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Irregularities and ethical violations in the conduct of the clinical trial for Bharat Biotech's COVAXIN | Bhopal Gas Peedit Mahila Stationery Karmchari Sangh, Bhopal Gas Peedit Mahila Purush Sangharsh Morcha, Bhopal Group for Information and Action, Children Against Dow Carbide

To,

Shri Narendra Modi
Hon'ble Prime Minister of India
South Block, Raisina
New Delhi 110011

Dr. Harsh Vardhan
Hon'ble Union Minister
Hill Ministry of Health and Family Welfare
(MOHFW)

10 January 2021

Dear Sirs,

Irregularities and ethical violations in the conduct of the clinical trial for Bharat Biotech's COVAXIN by People's Hospital, Bhopal and resultant exploitation of trial participants belonging to vulnerable groups: Survivors demand stoppage, punishment and compensation

On behalf of the survivors of the Union Carbide disaster in Bhopal and those poisoned by contaminated ground water, we wish to draw your attention to serious violations taking place in the Phase 3 clinical trial that is underway in People's College of Medical Sciences & Research Centre, Bhopal to assess the safety, immunogenicity and efficacy of the vaccine candidate COVAXIN.

As you know, COVAXIN is a COVID-19 vaccine candidate co-developed by ICMR-NIV, Pune and Bharat Biotech International Limited (BBIL) that was given restricted emergency use approval by the DCGI on 3 January 2021. The Phase 3, randomised, double-blind multi-centre study of the vaccine candidate is being sponsored by BBIL and the Indian Council of Medical Research

(ICMR). Many people from communities affected by the Union Carbide gas disaster in Bhopal and by contaminated water were recruited into the trial in violation of ethical procedures established under the law. Some of these individuals have faced adverse events since dosing in the trial, and even a death has taken place.

We are writing to you to apprise you of the on-ground situation with regard to the conduct of the trial. Evidence has emerged that the trial in Bhopal is being conducted in gross violation of laws and guidelines governing clinical trials in India. This is leading to exploitation and harm to a community of people that are not just economically and socially deprived, but whose health is compromised owing to the destructive impact of the Bhopal gas tragedy and its consequences. The same are elaborated below:

1. Vulnerable people being misguided and herded

In early December, People's Hospital, a private medical college & hospital, sent vehicles into communities situated behind the abandoned Union Carbide factory -Gareeb Nagar, Shankar Nagar, Oriya Basta, Kainchi Chhola, JP Nagar and others – and announced that COVID-19 vaccine injections were available and everyone would be paid Rs 750 as well for getting each vaccination shot. The amount of Rs 750 meant to be reimbursement of travel expenses and loss of daily wages to trial participants is in fact a substantial sum for such poor communities and appears to have been used as an inducement to make people come forward. These vehicles were accompanied by staff of the Hospital who recruited several hundred residents of these communities. In other cases, daily wage labourers were recruited from their *peetha* (gathering for daily wage labourers) for the trial.

Majority of the people who were recruited for this trial were those who have been exposed to poisons of Union Carbide and are poor and illiterate. Many of the residents claim that they were not told that they were being recruited for a trial but were under the belief that they were in fact getting the vaccination to protect them from COVID-19.

The *National Ethical Guidelines for Biomedical and Health Research involving Human Participant* of 20171 and the *National Guidelines for Ethics Committees Reviewing Biomedical and Health Research During COVID-19 Pandemic*2 of April 2020 published by ICMR deems communities that are socially, economically or politically disadvantaged; and those who are able to give consent but whose voluntariness or understanding is compromised due to their situational conditions, as vulnerable groups and mandates that additional safeguards in the conduct of research. The participants, owing to their economic, education and compromised health status owing to the gas disaster and water contamination clearly fall within the definition of vulnerable groups as per the above.

