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VIA ELECTRONIC FILING

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Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
Commissioner Stephen M. Hahn, M.D.
5630 Fishers Lane
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Rockville, MD 20852

UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES AND THE FOOD AND DRUG ADMINISTRATION

PETITION FOR ADMINISTRATIVE	**:**	
ACTION REGARDING PHASE III	**:**	
CLINICAL TRIAL OF ChAdOx1	**:**	**Docket No.**
nCoV-19 - NCT04400838	**:**	

CITIZEN PETITION

This petition for administrative action is submitted on behalf of Informed Consent Action Network[1] ("**Petitioner**") pursuant to 21 C.F.R. § 10.30 and related relevant provisions of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act to request that the Commissioner of Food and Drugs (the "**Commissioner**") require that the Phase III trial of ChAdOx1 nCoV-19 (NCT04400838) conforms with the requests in the "Actions Requested" section below before licensure.

Because of the compelling need to ensure the safety and efficacy of any COVID-19 vaccine licensed by the FDA, and to allow Petitioner the opportunity to seek emergency judicial relief should the Commissioner deny its Petition, **Petitioner respectfully requests that FDA act on the instant Petition by August 26, 2020.**

[1] Including, but not limited to, on behalf of its members that work for the Petitioner.

A. ACTION REQUESTED

1. It is hereby requested that the study design for the Phase III trial of ChAdOx1 nCoV-19 (NCT04400838)[2] be amended to provide that:

a. the control group will receive a placebo (saline injection);

b. any and all adverse events and reactions[3] will be documented for the entire duration of the trial;

c. such documenting of adverse events and reactions shall last at least twelve months for adults, thirty-six months for children, and sixty months for infants and toddlers;

d. it uses an adequate sample size, appropriately powered, in order to (i) detect an increase in rare adverse events or any untoward medical occurrence, whether or not considered vaccine related, and (ii) determine that the rate of adverse events from the vaccine will not exceed the rate of adverse events known to occur from SARS-CoV-2 in the group under review[4];

e. participants are tested for T-cell reactivity to SARS-CoV-2 pre-vaccination and post-vaccination; and

f. germline transmission tests are conducted for male participants.

B. STATEMENT OF GROUNDS[5]

2. The current study design for the Phase II/III clinical trial for ChAdOx1 nCoV-19 ("**nCOV-19 Vaccine**") provides that the control group will receive a "MenACWY vaccine" instead of a placebo.[6] Moreover, despite reviewing efficacy for at least 6 months, the current trial design for this vaccine will only capture "solicited systemic reactogenicity signs and symptoms for 7 days" and "unsolicited adverse events (AEs) for 28 days," when it could easily capture all

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[2] NCT04400838 available at https://www.clinicaltrials.gov/ct2/show/NCT04400838 (last visited August 11, 2020).

[3] Including, but not limited to, systemic adverse reactions, adverse events, non-serious adverse event, serious adverse events, medically-attended adverse events, new onset medical conditions, and any other health issue of any degree or type arising or exacerbated post-vaccination, whether suspected, unexpected, expected or otherwise, and whether or not considered related to the vaccine.

[4] For example, for children, the clinical trial should be properly sized and powered to determine that the vaccine is safer than a SARS-CoV-2 infection.

[5] The Petitioner hereby incorporates by reference as if fully set forth herein the Statement of Grounds from its Amended Citizen's Petition, dated July 20, 2020, available at, https://beta.regulations.gov/document/FDA-2020-P-1601-0028 (last visited August 11, 2020).

[6] *See* https://www.clinicaltrials.gov/ct2/show/NCT04400838 (last visited August 11, 2020).

adverse events for the entire duration of the trial.[7] Finally, this study will only include 10,260 participants, rendering it severely underpowered to assess safety for anything other than the most common adverse events.[8]

3. Petitioner will suffer irreparable harm if the action requested herein is not granted because once the FDA licenses this COVID-19 vaccine, states are expected to make this product mandatory. For example, the New York State Bar Association recently issued a report on COVID-19 recommending that "[w]hen the efficacy of a COVID-19 vaccine has been confirmed, enact legislation requiring vaccination of each person unless the person's physician deems vaccination for his or her patient to be clinically inappropriate."[9] Hence, without the FDA assuring proper safety trials of the vaccine *now*, the Petitioner will not have the opportunity to object to receiving the vaccine based on deficient clinical trials *later*.

