" decisions may legitimately be challenged by a party that has suffered "substantial prejudice" from the decision.[71] The unreasonably limited focus on hospitalisation and mortality rates, at the expense of more relevant outcome measures, inevitably led to a substantial prejudice against molnupiravir (which benefits from strong data in those other outcome measures). To have assessed molnupiravir in this way requires a proper rationale and explanation, which the Appraisal Committee failed to provide.

4. The assessment does not take into account a range of uncaptured benefits for molnupiravir

During the appraisal, MSD raised various examples of uncaptured benefit and value associated particularly with molnupiravir. These include:

- Reduced use of healthcare resource:
    - Of the patients in the PANORAMIC study, 19.6% of those receiving molnupiravir contacted a GP, compared with 23.7% receiving usual care.
- Oral treatment within a community setting:
    - Lower likelihood of face-to-face contact needed with frontline healthcare professionals.
    - Improved patient experience, particularly for patients in vulnerable categories.
- More efficient use of healthcare resource, as molnupiravir is associated with no known DDIs which need to be ruled out by clinicians.
- As a result of the above, a reduced risk of exposure of the NHS workforce to COVID-19.

McKenna M, Chalk J, Lavallee L, Hadley E, Cureton L, Benysek M, Andersson M, Coates M, Barrett S, Bateman C, Davies JC, Raymundo-Wood I, Ustianowski A, Carson-Stevens A, Yu LM, Little P; PANORAMIC Trial Collaborative Group. *Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial.* Lancet. 2023 Jan 28;401(10373):281-293. doi: 10.1016/S0140-6736(22)02597-1. Epub 2022 Dec 22. PMID: 36566761; PMCID: PMC9779781

[70] Paragraph 3.19 of the FDG

[71] *R(otao) Servier Laboratories Ltd v NICE* [2009] EWHC 281 (Admin), [171] - [176]

The EAG did not consider these additional factors. In some cases, the Appraisal Committee took the view that they were either outside the reference case or there was limited evidence to support them.[72] MSD submits that this rationale is misconceived.

The Guidance Manual emphasises the importance of a comprehensive review. Paragraph 3.1.4 states:

> "*In addition to evidence on the technology's effects and costs, health technology evaluation should consider a range of other relevant issues. For example:*
>
> [...]*the experience of having specific treatments or diagnostic tests for that condition, the experience of the healthcare system for that condition* [and][…]
>
> *organisational issues that affect patients, carers or healthcare providers.*"[73]

Paragraph 6.1.13 goes on to state:

> "*The committee may consider factors that may provide benefits to the NHS or the population, such as patient convenience. It may also consider costs and other positive or negative impacts on the NHS that may not be captured in the cost analysis, such as improved processes.*"[74]

These examples of value and benefit that MSD raised clearly affect the patient experience, the efficiency of delivering healthcare (particularly at times of a spike in infection rates) and the burden placed on the NHS, its workforce and patients. The Guidance Manual empowers the Appraisal Committee to take these additional factors into consideration. Simply stating that they fall outside the reference case is an inadequate justification not to explore these factors at all. Similarly, stating that there is "limited evidence" is illogical if neither the Appraisal Committee nor the EAG explored the evidence base in appropriate detail. Such an approach is manifestly unfair.

Ground 1b: In making the assessment that preceded the recommendation, NICE has exceeded its powers

Ground 1b.1 – NICE has breached its legal obligations under human rights and equalities laws

NICE must respect the obligations imposed on public bodies by human rights legislation, including the European Convention of Human Rights ("Convention"), as currently transposed into national law under the Human Rights Act 1998 ("HRA") and the Equality Act 2010 ("Equality Act"). Further, NICE, as a corporate body, may only exercise its functions on the direction of the Secretary of State for Health and/or NHS England and subject to those directions. NICE is therefore bound to take into account the State's obligations under human rights law.