The onus to ensure that the dignity, rights, safety and well-being of individuals belonging to vulnerable communities are protected rests on all stakeholders especially the sponsors, investigators and Ethics Committee. The Guidelines issued by ICMR specify that rewards/credits/incentives must be avoided as participants may feel intimidated or unduly pressured to participate in the trial in return for the reward. The guidelines also mandate setting up of support systems to deal with associated medical and social problems, and provision of ancillary care including medical care.

In the present clinical trial, all of the abovementioned requirements have been violated. Researchers did not take cognisance of the educational status and economic vulnerability of the participants, and take into account the fact that they are victims of the gas disaster.

Adequate of the clinical trial, and their rights related to the same. By converting the provision of reimbursement of expenses for participation into monetary inducement, the researchers made it difficult for members of this impoverished and poor community to refuse participation in the trial or assert their right to information, documentation and treatment for adverse events.

2. Violation of Informed Consent Procedures under the law and the New Drugs and Clinical Trials Rules, 2019

The informed consent form is a fundamental part of the trial as it explains the risks and benefits of the study, rights of trial participants and purpose of the study. The consent form for this trial clearly states that participants would be given a copy of the signed and dated consent form. In the majority of cases that we have interacted with, the participants from these communities had not received any hard copy of their signed consent forms even after receiving the first dose. Participants remembered signing in many places during the visit but they were not given copies of their consent forms. In several instances participants who wanted to read the participant information sheet and consent form were not given the time to read. This is a clear violation of ethical and regulatory requirements with regard to informed consent.

After the irregularities with regards to the informed consent forms were reported by the media, in some cases participants were given their informed consent forms at the visit to receive the second dose. However, these were not signed by the appropriate authorities.

The participant information sheet and consent form also provides the opportunity to trial participants to take a copy of the unsigned consent form to consult with family or friends, and decide whether to participate in the trial or not. Given that the trial participants belong to a vulnerable group, and given the additional safeguards provided in statutory provisions and ICMR ethical guidelines, this was a crucial safeguard to mitigate and minimise any possible duress or coercion any participant may feel to agree to be part of the trial. A consequence of the investigators not following informed consent procedures, participants were deprived of the option to refuse to take the first dose in the initial visit, which represents yet another violation of statutory and institutional safeguards.

We note that the Hindi participant information sheet and consent form contains technical language that is beyond the comprehension of any layperson, let alone persons with minimal education. This made it all the more critical for ethical safeguards to have not been bypassed during the consent process.

- ***New Drugs and Clinical Trials Rules, 2019 and Ethical Guidelines for Biomedical and Health Research***

The Third Schedule of the New Drugs and Clinical Trials Rules, 2019 prescribes the principles and guidelines to be followed in the conduct of a clinical trial for protection of trial subjects. As per 2(d) of the Third Schedule, trial participants who are unable to read or write, an impartial

witness has to be present during the informed consent process who must append their signature to the consent form. As per 2(g), an audio-video recording of the informed consent process is required in the case of vulnerable subjects. This recording is to include the procedure of providing information to the participant and his/her understanding of such consent. The Third Schedule prescribes that the responsibility to ensure that the trial is conducted as per protocol, and as per statutory provisions lies on the sponsor, investigator and ethics committee of the clinical trial.

Further, ICMR's *National Ethical Guidelines for Biomedical and Health Research involving Human Participant, 2017* mandate additional measures for informed consent such as recording of assent and re-consent when applicable including repeated education/ information about the research, benefits, risks and alternatives. The *National Guidelines for Ethics Committees Reviewing Biomedical and Health Research During COVID-19 Pandemic* similarly prescribes additional safeguards to ensure, inter alia, that there is no coercion, force, undue influence, threat or misrepresentation or incentives; that informed consent process is conducted in a respectful manner; and that privacy, confidentiality and rights are protected at all times. As per evidence, these too were violated by the actions of those conducting the trial.

- ***Audio–visual recordings of informed consent***

Most of the participants were illiterate and could not read or write. However, in complete violation of statutory provisions, audio visual recordings of the informed consent process were not made. The Participant Information Sheet and Informed Consent Form being used in the clinical trial contains a consent form for audio-visual recording. However, despite being included in the participant information document and consent form and being legally mandated, the same was not employed in the informed consent process.

