CCVAC
CHILDREN'S COVID VACCINE ADVISORY COUNCIL

Matt Westmore, CEO
Health Research Authority, 2 Redman Place, Stratford, London, E20 1JQ
cc: Stephen Tebbutt, Company Secretary, HRA
Sue Harrison, Chairman, South Central Berkshire B REC
Dr June Raine, CEO, MHRA
Shane DeGaris, CEO, Barts Health NHS Trust
Professor Mel Pickup, CEO, Bradford Teaching Hospitals NHS Foundation Trust
Philip Cruz, UK medical director, Moderna.
Maria Caulfield MP, Parliamentary Under Secretary of State, DHSC

19th February 2024

Dear Mr Westmore,

re: NextCOVE trial and child participants

I am writing to make a formal complaint regarding approval of the inclusion of healthy children in this trial. I also wish to complain about the tone and content of misleading and unethical participant recruitment advertisements, some of which the HRA have now admitted were not approved for use. I also wish to complain about publicly posted offers of payment for child participants.

This trial has drawn a lot of criticisms around the ethics (or rather lack of them) of approving research on an mRNA covid vaccine booster at a time when all covid vaccines were being discontinued for healthy children and in the knowledge of the extremely small risk of serious illness caused by SARS-CoV-2 infection in childhood. The specific reasons why this trial, and the process by which it was approved for conduct in the UK have drawn such criticism are listed below:

1. <u>The use of healthy child participants is unethical and noncompliant with Declaration of Helsinki (DoH)</u>

   a. In all the documentation provided to myself and others as a result of Freedom of Information Act (FOIA) requests, there has been no attempt to explain any direct benefit of the booster when given in the trial to healthy children. This is a requirement which is fundamental to research governance as legislated in the Medicines for Human Use (Clinical Trials) Regulations 2004[1], which enacted the Declaration of Helsinki

[1] https://www.legislation.gov.uk/uksi/2004/1031/pdfs/uksi_20041031_en.pdf

(DoH)[2] into UK law. The DoH paragraph 28 states, *"For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden."*

b. The Universal Declaration on Bioethics and Human Rights (2005)[3] Article 3 states, *"the interests and welfare of the individual should have priority over the sole interest of science or society"*. Article 7, referring to people without the capacity to consent, states, *"authorization for research and medical practice should be obtained in accordance with the best interest of the person concerned*" and that *"research should only be carried out for his or her direct health benefit"*. None of the documents we have now been given suggest in any way that these matters, relating to the ethics of recruiting healthy children, were specifically addressed either in the original clinical trial application (CTA) or during the review and consideration of that CTA by the Research Ethics Committee (REC).

c. The REC initially rejected the study on a number of grounds. In the minutes of 11/4/23 (attached) they requested, *"In the Parent Assent/ICF: Explain why the enrolment of children is necessary."* Moderna responded (19/04/2023), *"This study is enrolling children of 12 years of age and above. Like adults, children can become infected with SARS-CoV-2 virus and become unwell. Current recommendations in the UK are for children in high-risk groups and those children who are in contact with clinically vulnerable people to be vaccinated. We are asking for participants aged 12 and above to join the study to find out if the study vaccine is safe for children, whether it causes any side effects, and how much protection it may provide against COVID-19 in children."* But this reply does not address why healthy children were needed at all, rather than restricting recruitment to those groups who were eligible for the existing booster.

d. The HRA has recently responded publicly to a consultation on revisions to the DoH,[4] stating that this document is central to your work. The HRA's governance document[5] also places a specific requirement on RECs to consider whether/how any application complies with the DoH. From all the documents and records so far provided, none has specifically demonstrated that inclusion of healthy children in this study is compliant with the DoH. Nor have we seen any evidence that the REC specifically addressed this issue in their review, either in their comments about the documents provided, in their questions about them, or in their requests for further information. It is therefore not clear why the study was approved for conduct using healthy children before the vaccine under investigation was fully authorised for use in adults.