The Appraisal Committee considered various equality issues in this appraisal.[75] In particular, it noted that nirmatrelvir plus ritonavir was contraindicated for patients suffering particular diseases (such as severe renal and hepatic impairment) and taking certain medicines (including certain anticoagulants, anticonvulsants and antiarrhythmic medication). Nirmatrelvir plus ritonavir is likely to be contraindicated, and therefore not a viable treatment option, for patients with protected characteristics. In particular:

- A significant proportion of people taking medications that are contraindicated (*i.e.*, certain anticoagulants, anticonvulsants and antiarrhythmic medication) are likely to be in old age, suffer from long-term conditions, or have disabilities. These underlying conditions are more prevalent in the high risk patients who are the subject of this MTA.

- The prevalence of renal impairment is higher in people from Black, Asian and other minority ethnic family backgrounds. Nirmatrelvir plus ritonavir as a treatment for COVID-19 is more likely to be

[72] Paragraph 3.31 of the FDG

[73] Paragraph 3.1.4 of the Guidance Manual

[74] Paragraph 6.1.13 of the Guidance Manual

[75] Paragraph 3.32 of the FDG

> contraindicated for these patients. The risk of dying from COVID-19 is also disproportionately higher in people from Black, Asian and other minority ethnic family backgrounds.[76]

The FDG suggests NICE recognised that recommending nirmatrelvir plus ritonavir alone in the mild COVID-19 setting may leave patients with protected characteristics without a viable treatment option, and this may be indirectly discriminatory. At a late stage in the appraisal, the Appraisal Committee explored alternatives, eventually recommending sotrovimab where nirmatrelvir plus ritonavir is contraindicated.

While MSD acknowledges the Appraisal Committee's efforts to address equality issues, the recommendation of sotrovimab leads to *additional* equality issues for people with protected characteristics who cannot take nirmatrelvir plus ritonavir.

In contrast to nirmatrelvir plus ritonavir (and molnupiravir), sotrovimab is a monoclonal antibody that requires IV administration.[77] As such, patients must physically attend clinics to receive treatment and be monitored for at least one hour after infusion. IV therapies can be associated with increased infection, anaphylaxis and infusion-related reaction risks. The side-effect profile is also markedly different.

Patients who cannot take nirmatrelvir plus ritonavir (who, as established above, are more likely to have protected characteristics) would therefore encounter: (i) the additional burden of travelling for treatment (which may be significant depending on age and disability); (ii) increased exposure to other patients and healthcare workers and infectious disease; and (iii) potentially increased risks of adverse reactions and side effects associated with an IV treatment.

In its attempt to mitigate indirect discrimination, the Appraisal Committee has instead substituted one type of discrimination for another. The recommendation continues to breach human rights and equalities laws, including Article 14 of the ECHR, alongside the Equality Act.

MSD submits that the correct approach is to conduct a thorough and circumspect search for an alternative to nirmatrelvir plus ritonavir in a similar treatment setting, that minimises inequality of treatment. That entails carrying out a particularly comprehensive and detailed analysis of the viability of molnupiravir as an alternative. This must include a thorough review of all available evidence, and a critical assessment of whether the evidence relied upon is valid, relevant, and credible. As is clear from the other grounds in this appeal letter, particularly Grounds 1a.3 – 1a.5, the Appraisal Committee failed to do so.

ECHR

Article 2 of the Convention obliges the State to refrain from depriving persons of life intentionally.[78] While COVID-19 therapeutics are not, in themselves, life-saving, patients can and do die as a result of the disease. Mortality resulting from COVID-19 is more prevalent amongst people from Black, Asian and minority ethnic backgrounds.[79] The choice of treatment and treatment setting can affect mortality, as some patients may die as a result of complications associated with IV treatment, although the occurrence of such complications may be uncommon. Consequently, Article 2 is engaged in this appraisal.

Article 3 of the Convention prohibits inhuman or degrading treatment. Although this traditionally applies to torture, MSD submits Article 3 is engaged because, as an alternative to an oral therapy, NICE has chosen to recommend a physically invasive treatment that is associated with higher infection risk.