4. Furthermore, if the vaccine is licensed without a placebo control group and an appropriate safety review, ethical considerations prevent a placebo-controlled study post-licensure, thereby preventing any such study from ever occurring. This is especially troubling because when parents assert that when a licensed vaccine injured their child, the FDA and CDC regularly deny these assertions by stating that no cause and effect has been established between vaccination and the alleged injury. But as the FDA and CDC are well aware, without a placebo control trial, cause and effect is very difficult and often impossible to establish.[10]

5. The public interest also weighs strongly in favor of the requested relief because using a placebo control and adequate safety review protocols (i) will comport with the best scientific practices, (ii) increase public confidence in the safety and efficacy of a product expected to be mandated, and (iii) using a non-inert substance as a control will have the opposite result in that it will create uncertainties regarding the safety of this COVID-19 vaccine.

a. Placebo Control

6. The guidance issued by the FDA on June 30, 2020, titled *Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry* (the "**FDA COVID-19**

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[7] *Id.*

[8] *Id.*

[9] https://nysba.org/app/uploads/2020/05/HealthLawSectionTaskForceCOVID-19Report_5.13.20-1.pdf (last visited August 11, 2020).

[10] *See* https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/adverse-reactions.html ("establishing evidence for cause and effect on the basis of case reports and case series alone is usually not possible," rather, researchers need "to compare the incidence of the event among vaccinees with the incidence among unvaccinated persons") (last visited August 11, 2020); *see also* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3505292/ (The entire advantage of a randomized placebo-controlled trial "is the ability to demonstrate causality i.e., cause-effect relationship.") (last visited August 11, 2020); https://www.cdc.gov/vaccines/pubs/surv-manual/chpt21-surv-adverse-events.html (The Vaccine Adverse Events Reporting System (VAERS) is unable "to determine causation" because "there is a lack of an unvaccinated group for comparison in VAERS.") (last visited August 11, 2020).

Guidance") provides that "[l]ater phase trials, including efficacy trials, should be randomized, double-blinded, and *placebo controlled*."[11]

7. According to the FDA and the Center for Disease Control and Prevention ("**CDC**"), randomized placebo-controlled trials are the standard for determining the safety and efficacy of a new drug or biological product, including new vaccines. A "placebo" is defined as "[a] substance or treatment that has no effect on human beings."[12] Clinical trials for new pharmaceutical products typically do not use a non-inert substance as a control because, due to its pharmacological effects, a non-inert substance makes it impossible to isolate the effects of just the experimental product being studied.

8. Similarly, the National Institute on Aging, an institute within the National Institutes of Health, explains as follows regarding designing clinical trials:

> In undertaking a clinical trial, researchers don't want to leave anything to chance. They want to be as certain as possible that the results of the testing show whether or not a treatment is safe and effective. The "gold standard" for testing interventions in people is the "randomized, placebo-controlled" clinical trial. ... A placebo is an inactive substance.[13]

9. Where an effective vaccine already exists for an infection, ethical considerations may require using the existing vaccine, rather than a placebo, as the control (an "**active control**"). The FDA's industry guidance explains that an "active control must be a drug whose effect is well defined," which means "historical placebo-controlled trials are available to define the active control effect."[14] The importance of only using an active control that has already been licensed based on a placebo-controlled trial is explained by the FDA as follows:

> The placebo-controlled trial measures the total pharmacologically mediated effect of treatment. In contrast, an active control trial … measures the effect relative to another treatment. The placebo-controlled trial also allows a distinction between adverse events due to the drug and those due to the underlying disease or background noise.[15]

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[11] https://www.fda.gov/media/139638/download (emphasis added) (last visited August 11, 2020).

[12] https://www.cdc.gov/vaccines/terms/glossary.html (last visited August 11, 2020); *see also* https://www.fda.gov/media/71349/download (last visited August 11, 2020).

[13] https://www.nia.nih.gov/health/why-are-placebos-important (last visited August 11, 2020).

[14] https://www.fda.gov/media/78504/download (last visited August 11, 2020).

[15] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e10-choice-control-group-and-related-issues-clinical-trials (last visited August 11, 2020).

Because there is no licensed COVID-19 vaccine, an active control is not appropriate for the trial of the nCoV-19 Vaccine; hence, the trial of the nCoV-19 Vaccine should include a placebo control group.[16]

10. Without a placebo-controlled trial, cause and effect between a potential adverse effect and the vaccine being studied is very difficult and often impossible to establish.[17] Hence, once licensed, studying claims of injury occurring post-licensure becomes exceedingly difficult. This is because after licensure, it will be considered unethical to conduct a placebo-controlled clinical trial of a licensed COVID-19 vaccine. Having a scientifically valid and robust clinical trial prior to licensure will avoid this quagmire.