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[2] https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/

[3] http://portal.unesco.org/en/ev.php-URL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html

[4] https://www.hra.nhs.uk/about-us/news-updates/declaration-helsinki/

[5] https://s3.eu-west-2.amazonaws.com/www.hra.nhs.uk/media/documents/GAfREC_Final_v2.1_July_2021_Final.pdf

e. The REC requested expert advice from a paediatric oncologist[6] and which appears to be factually incorrect. The oncologist stated, *"as we are vaccinating young people, the inclusion of those 12+ is VERY reasonable."* But as shown in paragraph 2c below, spring boosters were not being given to healthy under 75s, let alone to healthy children. Indeed by the time this trial started recruiting, even a primary course of covid vaccination had been withdrawn for children in the UK. As a paediatric oncologist, the expert's own patients would indeed have been offered covid vaccines, but this group of immunosuppressed children were excluded from the trial. Furthermore, he/she did not answer the REC's specific request for *"Advice on the clinical, ethical and psychosocial problems that may arise in relation to the inclusion of children within trial."* However, s/he rightly questioned the size of the proposed payments. Could the REC comment on how they selected a paediatric oncologist for expert advice, rather than for example an infectious disease or respiratory consultant?

2. <u>Lack of potential benefit</u>

a. The recruitment leaflet (provided as a result of FOIA requests)[7] specifically states that, *"By enrolling in the NextCOVE Study, you or your child will be contributing to a potential solution to the evolving COVID-19 pandemic, which has affected the entire world."* Furthermore, the leaflet stated, *"We do not know if it is effective and safe to use".* The more detailed patient information sheet (PIS) states, *"There may or may not be a direct benefit to you because of taking part in the clinical research study. However, what is learned in this study may help in the prevention of COVID-19 in the future and may advance scientific knowledge."* DoH states, *"While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects."*

b. According to the JCVI,[8] for 16-19-year-olds, the number needed to vaccinate (NNV) with a booster to prevent one severe hospital admission is 193,500, which is far bigger than the entire trial. This number included teenagers with clinical risk factors. For healthy 20-29s, the same analysis stated a NNV of 706,500 for an autumn booster, thus the number for healthy 16-19s would be expected to be even higher. Furthermore, the vast majority of adolescents have already been repeatedly exposed to SARS-CoV-2 infection and will have good innate and naturally-acquired immunity.

c. The REC highlighted the need for the current UK policy to be spelled out near the top of the PIS: see Paragraph 8 of REC minutes 11/4/23: *"The Committee stated that it was important to put the study into context for UK participants with an explanation of the Department of Health (DOH) advice recommending COVID vaccinations added early in the PIS. The researcher stated as the DOH advice changed frequently it would be difficult to keep this information up to date. The Committee stated this could be covered by explaining the DOH advice in the PIS was up to date at the time of writing*

[6] Statement attached

[7] https://www.whatdotheyknow.com/request/nextcove_booster_trial_in_childr_2/response/2486022/attach/4/7.10%20mRNA%201283%20P301%20Recruitment%20Brochure%20UK%20English%20V2%2021Mar2023.pdf?cookie_passthrough=1

[8] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1131409/appendix-1-of-jcvi-statement-on-2023-covid-19-vaccination-programme-8-november-2022.pdf

and any changes or updates would be issued verbally. (Action 6)."

In the MHRA Grounds for Non-Acceptance (GNA) letter 19/4/23, in response to Question 9a), the Sponsor confirms that the latest guidance has been added to the PIS under the section "What is the purpose of the study?" *"Current guidance in England (06Apr2023) suggests that people aged 75 and older, residents in care homes for older people, and those aged 5 and older with a weakened immune system are to be offered a Spring booster dose 2023. If this information changes, your study doctor will let you know."* However, there is no direct mention of the fact that child participants in this study, ie healthy children aged 12-17 were specifically not being offered a booster in the UK. Perhaps the REC should have insisted that the PIS stated clearly that administration of a booster as part of this study was inconsistent with current DOH advice/recommendations.