Article 8 protects not only private and family life, but also the wider concept of physical and moral integrity.[80] The physical integrity of a vulnerable patient may be compromised by the additional burden of travelling to a treatment centre, undergoing a physically invasive IV procedure, incurring greater infection risk, and increased

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[76] Paragraph 3.32 of the FDG

[77] Paragraph 4.2, Xevudy 500 mg concentrate for solution for infusion, Summary of Product Characteristics

[78] *Osman v United Kingdom* [1997] 29 EHRR 245; *Scialacqua v Italy* [1998] 26 EHRR 164

[79] 'Risk factors for COVID-19 death revealed in world's largest analysis of patient records to date', *LSHTM* , hiips://www.lshtm.ac.uk/newsevents/news/2020/risk-factors-covid-19-death-revealed-worlds-largest-analysis-patient-records

[80] See, for example, *Bensaid v UK* 2001-I, [46]-[47]

exposure to other patients and NHS workers. This is particularly the case if an individual or family has chosen to isolate or reduce contact with others. In extreme cases, patients may even avoid treatment. Article 8(2) provides that "*there shall be no interference by a public authority with the exercise of this right except such as in accordance with the law and is necessary in a democratic society* […]." The recommendation of sotrovimab, without a thorough and circumspect analysis of molnupiravir, breaches public law principles and was "expedient" rather than "necessary." Article 8 is both engaged and breached.

Article 14 prohibits discrimination in the enjoyment of other Convention rights. Accordingly, for Article 14 to be engaged, one of the other Convention rights must be applicable (although not necessarily infringed). For the reasons set out above, Articles 2, 3 and 8 are engaged such that Article 14 applies. Where a public body, such as NICE, is providing a public service, it is bound by Article 14 to ensure that it does so in a non-discriminatory fashion.[81] Specifically, Article 14 states:

> "*The enjoyment of the rights and freedoms set forth in this European Convention on Human Rights* ***shall be secured without discrimination on any ground*** *such as sex, race, colour, language, religion, political or other opinion, national or social origin, association with a national minority, property, birth* ***or other status***" (emphasis added).

As is clear from the discussion above, the recommendation of sotrovimab for patients who are unable to receive nirmatrelvir plus ritonavir (and who are likelier to be older, disabled or from minority ethnic family backgrounds) is discriminatory.

Section 149 of the Equality Act

The Public Sector Equality Duty ("PSED") under Section 149 of the Equality Act requires NICE to give due regard to eliminating discrimination or victimisation and advancing equality of opportunity between persons who share a relevant protected characteristic and those who do not.

The PSED is breached if the decision-maker has failed to meet the expectations of "*a reasonable public authority in the circumstances*."[82]

It is unreasonable to seek to mitigate inequality by taking steps that lead to other forms of indirect discrimination against patients with protected characteristics. MSD submits that a reasonable public authority ought to have been aware of the marked differences in treatment and risk between nirmatrelvir plus ritonavir and sotrovimab, and thus ought to have robustly assessed the feasibility of other treatment options that reduced inequalities of treatment.

Section 29 of the Equality Act

Section 29(6) applies to NICE and prohibits discrimination in the provision of a public service. Under Section 29(7), NICE must make reasonable adjustments in its processes to take account of the protected characteristics of the patient population.

As noted above, MSD submits that "reasonable adjustments" must include a thorough assessment of molnupiravir as an alternative to nirmatrelvir plus ritonavir, including a robust assessment of all available evidence. The rejection of relevant evidence, and giving significant weight to evidence of questionable relevance (see Grounds 1a.3 – 1a.5 above), suggests the Appraisal Committee made no real adjustment in selecting sotrovimab as the next option.

