Clearance checklist

*Inclusion of this checklist is **mandatory**. Please complete the whole list and private office will remove before putting submission in the box. A submission without it will be sent back.*

***Note**: Contact names provided must have seen and approved the submission.*

Finance	Does this involve any spending or affect existing budgets?	☒ If yes, named official: Peter Appleton ☒ No
Legal	Does this include legal risk, a court case or decisions that can be challenged in court?	☒ If yes, named official NR NR (CLG) and NR NR (DHSCLA) ☐ No
Communications	Could this generate media coverage, or a response from the health sector?	☒ If yes, named official: NR NR and NR ☐ No
Analysis and fact-checking	Does this include complex data, statistics or analysis?	☒ If yes, named official: NR ☐ No
Devolved Administrations and the Union	Does this promote union wide policies, or will it affect Wales, Scotland or Northern Ireland?	☒ If yes, named official: Sophie Eltringham ☐ No
Legislation	Does this include options that may require or impact primary or secondary legislation/regulations? If yes, please discuss with the DHSC Legislation Team.	☐ If yes, named official ☒ No
Parliamentary Handling	Does this require engagement with parliamentarians or a statement in Parliament? If so, please discuss with the Parliamentary Affairs Team, and Intelligence, Insight and Engagement Team.	☒ If yes, named official: NR NR ☐ No
Fraud	Have you considered fraud risks?	☐ If yes, named official ☒ No
Commercial	Does this include commercial or contractual implications?	☒ If yes, named official: NR NR ☐ No
Technology, digital & data	Does this rely on or have crossover with a tech/digital/data solution?	☐ If yes, named NHSX official ☒ No
Health Data/Personal data use	Does this involve the use of sensitive health/care data? Discuss with the SIRO team. Could this require the processing of Personal Data (Data Protection Act 2018)? Discuss with the Data Protection Officer team.	☐ If yes, named SIRO/DPO official ☒ No
Strategy and Implementation Unit	Does this relate to cross-cutting or longer-term implications for wider DHSC strategy? Does this relate to one of the Secretary of State priorities or a manifesto commitment?	☐ If yes, named official ☒ No
Duties, Tests and Appraisals	Do the following tests apply and have they been considered; • Secretary of State Statutory Duties including on health inequalities • Public Sector Equality Duty • Family Test • Other (please specify)	☒ If yes, which test? Public Sector Equality Duty ☐ No

To: SoS, PS(VP), PS(TILS) **From:** NR

Clearance: David Hayward, Deputy Director
Date: 20/06/2022
Copy: NR
Private Office Submissions Copy List

Pre-Exposure Prophylaxis – Evusheld

Issue	You asked the Antivirals and Therapeutics Taskforce (ATTF) for advice on whether to deploy, trial, or not procure the pre-exposure prophylaxis (PrEP) antibody Evusheld following results from UKHSA in vitro testing against the Omicron subvariant BA.2, which is currently dominant in the UK.
Date a response is needed by	Routine 5 days. A response and decision will enable communication of the decision to interested parties who are keen for updates on next steps.
Recommendation	We are asking you to **agree** to the following recommendations: • That the Department should **not** seek to deploy Evusheld in a PrEP programme at this time. • That Evusheld is considered through NICE's topic selection process for potential formal referral to NICE's technology appraisal programme. We are asking you to **note**: • Evusheld could be included in the PROTECT-V trial to assess its clinical effectiveness against currently circulating variants. Further recommendations on this will follow.

Discussion

Pre-exposure prophylaxis (PrEP)

1. PrEP is designed to prevent the development of infection in people who have not been exposed to the SARS-CoV-2 virus. It may be useful for those who are unable to be vaccinated, or do not mount an adequate immune response to full vaccination, and who therefore remain at risk of progressing to severe disease, hospitalisation, or death. There is a risk that, without PrEP, these individuals feel the need to retain shielding behaviour and are distanced from society.
2. The Independent Advisory Group (IAG) has identified those who remain most at risk of severe COVID-19, hospitalisation, and death due to a weak immune system. These patients would be the highest priority for prophylaxis were this made available through the NHS. We have undertaken work to understand the scale of such a programme and which cohorts would be in scope. See **Annex A** for the report (subject to final clinical clearance).
3. The highest risk group, Group A1, comprises those in any risk group within the cohort who are unable to complete vaccination or who have completed vaccination and been admitted to hospital for COVID-19. In England, A1 numbers c.127,000. Uplifted for the UK, we estimate the A1 cohort to number c.152,000, however, to note this number includes those who have not completed vaccination for any reason, not just those medically unable to. An uptake rate has not been applied to this cohort and there is some uncertainty attached to these numbers.

Evusheld

4. Evusheld is the only PrEP product current viable in the UK. The other neutralising monoclonal antibody (NmAb) that has been authorised for prophylaxis use, Ronapreve, is ineffective against Omicron variants and no longer in use in the UK. Other pipeline products are not yet licensed in the UK for PrEP.