3. Potential for harm

a. There was no mention in the Recruitment leaflet of any of the known severe side effects of the existing Moderna vaccine. The PIS similarly only quote mild transient side effects such as a sore arm at the top and do not cover more serious side effects until page 13 (after details of diary cards and payments), thus potentially further compromising the DoH requirement for fully informed consent.

b. The REC asked for some modifications to the patient information leaflet,[9] including asking the researcher to address *"the current high profile media coverage of some medical professionals who dispute the safety of COVID vaccinations"*. The researchers stated they would add this to the PIS but would need to carefully consider the language they would use. The Committee stated the researchers should simply acknowledge that the participants may have seen conflicting opinions regarding the safety of the vaccine in the news. When the PIL was resubmitted, it stated, *"The general public may see conflicting opinions of some health professionals regarding safety of the COVID-19 vaccines, due to the high-profile nature of the media coverage. Please discuss with your study team any concerns you may have."* This statement is misleading, as it implies these are merely 'opinions' and gives no balance to evidence from the large peer-reviewed literature on a number of different vaccine injuries, including from sources such as the CDC.[10]

c. Although myocarditis is mentioned as being commoner in younger males, the leaflet makes no attempt to quantify the risk for different participants, thus reducing the possibility of fully informed consent. It is also notable that potential symptoms of myocarditis, namely chest pain, rapid pulse or palpitations, are all missing from the list of items for the diary cards. It is also nowhere mentioned that reports of myocarditis have been higher after Moderna than other covid-19 vaccines, which in one large

[9] REC minutes, attached

[10] Oster M. mRNA COVID-19 Vaccine-Associated Myocarditis, October 2021. https://www.fda.gov/media/153514/download

study from Canada[11] was 5 times higher than the already acknowledged risk from Pfizer's mRNA vaccine.

d. The REC minutes require the sponsor *"Revise the unqualified use of the word "safe", e.g., on page 3 of the assent document. Use "acceptable safety profile" or similar."* This individual change was made by Moderna but there remain other unqualified uses of "safe" in these documents for participants (eg the parent PIS states, *"mRNA-1273.222 has been proven to be safe"*) and yet they were still approved by the REC.

e. The REC minutes, (paragraph 4) record that the REC made a very sensible recommendation to enhance understanding of the benefit/risk for any participant in this study: *"The committee recommended that the PIS information re. risk/benefit would be enhanced by using a graphic showing the documented risk/benefits of vaccination in the population versus perceived. (Recommendation 1)".* The response was, *"The Sponsor appreciates the recommendation by the REC for inclusion of a graphic to show the documented risk/benefits of vaccination in the population versus the perceived and will take this into consideration for future clinical trials.".* The REC then apparently simply accepted this refusal to incorporate this enhancement without any further comment and without asking for an explanation.

4. <u>Use of recruitment advertisements aimed at children and parents that were misleading, unethical and sometimes unapproved. Unethical and illegitimate payment offers for children</u>

a. One of the trial centres, Bradford, was using an approved advertisement[12] the cover picture of which was emotionally loaded, as was the text stating, *"The COVID-19 pandemic is like nothing we've seen in more than a century and it has altered each and every one of our lives. Now, you or your child could be a part of important research on an investigational COVID-19 vaccine. You or your child's participation could contribute to a potential solution to the evolving COVID-19 pandemic, which has affected the entire world."* It is hard to see how the REC could have decided that this emotionally loaded recruitment document was consistent with the requirement of your Integrated Research Application System (IRAS) guidance, specifically Q A28, that *"Recruitment material should be restrained in tone."* Please could you clarify whether or not the REC referred to the requirements of IRAS Q A28 when approving this recruitment advertisement.

b. You will be aware that there are also other advertisements, used by the Bradford centre, to recruit children into this study. The HRA have already acknowledged that a number of these advertisements were not approved by the REC, which was a breach of the conditions for the ethical approval for this study. It was therefore disappointing to learn that the HRA is apparently powerless to deal with complaints about the grossly