3. **Denial of medical management to participants experiencing adverse reactions and adverse events**

Trial participants who experienced complications after receiving their first shot were refused treatment by the trial site. Only after the media reported on the adverse events were efforts made by the trial site to investigate the adverse events and their connection to the trial.

to provide medical treatment and compensation to trial participants who experience adverse events or injuries as a result of the clinical trial. Not taking immediate cognizance of adverse events and illness reported by participants and denying them medical treatment for the same is a violation of the New Drugs and Clinical Trials Rules, 2019.

- ***Insurance policy***

The consent form mentions that as a liability/responsibility of the sponsor, participants will be covered by an insurance policy. However, no details have been provided to any of the participants about the nature of the insurance. The sponsors have also maintained that all applicable laws regarding insurance of trial subjects will be followed in the trial. Yet the liability and insurance provisions of the study as specified in the arrangement between the

sponsors and investigators are so far unknown to the intended beneficiaries, i.e., trial participants.

- ***Non–reporting of adverse events in trial***

If the trial participants are not even being provided free medical management at the trial site, then it is highly unlikely that any of their problems are being recorded as adverse events. Non- reporting of adverse events experienced by the trial participants will directly impact the safety analysis of the vaccine candidate and produce erroneous results from this trial site.

4. **No monitoring and follow up of participants**

As per the New Drugs and Clinical Trials Rules, 2019, it is incumbent upon the Ethics Committee for the clinical trial to oversee the conduct of the clinical trial, to ensure that the rights, safety and well-being of trial participants is safeguarded, and that good clinical practices are being followed by the investigators. As per the Third Schedule of the New Drugs and Clinical Trials Rules, 2019 the sponsors are duty bound to make payment for medical management of the participant and provide financial compensation for clinical trial related injury or death. The investigator is duty bound to ensure that adequate medical care is provided to participants for any adverse events.

Thus, it is the duty of the sponsors, investigators and ethics committee to ensure that the health and well-being of trial participants is being regularly and effectively monitored, particularly so when the trial participants belong to a vulnerable group.

Evidence suggests that there were glaring irregularities on the part of the investigators and the Ethics Committee to ensure that the trial participants were being monitored for signs and symptoms of adverse events. It seems the onus of such monitoring was shifted onto the trial

participants by providing them with blank sheets to record health problems experienced after the shot. The investigators did not take into account that most of the participants are illiterate and are not able to fill any of these forms, and would thus require more hands on monitoring and support.

The participants are also economically disadvantaged and therefore are not always in a position to keep their phones recharged to receive phone calls. The limited telephonic follow up efforts of the study investigators were not contextually sensitive to the circumstances of the trial participants, and were inadequate as trial participants were not always reachable by phone such as when their balance ran out. This constitutes a violation of the Third Schedule of the New Drugs and Clinical Trials Rules, 2019, the *National Ethical Guidelines for Biomedical and Health Research involving Human Participant* of 2017 and the *National Guidelines for Ethics Committees Reviewing Biomedical and Health Research During COVID-19 Pandemic,* which require additional measures to protect the health, safety and well being of vulnerable communities

According to the trial protocol, the study excludes participants from immunogenicity and efficacy analysis if there is evidence at baseline that they have had or currently have COVID-19. In the trial, the first dose is given on the first visit rather than keeping a gap for screening of

participants. Therefore, if any person gets a positive result for the COVID tests done on the first day (i.e., at baseline), they are subsequently excluded from immunogenicity and efficacy analysis but are nonetheless supposed to be followed up for safety outcomes. One person who was found to be COVID-19 positive after the first visit and developed symptoms that required medical attention was not provided free care, was asked to purchase expensive medicines at his own cost and his condition was not followed up.