11. Fortunately, most of the FDA-approved Phase II and III study designs for potential COVID-19 candidate vaccines appear to include a saline placebo control group. For example, the leading candidate COVID-19 vaccine in the United States, developed with the National Institute of Allergy and Infectious Disease ("**NIAID**"), lists "Placebo: Saline" as the control for its Phase II clinical trial.[18] As another example, the leading COVID-19 vaccines being developed in China both list a placebo control group in their Phase II study designs approved by the FDA.[19]

12. Unfortunately, this is not true for the trial of the nCoV-19 Vaccine. Oddly, after registering the study design for this vaccine using a "Placebo Control," the control was inexplicably changed to "MenACWY." It is ethically and scientifically indefensible to use

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[16] Moreover, even after a COVID-19 vaccine has been licensed, there are still many considerations which must be taken into account before using a COVID-19 vaccine as a control, rather than a placebo, for any new potential COVID-19 vaccine. *See* https://www.fda.gov/RegulatoryInformation/Guidances/ucm126501.htm ("There are three principal difficulties in interpreting active-control trials. … One problem is that there are numerous ways of conducting a study that can obscure differences between treatments, such as poor diagnostic criteria, poor methods of measurement, poor compliance, medication errors, or poor training of observers. As a general statement, carelessness of all kinds will tend to obscure differences between treatments. Where the objective of a study is to show a difference, investigators have powerful stimuli toward assuring study excellence. *Active-control studies, however, which are intended to show no significant difference between treatments, do not provide the same incentives toward study excellence, and it is difficult to detect or assess the kinds of poor study quality that can arise.* The other problem is that a finding of no difference between a test article and an effective treatment may not be meaningful.") (emphasis added) (last visited August 11, 2020).

[17] https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/adverse-reactions.html ("establishing evidence for cause and effect on the basis of case reports and case series alone is usually not possible," rather, researchers need "to compare the incidence of the event among vaccinees with the incidence among unvaccinated persons") (last visited August 11, 2020); https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3505292/ (The entire advantage of a randomized placebo-controlled trial "is the ability to demonstrate causality" i.e., cause-effect relationship.) (last visited August 11, 2020).; https://www.cdc.gov/vaccines/pubs/surv-manual/chpt21-surv-adverse-events.html (The Vaccine Adverse Events Reporting System (VAERS) is unable "to determine causation" because "there is a lack of an unvaccinated group for comparison in VAERS.") (last visited August 11, 2020).

[18] https://www.clinicaltrials.gov/ct2/show/NCT04405076 (last visited August 11, 2020).

[19] https://www.clinicaltrials.gov/ct2/show/NCT04341389 (last visited August 11, 2020); https://www.clinicaltrials.gov/ct2/show/NCT04383574 (last visited August 11, 2020).

MenACWY vaccine as a control for this trial, including because the safety of MenACWY was not established in a placebo-controlled clinical trial.[20]

13. Permitting licensure of nCoV-19 Vaccine without a placebo control group is inappropriate, scientifically and ethically, especially given the above. The use of a non-inert substance as a control creates significant uncertainty in confirming, among other things, the safety of this vaccine. There is no reason to create such uncertainty or to compromise the scientific validity and robustness of the clinical trial for this candidate COVID-19 vaccine by having a control that is anything other than a saline placebo.

b. Tracking All Adverse Events

14. To increase assurance that potential adverse events from the nCoV-19 Vaccine are captured, all adverse events and reactions should be documented for each subject post-vaccination, whether or not they are considered vaccine-related by the investigator or sponsor, for the full duration of the clinical trial.[21] All adverse events and reactions include, but are not limited to: all systemic adverse reactions, adverse events, non-serious adverse events, serious adverse events, medically-attended adverse events, new onset medical conditions, and any other health issue of any degree or type arising or exacerbated post-vaccination, whether suspected, unexpected, expected or otherwise, and whether or not considered related to the vaccine.