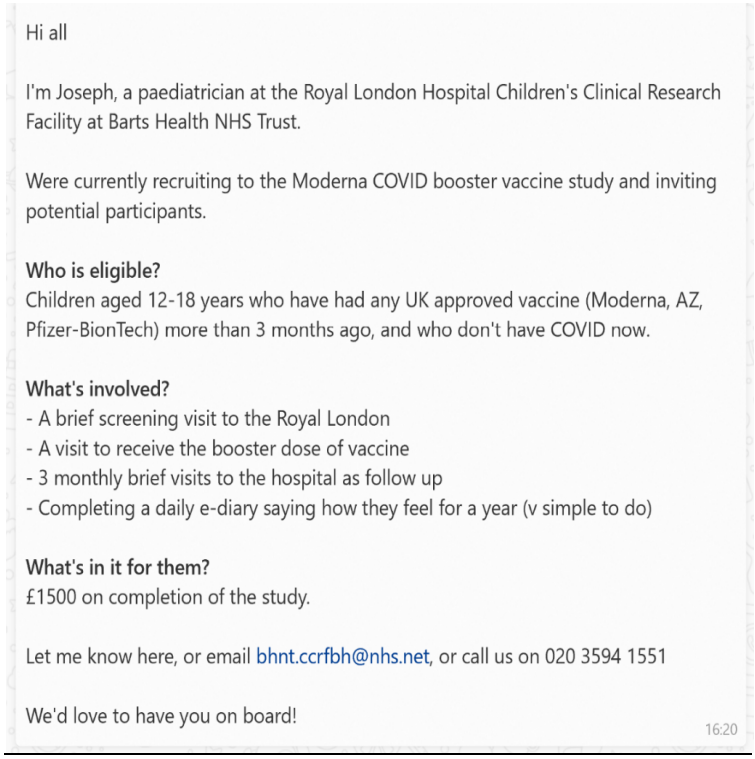
[11] Naveed Z, Li J, Wilton J et al. Comparative Risk of Myocarditis/Pericarditis Following Second Doses of BNT162b2 and mRNA-1273 Coronavirus Vaccines, Journal of the American College of Cardiology, 2022: **80:** 1900-1908, https://doi.org/10.1016/j.jacc.2022.08.799.

[12] https://www.whatdotheyknow.com/request/nextcove_booster_trial_in_childr_2/response/2486022/attach/4/7.10%20mRNA%201283%20P301%20Recruitment%20Brochure%20UK%20English%20V2%2021Mar2023.pdf?cookie_passthrough=1

misleading and unethical nature of these unapproved clinical trial adverts and cannot even suggest any other public body to which such complaints should be addressed. In addition, I was surprised to discover that despite the fact that these unapproved adverts, directed at children, contain statements and claims which are at variance with approved recruitment material (eg a claim of "minimal risks"), the HRA has refused to contact, or to ask the sponsors or investigators to contact, recruited children or their families to point this out. This may have potential legal implications regarding failure to obtain (and maintain) fully informed consent, which, as stated on your website, is an iterative, ongoing process rather than a single event. I am informed that most of these unapproved advertisements have now disappeared (although only after recruitment into the study had ceased anyway). However I believe that two of them are still accessible to the public at https://www.asianstandard.co.uk/dr-anil-shenoy-leads-latest-covid-19-vaccine-study-in-bradford-recruits-first-participants/ and https://bradfordzone.co.uk/2023/06/bradford-launches-covid-19-vaccine-trial-with-first-participants-enrolled/. I would be interested to hear what steps you are taking to attempt to ensure that this unethical and misleading material, produced at the instigation of the NHS recruitment centre in Bradford, is taken down forthwith.

c. At the Berkshire REC, the Approvals Manager was clearly concerned by the large amount of money Moderna was proposing to offer to trial participants and stated, *"this amount seemed much higher that what would be considered a reasonable reimbursement and therefore would contravene clinical trial regulations. The Medicines for Human Use (Clinical Trials) Regulations (2004) explicitly prohibit the giving of incentives or financial inducements to children… or their parents."* The revised leaflet gave a greatly reduced schedule of payments, which amounted to a total of £185, down from the original £1505.