5. Evusheld is a long-acting antibody cocktail developed by AstraZeneca and delivered as two intramuscular doses, one of 150mg tixagevimab and one of 150mg cilgavimab. To date, the ATTF has been assessing whether to procure Evusheld outside of business-as-usual processes, as has been the case with other antivirals and therapeutics during the pandemic.

6. Clinical trials that took place before the Omicron variants showed that the relative risk of developing COVID-19 decreased by 82.8% in the six months following administration. However, there is limited clinical evidence of Evusheld's effectiveness against Omicron variants.

7. UKHSA have completed live virus neutralisation testing against Omicron variants including BA.2. See more detail in **Annex B**. The expert Prophylaxis Oversight Group (POG) have analysed these data alongside other available data and concluded that the tixagevimab antibody is substantially compromised against the BA.2 subvariant. Therefore, the combination acts as prophylaxis monotherapy against COVID-19, for which clinical trial data does not exist.

8. There have been extensive discussions on the interpretation of the data with AstraZeneca, who believe that the in vitro testing shows effectiveness against BA.2. They are viewing the combination of the two antibodies as a whole, rather than evaluating the differential impacts of the two NmAbs on BA.2. The multi-agency group RAPID C-19 and the NHS Expert Working Group have both advised that the available data, including the UKHSA in vitro data, are insufficient to recommend deployment at this time and outside normal processes that provide access to novel medicines for NHS patients. **The CMO is content with their recommendations that at this stage the expert groups do not think there is sufficient evidence of benefit to recommend widespread deployment**.

9. Widespread deployment without certainty of effect would come with significant risks if patients believe they have protection and therefore change their behaviour. Additionally, deploying to a large cohort carries the risk of driving new variants through placing selective pressure on the virus given that the tixagevimab antibody component is compromised against BA.2. To note that if a deployment programme were recommended, this would come with significant costs and is unaffordable within current budgets.

10. Note that if you agree not to deploy Evusheld as prophylaxis for this autumn or winter, there will be **no PrEP programme available** on the NHS this year.

11. The POG have recommended that Evusheld be added to the PROTECT-V trial. This would be subject to I&S funding, as previously discussed with SoS and finance colleagues on 9 May. This I&S is also unaffordable and should the trial go ahead, this would need to be added to the Department's overcommitments, and therefore prioritised against other unfunded requirements.

National Institute of Health and Care Excellence evaluation

12. NICE is responsible for assessing the clinical and cost effectiveness of medicines. Evusheld has not been referred to NICE for evaluation as prophylaxis as to date it has been considered through the pandemic response processes. AstraZeneca has

said that they are keen for Evusheld to undergo a NICE appraisal and that they have the necessary data. However, they are likely to expect this in addition to current pandemic decision processes which, in theory, could provide a procurement decision more quickly.

13. A NICE technology appraisal to evaluate the clinical and cost effectiveness of Evusheld for PrEP would take at least **6 – 12 months**. NICE have suggested that an appraisal could begin in autumn 2022.

14. A technology appraisal would therefore not be completed in time to support decisions around whether to deploy or run further evaluation of the product for this autumn. However, it could be a way of building the long-term evidence base for future decisions on Evusheld. This would also **return procurement to business-as-usual NHS processes**, rather than centrally funded procurement.

15. NICE have confirmed that prophylaxis use of Evusheld will not be included in the ongoing Multiple Technology Assessment (MTA) they are undertaking on therapeutics for treating COVID-19. You are receiving advice on 17 June on whether Evusheld should be included in the MTA as a treatment (after a positive test), should it receive regulatory approval for this indication.

16. A NICE evaluation could be completed simultaneously with a trial. Given the limitations of the evidence base, an appraisal will be challenging, and the NICE appraisal may result in a recommendation for further research, potentially through managed access which would mean that it was available to NHS patients while further real-world evidence is collected to inform a re-evaluation by NICE.

17. The ATTF recommend that Evusheld is considered through NICE's topic selection process for potential formal referral to NICE's technology appraisal programme.

18. AstraZeneca have suggested an accelerated approval process alongside emergency access. Note, this would need NICE approval and, as outlined above, there is the possibility that the appraisal may recommend further research. AstraZeneca have given no details of emergency access. Their proposal is outlined in **Annex I.**

Further clinical evaluation (further recommendation to follow)

19. You asked for advice on a trial of Evusheld, given the uncertain effectiveness against variants, and for an indication of what research would be possible for I&S At present this is unfunded and therefore would need to **be added to the Department's existing overcommitments and be prioritised ahead of other unfunded requirements.**

20. The most efficient way to generate further clinical data would be to add Evusheld to the PROTECT-V trial platform, which has already enrolled over 1000 patients to investigate whether certain drugs provide protection against COVID-19[1]. This additional arm could commence by the autumn and would enable a limited number of patients to access Evusheld whilst generating further data. Results may not be available for approximately **2 years,** although preliminary results may be available sooner**.**

21. It is anticipated that I&S for a trial would cover ~1,760 patients, with 880 receiving one dose of Evusheld and 880 receiving placebo. If the dose were doubled, this would have significant cost implications. A full breakdown of costs is at **Annex C.** We anticipate that enrolling between **1,760 and 2,650** patients would provide a statistically significant result, with half (880 to 1,325) receiving Evusheld. The enrolment numbers needed to give a significant result depend on the case rate.