Ground 2: The recommendation is unreasonable in light of the evidence submitted to NICE

> **Ground 2.1 – By evaluating evidence selectively, inappropriately, and in a methodologically unsound and unfair manner, the Appraisal Committee's conclusions in respect of molnupiravir are necessarily unreasonable in light of the available evidence**

[81] *See*, for example, *Belgian Linguistic* Case (No 2) [1968] I EHRR 252

[82] *R (otao Elizabeth Rose) v Thanet CCG* [2014] EWHC 1182 (Admin)

The above grounds demonstrate with clarity that the Appraisal Committee:

a. improperly departed from established MTA procedures in a manner that negatively affected the standard and rigour of evidence review (Ground 1a.1);

b. instead, followed an *ad hoc* procedure that was inconsistent, unclear and unfair (Ground 1a.2);

c. failed even to consider certain highly relevant RWE that could have informed and remedied uncertainties and issues in the RCT evidence base (Ground 1a.3);

d. adopted an inconsistent and selective approach as to reviewing RWE (Ground 1a.4);

e. over-relied on incomplete and deeply flawed evidence of questionable relevance, and failed to adjust for obvious causes of bias (Ground 1a.5);

f. failed to fairly consider the applicability and impact of its blanket cap on efficacy levels to each treatment (Ground 1a.6); and

g. unduly focused on a narrow pair of outcome measures which were increasingly irrelevant to the context of the review, and failed to give due consideration to other highly-relevant and in-scope measures (Ground 1a.7).

MSD submits that a negative recommendation that is arrived upon from such a significantly flawed process are unreasonable *per se*.

As noted above, Grounds 1a.3 to 1a.7 also contain elements that go to reasonableness. For succinctness, we have not duplicated these points under Ground 2, but could do so if the Chair or Scrutineer considered this helpful.

Ground 2.2 – The Appraisal Committee's administration cost assumptions for molnupiravir and nirmatrelvir plus ritonavir are unreasonable

MSD acknowledges that the Appraisal Committee's primary reason for the decision not to recommend molnupiravir related to its clinical benefit. Subject to the other grounds in this appeal letter addressing that point, MSD further submits that the Appraisal Committee drew unreasonable conclusions regarding the cost of molnupiravir, both in itself and in relation to the cost attributed to nirmatrelvir plus ritonavir.

a) Unreasonably high administration cost for molnupiravir

The Appraisal Committee assumed an administration cost of £410 per person for oral antivirals. In the case of molnupiravir, such an assumption is unjustifiably high. This assumption fails to take into account that the current deployment costs for oral therapies will reduce significantly when the delivery of oral antivirals is moved to the primary care setting.

The Personal Social Services Research Unit ("PSSRU") reported a prescription cost per consultation of £33.10 in 2021, which is considerably lower than the £410 administration cost applied in the Appraisal Committee's model.[83] The cost of £33.10 is more accurate and reasonable for molnupiravir, in light of the minimal risk of contraindications.[84]

The EAG set out in its critique of company comments on the ACD that it: "*received no further information on the costs of administration of treatment in the community and has maintained the values in the original report*."[85]

[83] Jones, K., Burns, A., *Unit Costs of Health and Social Care 2021*

[84] Puenpatom, A., Williams, M. G., Song, Y., et al, *Prevalence of potential drug-drug interactions with ritonavir-containing COVID-19 therapies*, presented at the 24th Annual MAD-ID Meeting; Orlando, FL, USA; May 18-21, 2022

[85] 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

However, it notes that "*should the committee believe that an alternative value is more appropriate, then this can be adjusted for within the net monetary benefit (NMB) approach used by the EAG or by changing the incremental costs within the ICER. For example, 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*."[86]

It is unclear how (if at all) the Appraisal Committee addressed the EAG's comments. As far as MSD is aware, no further steps were taken.

