Health Research Authority

2 Redman Place
London
E20 1JQ

31 October 2024
Ref: 24.TP.11

Dr Peter Selley
peterjselley@gmail.com

Dear Dr Peter Selley,

Re: Complaint regarding mRNA-1345 safety and immunogenicity in pregnant women and their infants (IRAS ID: 1008181)

Thank you for your email to the Health Research Authority (HRA) dated 21 July 2024, where you outlined your concerns about the above clinical trial in light of a change in guidance issued by the Joint Committee on Vaccination and Immunisation (JCVI). The updated guidance now recommends that, from 1 September 2024, all pregnant women should receive the Abrysvo vaccine as part of the NHS vaccination programme.

The specific concerns you have raised are as follows:

1. Trial participants may be unlikely to take up the offer of an Abrysvo vaccine despite this now being recommended as part of the NHS vaccination programme.

    a. It is unclear whether it is safe to receive both vaccines (mRNA-1345 and Abrysvo) during the same pregnancy.

    b. The trial exclusion criteria excludes anyone who has already received an Abrysvo vaccine and prevents participants from doing so during study participation. Participants are not informed of this within the Participant Information Sheet (PIS).

    c. The PIS informs participants that they should not receive any non-trial vaccines within 2 weeks before or after receipt of the trial vaccine or placebo.

2. Participants allocated to the placebo arm of the trial will remain unprotected from RSV infection despite being eligible to receive the Abrysvo vaccine.

3. Concerns about the information provided to participants via the Participant Information Sheet (PIS):

    a. The Participant Information Sheet (PIS) advises that 100, 000 deaths in children were associated with RSV in 2019 however does not explain that >97% of the deaths occurred in low-income countries, with preventable deaths in UK being rare.

b. The PIS does not inform participants that breastfeeding has been found to reduce morbidity in babies from RSV by around half.

4. The compensation payment of £1110 offered to participants is an excessive inducement to take part.

Your concerns have now been considered in accordance with the HRA policy and procedure for managing complaints relating to third parties. Our response is as follows:

- As part of our investigation, we have been in contact with the study sponsor, Moderna, to request that they respond to each of your concerns. In their response, the sponsor informed us of the following:

1. Trial participants may be unlikely to take up the offer of an Abrysvo vaccine despite this now being recommended as part of the NHS vaccination programme.

The sponsor has advised that research sites have been instructed to only recruit participants who will reach 40 weeks gestation before 1 September 2024. As the NHS RSV vaccine programme will only administer the licensed Abrysvo vaccine to women between 28-40 weeks of gestation, no trial participants would be eligible to receive both vaccines.

The sponsor highlighted that the Participant Information Sheet (PIS) was updated to reflect the introduction of the NHS RSV vaccine programme and inform participants of the timeline.

a. It is unclear whether it is safe to receive both vaccines (mRNA-1345 and Abrysvo) during the same pregnancy.

As outlined above, no trial participants would be eligible to receive both vaccines during the same pregnancy.

b. The trial exclusion criteria excludes anyone who has already received an Abrysvo vaccine and prevents participants from doing so during study participation. Participants are not informed of this within the Participant Information Sheet (PIS).

The sponsor highlighted that the Participant Information Sheet (PIS) includes information about the NHS vaccination programme and other RSV prevention options such as Palivizumab and Nirsevimab. Additionally, the trial would only be recruiting participants who will reach 40 weeks gestation before the beginning of the NHS vaccine programme, meaning that they would not be eligible to receive the Abrysvo vaccine.

c. The PIS informs participants that they should not receive any non-trial vaccines within 2 weeks before or after receipt of the trial vaccine or placebo.

While the PIS advises against receiving any non-trial vaccines two weeks before or after the trial vaccine or placebo as a standard protocol requirement, the sponsor has informed us that they have emphasised to sites that routine immunizations should take precedence over study participation. They have advised that the protocol allows participants to receive the necessary standard care while enrolled in the study.

2. **Participants allocated to the placebo arm of the trial will remain unprotected from RSV infection despite being eligible to receive the Abrysvo vaccine.**

   The sponsor advised that the trial design, which includes a 50% chance of receiving a placebo, is transparently communicated to participants via the PIS. Participants in the trial would not be eligible for the NHS Abrysvo vaccine programme as they would reach 40 weeks gestation before the time the programme is due to commence**.**

3. **Concerns about the information provided to participants via the Participant Information Sheet (PIS):**

a. **The Participant Information Sheet (PIS) advises that 100, 000 deaths in children were associated with RSV in 2019 however does not explain that >97% of the deaths occurred in low-income countries, with preventable deaths in UK being rare.**

   The sponsor informed us that the statement regarding RSV being associated with over 100, 000 deaths of children globally in 2019 is accurate and provides a global context for the study. While the majority of these deaths occurred in low-income countries, the sponsor has argued that it is essential to present a comprehensive perspective to underscore the significance of RSV and the potential impact of the vaccine.

b. **The PIS does not inform participants that breastfeeding has been found to reduce morbidity in babies from RSV by around half.**

   The sponsor has recognised the role of breastfeeding in reducing RSV morbidity and highlighted that the PIS informs participants that the vaccine might increase antibodies in breastmilk and offers the option for participants to provide breastmilk samples for analysis.