[1] PROTECT-V (camcovidtrials.net)

22. The ATTF have not discussed this option with AstraZeneca. In May, the Office for Life Sciences advised that a trial option is likely to worsen the relationship with AstraZeneca because of the delay to any potential procurement by ~2 years. It could also risk reputational damage for AstraZeneca by publicly questioning Evusheld's neutralisation effectiveness against currently circulating variants. More information on the relationship between HMG and AstraZeneca is at **Annex E.** To note, a trial would depend on AstraZeneca being willing to sell product to HMG for this purpose.

23. Further advice on options for UK research, including an existing trial platform or an observational study, on Evusheld will follow. This advice will consider whether a trial would support a future decision and/or be useful for furthering our understanding of how in vitro data relates to clinical outcomes. There is limited clinical evaluation being completed by other countries (**Annex D**).

24. A business case would be needed for any trial, and for any procurement, noting the position on affordability.

Finance – cleared by Peter Appleton

25. RAPID C-19 and the NHS Expert Working Group have recommended that we do not deploy Evusheld as PrEP at this time and CMO is content with this recommendation. It is clear that any potential deployment of Evusheld is unaffordable. Following the recent reprioritisation across the DHSC group in 2022/23 the Department remains over committed, with further unfunded priorities and pressures emerging. HMT have been clear on their position regarding additional claims on the Reserve, and as such any potential procurement of Evusheld would need to be funded by further Departmental reprioritisation and involves returning to the difficult options rejected previously as part of the reprioritisation exercise. This should be considered alongside the other pressures and unfunded recommendations and would need to be prioritised against them and any other calls and over commitments.

26. AstraZeneca indicated in December 2021 that each dose of Evusheld would cost I&S. The initial list price proposed by the company is I&S The ATTF has not discussed costs as formal commercial negotiations have not commenced, but it may be possible to negotiate the price point. The current cost effectiveness analysis **assumes a final cost of** I&S **per dose**.

27. The cost effectiveness analysis is outlined in **Annex F** and is based on the PROVENT trial results. Overall, analysis suggests that Evusheld may be cost effective for very vulnerable cohorts. This is based on single dosing (a dose of 300mg) and a high case rate. If **double dosing is required, the costs required to achieve a similar level of benefit could double, making this less cost effective.**

28. However, there is uncertainty over the dose and duration of protection against Omicron. Initial cost projections for a limited procurement of I&S doses is I&S Note that this is a more limited cohort than that highlighted in paragraph three, given that we understand supply to be limited. This is based on single dosing, and we understand that procurement costs could potentially double if a double dose were needed and depending on supply may mean fewer patients could receive it. More details, including deployment costs, are at Annex F. Availability and costings would be subject to discussions with the company.

29. As mentioned previously I&S **for a trial would need to be added to the Department's existing overcommitments and would therefore need to be prioritised ahead of other unfunded requirements.**

Commercial – cleared by NR

30. If we were to conduct a trial, we would need to procure at least 880 treatment courses. Note that this would be the minimum volume for a read out and would

[redacted]

Communications – cleared by NR

45. Media and patient group interest in Evusheld remains high, including recent mentions at PMQs. Some patients that were previously considered clinically extremely vulnerable have been awaiting a decision on the procurement of Evusheld, some of whom continue to shield despite formal guidance being removed. There is a desire for more information on the decision-making process (particularly timings) and the outcome of UKHSA testing.

46. We would anticipate challenges with communicating the decision not to procure Evusheld prior to a decision on a clinical trial, as patients report feeling "left behind" by the government. However, an announcement of a clinical trial could mitigate some of this, as some patients will be able to access Evusheld through the trial. We recommend that communications on both the decision not to procure Evusheld and the decision on whether to clinically evaluate Evusheld are done concurrently.

47. We will handle all media queries reactively with a robust policy Q&A developed by the ATTF. This includes a narrative that accounts for the rationale for any decision on Evusheld, the underpinning advice and the final decision maker (**Annex I**).

48. Communications will highlight that a NICE evaluation could lead to access via the NHS and will highlight that important work continues on determining cohorts for any potential prophylaxis. **Annex I** also contains a handling strategy for the relationship with AstraZeneca.

Conclusion

49. Given the continued uncertainty regarding Evusheld's effectiveness against Omicron subvariants and in line with clinical steers, and considering that any deployment would be unaffordable, we recommend:

a. That the Department should **not** seek to deploy Evusheld in a PrEP programme at this time.

b. That Evusheld as a PrEP is considered through NICE's topic selection process for potential formal referral to NICE's technology appraisal programme.

50. If you are content with these recommendations, please note that further advice on research investigating Evusheld's efficacy as PrEP for COVID-19 will follow.

NR **Policy Advisor,** I&S

NR **Head of Antibodies, Variants and International Team**

Antivirals and Therapeutics Taskforce