Any participant who is discontinued early from the study also needs to be followed up for safety and occurrence of adverse events. Yet, some participants that were made to discontinue the trial because of health problems are not being followed up for safety, which is against the study protocol.

- ***Unexpected success of People's Hospital in recruiting trial participants***

We note People's Medical College's unexpected successful in enrolling more than 1700 participants in the Phase III trial, after meeting the initial target of 1000 participants3, at a time when it was reported that other sites including AIIMS New Delhi, were facing difficulties in recruiting volunteers[4.]

According to news reports, Gandhi Medical College also in Bhopal was unable to qualify t o become a trial site for the Phase III trial as it was unsuccessful in recruiting even 100 volunteers which was the minimum number needed.5

Indeed, People's Hospital's haste to enroll participants was without regard for the rights of the individuals being actively recruited from particularly vulnerable communities.

5**. Death of participant following dosing in the trial**

We have grave concerns around the death of a participant on 21 December 2020, around 9 days after being dosed in the trial. There was no follow up done by the trial site with the participant during the 9 days. Given the ethical violations in consenting participants, it is no surprise that the participant did not approach the trial site when he started experiencing symptoms and his health deteriorated. Had the investigators and Ethics Committee ensured follow ups and monitoring of participants, his deteriorating health would have perhaps been taken note of earlier and his life may have been saved by providing him the necessary and legally mandated medical attention.

The occurrence of the death in the trial was never made public by the sponsors or the regulator and only came to light when the media reported it. There is no information about the procedure being followed by various parties – the PI, Institutional Ethics Committee, Data Safety Monitoring Board and DCGI – in investigating the death or its current status.

The deceased's family managed to access a copy of the Post Mortem report only after weeks of the event, and several days after People's Hospital obtained the report. The family has still not been given a copy of the deceased's informed consent form or any documents related to his participation in the COVAXIN trial.

- ***Death is not recorded in meeting minutes of the COVID-19 Subject Expert Committee (SEC)***

It is alarming that during the SEC's consideration of the company's application for emergency approval, there was no deliberation of the death in the trial, as gleaned through the publicly available SEC meeting minutes.

On 30 December 20206, the SEC noted that BBIL presented the updated recruitment status and safety data including SAE data of the ongoing Phase III clinical trial in the country.

However, it did not explicitly mention the death of a trial participant, which is still under investigation. In each of the two successive SEC meetings on 1 and 2 January 20217, the SEC noted that more than 22,000 participants had been enrolled in the trial, including subjects with comorbid conditions, and stated that the trial "demonstrated safety till date".

The lack of any serious adverse events even in participants having comorbid conditions played a critical role in the grant of emergency approval of COVAXIN, especially amid the lack of any interim efficacy data from the Phase III trial. However, it appears that the SEC may not have been aware of the death that took place in the trial on 21 December 2020 and which is still under investigation. This calls into question the basis of the restricted emergency use approval, albeit with all its caveats, that was granted by the DCGI on the recommendation of the SEC.

! **URGENT INTERVENTION SOUGHT**

That a trial co-sponsored by ICMR is committing such glaring and grave violations of statutory provisions and the ethical guidelines laid down by ICMR itself is alarming and deeply troubling. That one of the oldest biomedical research institutions of national importance and international repute, and one that is tasked with ensuring ethical conduct of research is complicit in endangering lives of Indian citizens is a national tragedy that must be immediately addressed to ensure that people do not lose faith in the COVID-19 vaccinations. Loss of faith in vaccines would amount to a fear and panic in individuals who may refuse to get vaccinated and thereby damaging the national effort to curtail the COVID-19 pandemic.

In view of the above egregious violations by the trial site, we urge you to:

(a) Immediately stop the clinical trial for Bharat Biotech's COVAXIN at People's College of Medical Sciences & Research, Bhopal given the severity of the violations of ethical standards set by the ICMR and statutory provisions, and the gross negligence in taking care of the trial participants.

(b) Form an independent body to conduct an impartial, transparent, thorough, and time-bound investigation to ascertain violations of ethics, protocols and legal requirements pertaining to conduct of the clinical trial. The findings of this enquiry must be put in public domain.