4. **The compensation payment of £1110 offered to participants is an excessive inducement to take part.**

   The sponsor has highlighted that the compensation amount of £1110 is the net compensation across the entire duration of the study (up to 15 months including 8 maternal study visits, 1 study call, 4 infant study visits and 3 safety calls). This was reviewed and approved by the REC who ensure that the compensation is both fair and appropriate for participants' time and involvement in the study. On this basis, the compensation is intended to be reasonable and not an inducement to participate.

Following consideration of the above information provided by the sponsor, we noted that action had been taken to ensure that trial participants would not be eligible to receive both vaccines. However, we were not able to identify any record of this change in recruitment being formally notified to the REC in line with normal process.

In light of the new information established as part of the complaints process, we shared your complaint, along with the sponsor's response outlined above, with the Cambridge Central Research Ethics Committee (REC) at the monthly meeting held on 11 October 2024.

During the meeting, the Committee was asked to review its favourable opinion of the trial. The Committee considered the timeline of the review of the trial and noted that the original REC favourable opinion was given before the roll out of the NHS RSV vaccine programme on 1 September 2024. The Committee was content that this decision was appropriate at the time of initial review however it agreed that the favourable opinion would not have been given had the information about the NHS vaccine programme been relevant at the time. As the 1 September has now passed, the Committee felt that the study's current validity was in question and with current information it should not go ahead.

The Committee highlighted that it is the sponsor's responsibility to appropriately inform the REC of any changes that affect the research. It was noted that, on 19 June 2024, an amendment had been submitted by the sponsor which included revised participant information materials intended to mitigate for the RSV vaccine becoming available on 1 September. However, the Committee agreed that the information in the amendment did not sufficiently explain the scope of the RSV vaccine programme, or how this affected the ongoing validity of the study.

Given the now NHS-wide vaccine programme, the Committee agreed that the study now lacked equipoise and that it was no longer ethical to recruit new participants. It was unclear to the Committee who would be recruited into the study and which clinicians would be recommending participation into the study over the NHS approved vaccine. Moreover, the potential to receive placebo in the study was considered unethical when there is an alternative licensed vaccine to protect from potential illness. The Committee advised that the only suggested way forward with this study would be to compare the experimental vaccine with the licenced vaccine being used in the NHS vaccine programme. The Committee wished to know how the sponsor proposed to continue with participants already consented to the study.

The Committee did not agree with the comments raised in the complaint around excessive or coercive reimbursement and agreed that this was appropriate based on the number of extra visits.

It is important to highlight that, under the Clinical Trial Regulations, the decision to suspend or terminate the Clinical Trial Authorisation (CTA) and therefore to halt the trial lies solely with the MHRA. The Research Ethics Committee has no power under the Regulations to suspend or terminate the CTA or to legally withdraw the ethical opinion given previously.

However, the REC may review its opinion in light of new ethical concerns and notify the MHRA that, had it received the information with the initial application, its opinion of the trial would not have been favourable. In line with this process, the REC notified the MHRA of its concerns following the meeting and requested that they considered suspending or terminating the CTA for the trial.

This week, we received a response from the MHRA which acknowledged that the NHS RSV vaccine programme is the new Standard of Care that applies to the study population in this trial. As a result, participants on placebo are considered to be at an increased risk compared to Standard of Care. The MHRA also noted that the most recent study amendment submitted by the sponsor did not halt the trial or give consideration to the vaccine programme. The MHRA informed us that they have been in contact with the sponsor in light of this and received confirmation that recruitment was halted via a site communication on 9 August 2024, before the start of the programme on 1 September. We understand that two participants were recruited to date, for whom the ICF was updated and reconsented, along with follow up assessment.

Given that the study had already been halted, the MHRA did not decide to terminate the CTA for the trial. However, in their communications with the sponsor, the MHRA has reminded them of their regulatory responsibilities and the action required from them following a trial halt. The sponsor has now submitted an amendment to formally halt the trial in line with this.

Thank you for bringing this matter to our attention and providing us with the opportunity to investigate.

We hope this information is helpful to you and that it provides reassurance that we have given careful consideration to the concerns that you raised.

Yours sincerely,

Emma Davies
Information Governance & Complaints Support Manager