   Despite this change, a paediatrician at one of the trial centres, Barts Health NHS Trust, posted an unapproved offer of £1500 in a WhatsApp group.



Hi all

I'm Joseph, a paediatrician at the Royal London Hospital Children's Clinical Research Facility at Barts Health NHS Trust.

Were currently recruiting to the Moderna COVID booster vaccine study and inviting potential participants.

Who is eligible?
Children aged 12-18 years who have had any UK approved vaccine (Moderna, AZ, Pfizer-BionTech) more than 3 months ago, and who don't have COVID now.

What's involved?
- A brief screening visit to the Royal London
- A visit to receive the booster dose of vaccine
- 3 monthly brief visits to the hospital as follow up
- Completing a daily e-diary saying how they feel for a year (v simple to do)

What's in it for them?
£1500 on completion of the study.

Let me know here, or email bhnt.ccrfbh@nhs.net, or call us on 020 3594 1551

We'd love to have you on board!

16:20

When I wrote to their CEO and chairman, I initially received no reply, but then after an FOI request, the Trust replied that the payments were authorised and *"the message was in line with the offer of reimbursement by the sponsor".* On pressing them further, through an Internal review, they acknowledged that the offer was based on version 1 leaflet which had not been approved by the REC - another example of a breach of the conditions of the ethical approval of this study.[13]

It is notable that the version 1 of the leaflet nowhere mentions that it is still a draft awaiting approval and it was clearly circulated to potential recruitment centres prior to approval, with the Sponsor presumably assuming all would go ahead without changes. This poor practice regarding version control, could potentially have led to children being enrolled after an illegal inducement. Indeed I am aware of a mother of four children who rang the trial centre after seeing this WhatsApp but by then the trial had stopped recruiting.

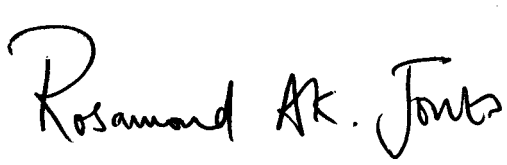
Please would you address the following points in answering this complaint:

- What numerically was the potential benefit of this study to its child participants.
- What was the calculated numerical risk of a serious adverse event for 12-17s and hence what risk:benefit ratio was used in decision making for approving this trial?
- Why was an unauthorised offer of £1500 payment made on WhatsApp and what action has been taken to ensure such a breach of research governance cannot happen in future?
- Why was it thought necessary to conduct such a study in healthy children before the vaccine under investigation has been licensed in adults?
- As stated above, none of the documents we have seen so far, as a result of numerous FOIA requests demonstrate that the specific DoH ethical considerations around the recruitment of healthy children into a clinical trial (from which they are exposed to risk but can have no reasonable expectation of benefit) were either addressed in the original CTA or raised as questions or discussion points by the REC. If there are indeed documents relating to this submission for ethical approval, which have not yet been provided under any FOIA request, but which do address these specific ethical matters then I would like to offer you this opportunity to provide them. I am particularly thinking about the study protocol and Investigators' brochure. If you are unable or willing to provide me with these documents but you do not think that either of these documents contains the information that I am seeking, then I would be grateful if you would state this clearly and unequivocally.
- It is my contention that this study does not comply with the Declaration of Helsinki and the inclusion of healthy children should not have received ethical approval. An independent review of the REC process and decision-making for this study is required. A full analysis of the REC's consideration of the requirements of the DoH and its compliance with the HRA's own governance document is needed. The special

[13] Correspondence attached

rights and protections afforded to those who are vulnerable or unable to provide fully informed consent are an essential part of the ethical governance of clinical research. Their proper consideration should be a fundamental and essential part of any ethics review process and not just an after-thought or something which can be taken for granted.

Yours sincerely,



Dr Rosamond Jones, MBBS (Hons), MD, FRCPCH, retired consultant paediatrician

Convenor of Children's Covid Vaccines Advisory Council (www.childrensunion.org/ccvac)