15. The adverse events captured beyond a short duration should not be limited to "serious adverse events," since there are many autoimmune, neurological, and chronic health disorders which have a major impact on the quality of life, yet are categorized by the FDA as "adverse reactions" and not categorized as "serious adverse reactions." [22] To wit, there are a myriad of post-licensure adverse reactions reported by consumers and physicians and are also

[20] *Ibid*. The trade name for MenACWY vaccine in the United States is Menveo. This product was licensed for adults based on a clinical trial in which the control group of 1,966 participants received either Menomune (209 participants) or Menactra (1,757 participants). *See* https://www.fda.gov/media/78514/download (last visited August 11, 2020). Menactra was licensed based on a clinical trial in which Menomune was the active comparator. *See* https://www.fda.gov/media/75619/download (last visited August 11, 2020). Quizzically, the clinical trials section of the package insert for Menomune only lists the clinical trial in which it was used as a comparator against Menactra. *See* https://www.fda.gov/media/83562/download (last visited August 11, 2020). Meaning, the same clinical trial in which Menactra was studied with Menomune as its active control is apparently relied upon by the FDA to support the safety of both of these products. Using any of these products as an active control for a COVID-19 vaccine is unscientific and unacceptable. The control should be a saline placebo.

[21] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32 (last visited August 11, 2020) (defining "Adverse event" as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related"); https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event (last visited August 11, 2020).

[22] The FDA defines an adverse event to be "serious" if it results in one of the following specific outcomes: "death, a life threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect." FDA Guidance for Industry and Investigators, https://www.fda.gov/media/79394/download (last visited August 11, 2020).

listed in the package inserts for one or more vaccines that any individual living with would categorize as "serious"; yet the FDA, under its current guidelines, may not. These include, but are not limited to: alopecia, autoimmune disease, lupus erythematosus, vasculitis, Bell's Palsy, hypotonia, migraine, myelitis, neuropathy, seizures, mental disorders, rhinitis, and vertigo.[23]

16. The study design for nCoV-19 Vaccine provides that these adverse events should be captured for only 28 days after vaccination while "serious adverse events" should continue to be captured for 6 months.[24]

17. Given that "serious adverse events" are already being captured for 6 months, it appears foolhardy to not also capture all adverse events. If nCoV-19 Vaccine causes a systemic autoimmune issue to arise two months after vaccination, it would be irresponsible and unethical not to capture that reaction just because an autoimmune issue falls into the artificially defined zone of being an "adverse event" or "non-serious adverse event," rather than what the FDA labels as a "serious adverse event."

c. Minimum Period to Track Adverse Events

18. At a minimum, all adverse events and reactions should be documented for each subject post-vaccination for at least: (i) twelve months for adults, (ii) thirty-six months for children, and (iii) sixty months for infants and toddlers. These minimal timeframes provide an opportunity to capture adverse and non-specific health issues that nCoV-19 Vaccine may cause.

19. The importance of capturing all potential health issues for the duration of the clinical trial can be seen in the designs of the clinical trials of numerous drugs, including for example, Enbrel[25], Lipitor[26], and Botox,[27] which had safety review periods of 6.6 years, 4.8 years, and 51 weeks respectively, with a placebo control group. As another example, the weight loss drug Belviq was safety tested in a placebo-controlled trial for two years before being licensed by

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[23] *See* https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm093833.htm (last visited August 11, 2020). Also, the determination of whether an adverse reaction is a "serious adverse event" is typically left to the discretion of the sponsor of the clinical trial or the clinical investigators, who are paid by the sponsor, and therefore subject to bias. *See* 21 C.F.R. § 312.32, explaining that an adverse event may be categorized as "serious" if "in the view of either the investigator or sponsor, it results in any of the" listed outcomes.

[24] As the Principal Deputy Commissioner of the FDA, along with her colleagues at the FDA, wrote with regard to monitoring safety during a clinical trial: "sponsors are expected to monitor all adverse events, including nonserious ones, during drug development." https://www.nejm.org/doi/pdf/10.1056/NEJMp1103464 (last visited August 11, 2020).

[25] *See* https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103795s5503lbl.pdf (last visited August 11, 2020).

[26] *See* https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf (last visited August 11, 2020).

[27] *See* https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103000s5302lbl.pdf (last visited August 11, 2020).

the FDA in 2012.[28] Nevertheless, despite this two year period, in February 2020 the drug was voluntarily removed from the US market due to emerging data showing that people who had taken the drug as part of a large clinical trial had an increased occurrence of cancer five years later.[29]

20. The FDA states that the length of study for phase III clinical trials is typically "1 to 4 years"[30] and that the duration of a clinical trial should "reflect the product and target condition."[31] In accord with this guidance, and the fact that a COVID-19 vaccine will be an entirely novel product, the safety review period for adults should be at least 1 year. The need for this minimum safety review period following injection is further supported by the indications that the immunity conferred by a COVID-19 vaccine is expected to last approximately one year or maybe a few years, requiring repeated injections of the product during a person's life.