The FDG notes at paragraph 3.18 that:

> "*NHS England provided Covid Medicines Delivery Unit (CMDU) deployment costs for the administration of oral antivirals (£410) and neutralising monoclonal antibodies (£820). Some companies disagreed with using CMDU deployment costs because these include costs based in secondary care. However,* ***future delivery may be in primary care, which would likely reduce these costs****. The NHS England representative explained that the delivery of service is subject to change. In future, integrated care boards will be responsible for treatment delivery currently done by the CMDUs*" (emphasis added).[87]

However, despite this acknowledgment of the likely inaccuracy of the deployment cost assumption for oral antivirals going forward, the Appraisal Committee did not adjust its approach to administration costs. This is self-evidently unreasonable in light of the evidence available. This also contrasted with the process followed which led to sotrovimab's approval, involving the application of halved IV infusion costs proxying the costs of oral treatments.[88]

b) Unreasonable underestimation of the administration cost of nirmatrelvir plus ritonavir

Notwithstanding the fact that the administration cost of molnupiravir used in NICE's modelling is unreasonably high, the assumed cost of prescribing nirmatrelvir plus ritonavir does not take into account the time required to ensure it is not prescribed to patients who are contraindicated or where there may be DDIs. As such, the costs of administering nirmatrelvir plus ritonavir in the community should be higher than for other oral antivirals, particularly given that it has been "*clinically validated that prescribing nirmatrelvir with ritonavir safely (taking account of contraindications and DDIs) would take substantially longer than prescribing molnupiravir.*"[89]

As set out in MSD's response to the ACD:

> "*the application of the same high administration costs for molnupiravir and nirmatrelvir with ritonavir in* ***the economic model unnecessarily increases the cost and therefore decreases the cost-effectiveness of molnupiravir****, a treatment that is straightforward to prescribe, is not associated with any drug-drug interactions (DDI), and could easily be deployed in the primary care setting*" (emphasis added).[90]

Ultimately, the unreasonably low estimate for the administration cost of nirmatrelvir plus ritonavir was not increased in the FDG, as no additional cost was applied to account for the time for healthcare professionals to assess for contraindications and minimise the risk of DDIs.

Accordingly, the cost comparison between molnupiravir and nirmatrelvir plus ritonavir that forms part of NICE's cost effectiveness evaluation process is unreasonable in light of the available evidence.

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[86] 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

[87] Paragraph 3.18 of the ACD

[88] Paragraph 3.28 of the FDG

[89] Executive Summary of MSD's comments on the ACD

[90] Executive Summary of MSD's comments on the ACD

Next Steps

MSD therefore requests that: (i) this appeal be determined at an oral hearing; and (ii) if the appeal is successful, the Appraisal Committee reconvenes to reconsider its decision in respect of molnupiravir.

MSD is available to answer any questions NICE may have about the appeal letter, including at the scrutiny phase.

Yours sincerely

[redacted]

[redacted]

[redacted]

Appendix 1

ID 4038

Therapeutics for People with COVID-19

Key Departures from NICE's Usual MTA Process

Established MTA Evidence Submission, Review and Evaluation Processes	Process in ID 4038
Opportunity for Initial Discussion	
• "*Before the start of the evaluation, for technology appraisals and highly specialised technologies,* ***the company has the opportunity to discuss the decision problem*** *that follows from the draft scope with the NICE team and EAG representatives.*" (Paragraph 5.5.3 of the NICE Health Technology Evaluations Manual (the "Guidance Manual")) • "*The company must* ***submit an outline of how it intends to approach the decision problem when preparing the evidence submission****. This outline should include, but is not limited to,* ***evidence sources to be used, evidence likely to become available during the evaluation and how this might be managed, the planned approach to disease and economic modelling, potential challenges in interpreting the evidence, and the proposed approach to handling of uncertainty***." (Paragraph 5.5.3 of the Guidance Manual)	• Consultees were not given the opportunity to discuss the decision problem and to outline the relevant evidence and any challenges relating to such. • Rather, following the Stakeholder Information Meeting on 14 April 2022, the External Assessment Group ("EAG") developed an MTA protocol and began its assessment of the clinical outcomes and cost effectiveness of the technologies, based on a synthesis of selective publicly available evidence, without consultee input. • Participating companies had limited opportunity to input on the MTA protocol after the Stakeholder Information Meeting had taken place. This included the health economic modelling aspects that required reconsideration because of the clinical data limitations identified by the EAG in the first version of the EAG report shared with stakeholders. The scope for stakeholder input was limited (see the proforma comments on the Executable Model submitted by MSD at first review of the EAG report on 19 July 2022), and most of the suggestions made by stakeholders were not considered further.
Invitation for Evidence Submissions	
• NICE invites companies "*to provide an evidence submission using a detailed submission template*." (Paragraph 5.5.8 of the Guidance Manual) • Companies are given **84 days** from the invitation to participate in the multiple technology appraisal ("MTA") to make evidence submissions.	• No such initial window for evidence submission was provided to companies participating in this MTA, as the EAG conducted its assessment of the clinical outcomes and cost effectiveness of the technologies before any invitation for consultee or commentator evidence submissions.