21. The importance of the typical duration of a clinical trial was underscored by an AstraZeneca senior executive team member when he acknowledged the very real potential of side effects being discovered years down the line. In explaining why AstraZeneca needs protection from future product liability claims against its COVID-19 vaccine, Ruud Dobber stated: "This is a unique situation where we as a company simply cannot take the risk if in ... four years the vaccine is showing side effects."[32]

22. Moreover, taking into account the FDA's guidance that clinical trials should "reflect the product and target condition,"[33] the time frame for the safety review should be longer for minors, and in particular for infants and toddlers, since autoimmune, neurological, and developmental disorders will often not be diagnosed until after children are at least a few years old.[34] Indeed, a 2019 review, authored by researchers at the FDA and Duke University, reviewed 306 pediatric clinical trials and found that short-term

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[28] *See* https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022529lbl.pdf (last visited August 11, 2020).

[29] *See* https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-withdrawal-weight-loss-drug-belviq-belviq-xr-lorcaserin-market (last visited August 11, 2020); *see also* https://www.health.harvard.edu/blog/weight-loss-drug-belviq-recalled-2020040919439 (last visited August 11, 2020).

[30] https://www.fda.gov/patients/drug-development-process/step-3-clinical-research (last visited August 11, 2020).

[31] https://www.fda.gov/media/102332/download (last visited August 11, 2020).

[32] https://in.reuters.com/article/us-astrazeneca-results-vaccine-liability/astrazeneca-to-be-exempt-from-coronavirus-vaccine-liability-claims-in-most-countries-idINKCN24V2EN (last visited August 11, 2020).

[33] https://www.fda.gov/media/102332/download (last visited August 11, 2020).

[34] For example, according to the CDC, even for a common neurological disorder such as ADHD, "5 years of age was the average age of diagnosis for children reported as having severe ADHD." https://www.cdc.gov/ncbddd/adhd/features/key-findings-adhd72013.html (last visited August 11, 2020). As another example, learning disabilities, a group of common developmental issues, are often "identified once a child is in school." https://www.nichd.nih.gov/health/topics/learning/conditioninfo/diagnosed (last visited August 11, 2020). Even for asthma, a very common autoimmune condition, whose symptoms are obvious, diagnosis can be difficult for children under 5 years of age because lung function tests aren't accurate before 5 years of age and "[s]ometimes a diagnosis can't be made until later, after months or even years of observing symptoms." https://

> pediatric studies may not provide complete safety data across all critical periods of growth and development. This observation may be important because multiple periods of critical pediatric growth and development exist… Although the first 3 years of life are often considered more critical than older ages for brain development, biochemical studies of brain metabolism suggest that high brain metabolic rates characteristic of early childhood may not decline to adult levels until ages 16 to 18 years, suggesting that the school-age and adolescent periods are equally critical periods of brain development. Given this information, even the longest trial duration identified in our study (364 weeks/7 years) does not completely evaluate potential critical stages of all pediatric growth and development periods.[35]

The FDA and Duke authors explained that, compared to licensing a drug for adults, "data on drug efficacy and safety in children may require an additional 6 years."[36] Since children have not been seriously affected by COVID-19, the risk of any vaccine for SARS-CoV-2 must be fully understood in order to weigh it against any potential benefit.

d. Adequately Powered Sample Size

23. The study design for nCoV-19 Vaccine provides for only 10,260 individual study subjects, which presumably means only 5,130 individuals will be in the study group that will receive the nCoV-19 Vaccine and 5,130 individuals will be in the control group that will receive the MenACWY vaccine.

24. A Phase III trial for nCoV-19 Vaccine with 10,260 subjects cannot produce an adequate safety profile for this product. SARS-CoV-2 poses a statistically insignificant risk of harm to children and young healthy adults. For this enormous cohort of the American population, the threshold for establishing that this vaccine is safer than the infection is exceedingly high and requires a highly powered trial. Even within so-called higher risk groups, the percent of individuals suffering serious health issues from SARS-CoV-2 is statistically small on a population level, which again demands a well-powered trial to assess the safety of the vaccine versus natural infection, since it is anticipated that this vaccine will be mandatory for most Americans.

25. Reflecting the foregoing, even Dr. Paul Offit, a member of VRBPAC and a staunch advocate for removing hurdles to the licensure of vaccines, has said that to determine whether a COVID-19 vaccine is safe and effective, "we are waiting for the big trial … the large prospective placebo controlled trial, we have 20,000 people who get a vaccine, 10,000 people who get a

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www.mayoclinic.org/diseases-conditions/childhood-asthma/diagnosis-treatment/drc-20351513 (last visited August 11, 2020).

[35] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6526087/ (last visited August 11, 2020).

[36] *Id*.

placebo, then and only then will you know whether a vaccine is safe and effective."[37] But even 20,000 subjects in the group receiving the experimental vaccine may not be sufficient, according to a report from the Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research at the FDA, with regard to assessing its safety of the nCoV-19 Vaccine for anything other than the groups with the highest risk of complications from SARS-CoV-2.[38]

26. The trial should have an adequate sample size, appropriately powered, in order to (i) detect an increase in rare adverse events or any untoward medical occurrence, whether or not considered vaccine related, and (ii) determine that the rate of adverse events from the vaccine will not exceed the rate of adverse events known to occur from SARS-CoV-2 in the group under review.

e. T-cell Reactivity and Response

27. Clinical trial participants should be tested for T-cell reactivity to SARS-CoV-2 prior to vaccination and then again after vaccination.

28. This is necessary because, as recently explained in the journal Nature Reviews Immunology, by researchers at the Center for Infectious Disease and Vaccine Research at La Jolla Institute for Immunology, "if subjects with pre-existing reactivity were sorted unevenly in different vaccine dose groups, this might lead to erroneous conclusions. Obviously, this could be avoided by considering pre-existing immunity as a variable to be considered in trial design."[39]

29. Dr. Sette, a member of this group, further explained that "if you have 10 people that have reactivity and 10 people that don't have the pre-existing reactivity and you vaccinate them with a SARS CoV-2 vaccine, the ones that have the pre-existing immunity will respond faster or better to a vaccine ... So, we have been suggesting to anybody that is running vaccine trials to also measure T-cell response."[40]

f. Germline Transmission Tests

30. According to the European Medicines Agency, non-viral vectors may be associated with a risk of vertical germline transmission of vector DNA.[41] While "currently there are no non-invasive means to monitor women for germline transmission," male participants in the clinical trials can and should be monitored.[42]

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[37] https://www.cnn.com/videos/health/2020/05/24/coronavirus-covid-19-vaccine-trials-vaccinologist-concern-ip-vpx.cnn (emphasis added) (last visited August 11, 2020).

[38] *See* https://pubmed.ncbi.nlm.nih.gov/11802587/ (last visited August 11, 2020).

[39] https://www.nature.com/articles/s41577-020-0389-z (last visited August 11, 2020).

[40] https://amp.cnn.com/cnn/2020/08/02/health/gupta-coronavirus-t-cell-cross-reactivity-immunity-wellness/index.html (last visited August 11, 2020).

[41] *See* https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-non-clinical-testing-inadvertent-germline-transmission-gene-transfer-vectors_en.pdf (last visited August 11, 2020).

[42] *Id.*

31. "Since one cycle of spermatogenesis takes approximately 64-74 days in man, the timing of the appearance of transduced progenitor daughter cells in the semen is predictable. This can be taken into account in the planning of germline transmission tests as part of clinical trial protocols."[43] Further, "this can be accomplished by investigating sperm at different time points taking into account the duration of spermatogenesis…The earlier the differentiation stage at which germline transmission takes place in the spermatogenesis process, the greater the risk that the germline alteration is permanent and the greater will be the fraction of transduced sperm cells."[44]

32. Requiring this simple test will not delay the study, would add very little burden to the sponsor, and will provide comfort that the vaccine is not having deleterious effects on the male germline.

C. ENVIRONMENTAL IMPACT

33. The undersigned hereby states that the relief requested in this petition will have no environmental impact and therefore an environmental assessment is not required under 21 C.F.R. Sections 25.30 and 25.31.

D. ECONOMIC IMPACT

34. Economic impact information will be submitted upon request of the commissioner.

E. CERTIFICATION

35. The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

36. The Petitioner therefore respectfully urges that this request be granted forthwith.

Respectfully submitted,

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[43] *Id.*

[44] *Id.*

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