(Paragraph 5.5.9 of the Guidance Manual) • After receiving the evidence submissions, NICE sends these to the EAG for review. (Paragraph 5.5.12 of the Guidance Manual)	• When the companies were invited to provide evidence, this was in the form of targeted submissions in relation to the EAG's assessment report which consisted of four questions, one of which was focused on the marketing authorisation and pricing aspects of the technologies under assessment. • The window provided for targeted evidence submissions was **28** days.
• "*NICE **invites non-company stakeholders to make a submission** providing information on the potential clinical effectiveness and value for money of a technology.*" (Paragraph 5.5.31 of the Guidance Manual)	• No such initial window for evidence submission was provided to non-company stakeholders, as the EAG conducted its assessment of the clinical outcomes and cost effectiveness of the technologies before any invitation for consultee or commentator evidence submissions.
Opportunity for Discussion Prior to Evidence Submission	
• "*NICE will provide an opportunity for the company to discuss key issues with NICE and, if needed, the EAG before the company's submission date.*" (Paragraph 5.5.15 of the Guidance Manual)	• No dedicated and defined opportunity for the discussion of key issues with NICE and/or the EAG was provided to the companies between the invitation for targeted evidence and the submission deadline.
NICE's Aim to Ensure that Companies Prepare Best Possible Submissions	
• "***NICE aims to ensure that the company prepares the best possible evidence submission** for the committee* […] *it will **help clarify substantive issues**.*" (Paragraph 5.6.7 of the Guidance Manual)	• No assistance was provided to companies in preparing the targeted submissions in the shortened timeframe.
External Assessment Report	

• "*The EAG critically evaluates any evidence submissions*." (Paragraph 5.6.14 of the Guidance Manual)	• No company or non-company stakeholder evidence submissions were invited prior to the EAG preparing its report. Consequently, evidence submissions were not critically evaluated by the EAG in preparing its initial report. • In respect of the targeted evidence submitted in response to the Assessment Report, the EAG did not thoroughly engage with and evaluate the submissions. • In addition, the Process Statement suggests that stakeholder submissions would be considered in accordance with Sections 5.7.2 to 5.7.22 of the Guidance Manual, which in fact only deals only with appraisal committee meetings. In reality, these submissions fell into a methodological vacuum.
• "*For multiple technology evaluations in technology appraisals and highly specialised technologies, the companies are invited to provide an evidence submission but are not formally required to do so. The EAG does an assessment of the clinical outcomes and cost effectiveness of the technologies* […] [t]*he* ***assessment is based on systematic reviews of the literature, data provided by the companies, information from the experts or specialist committee members, and modelling of patient outcomes, costs and cost effectiveness***." (Paragraph 5.6.15 of the Guidance Manual)	• The EAG did not conduct a systematic literature review of the clinical evidence for this MTA, but rather relied on the results from two living systematic reviews, without carrying out a critical appraisal of the generalisability of the studies to the populations encompassed by the MTA, or critiquing the quality of the studies identified. A systematic literature review on economic modelling and health related quality of life studies was also not conducted. Thus, the data forming the basis for the assessment of clinical outcomes and cost effectiveness of the technologies were not derived through a systematic approach. • The Assessment Report was not based on data provided by companies, or information from the experts, as no submissions from such were invited prior to the EAG preparing its report.