The independent body must consist of experts, especially civil society representatives who do not have any conflict of interest or connection with the sponsors (BBIL and ICMR), the site (People's College of Medical Sciences & Research, Bhopal) or the researchers.

(c) The Principal Investigator and the Co-investigators of the clinical trial at the site, the People's Hospital, have failed to adhere to the scientific and ethics standards, legal requirements, and have been insensitive and negligent in ensuring safety, well being and the rights of the participants of the trial. All the responsible parties found to be negligent of their duties must be punished. They must be suspended from all research forthwith and their competence to do such research must be reviewed in addition to making them accountable for the violations and negligence.

(d) The People's College Institution Ethics Committee is a body registered with the CDSCO. It has failed to demonstrate its independence and competence in monitoring the COVAXIN trial and ensuring that all protocols and statutory requirements are adhered to. Its registration may be suspended forthwith and the CDSCO must inspect and audit its functioning and make its Chair and Member-Secretary accountable for the lapses in the conduct of the clinical trial, and resultant harm to people's lives.

(e) Conduct a separate audit of the People's College of Medical Sciences & Research, Bhopal for its scientific and ethical standards of drugs, biomedical and health research. If such standards are found to be deficient, it should not be allowed to undertake any research unless the institution carries out necessary improvements.

(f) Due to shoddy follow up of the participants, prima facie it appears that the COVAXIN trial at People's College has violated not only ethics, but also compromised scientific integrity. The deficient scientific data would lead to wrong and misleading conclusions of the research. Thus, the vaccine trial data of this site should be separated out and not used in the trial outcome analysis.

(g) Ensure that all the trial participants from the vulnerable sections who were enrolled in the trial get access to free medical care and compensation for any injuries or death related to the trial.

(h) Share details of the process and timelines through which the death of the trial participant is being investigated by the various parties – the PI, Ethics Committee, DSMB, and DCGI – and the findings when the final determination has been completed.

We look forward to your urgent intervention in consideration of our plea.

Sincerely,

Rashida Bee
Bhopal Gas Peedit Mahila Stationer Karmchari Sangh

Nawab Khan
Bhopal Gas Peedit Mahila Purush Sangharsh Morcha

Rachna Dhingra
Bhopal Group for Information and Action

Nausheen Khan
Children Against Dow Carbide

Copy to:

1. Dr. V. G. Somani, Drugs Controller General (India), CDSCO
2. Dr. S. Eswara Reddy, Joint Drugs Controller (India), CDSCO

3. Shri A. K. Pradhan, DDC (I), CDSCO
4. Dr. Vinod K. Paul, Member, Niti Aayog and Chair, NEGVAC
5. Shri Rajesh Bhushan, Secretary, MOHFW and Co-Chair, NEGVAC
6. Ms. S. Aparna, Secretary, DOP, Ministry of Chemicals and Fertilizers
7. Dr. Renu Swarup, Secretary, Department of Biotechnology
8. Dr. Randeep Guleria, Director, AIIMS, New Delhi
9. Dr. Shekhar C. Mande, Secretary, DSIR and DG, Council of Scientific & Industrial Research
10. Prof. K. VijayRaghavan, Principal Scientific Adviser to the Government of India
11. Dr. Balram Bhargava, Director General, ICMR
12. Dr. Samiran Panda, Director, ICMR-National AIDS Research Institute
13. Dr. Nivedita Gupta, Scientist F, Epidemiology and Communicable Diseases, ICMR
14. Dr. P K Mishra, Principal Secretary to Hon'ble PM
15. Shri P. K. Sinha, Principal Advisor to Hon'ble PM
16. Shri S. Gopalakrishnan, Additional Secretary to Hon'ble PM
17. Ms. P. Amudha, Joint Secretary to Hon'ble PM
18. Shri. Mohammad Suleman, Additional Chief Secretary-Health, Govt of Madhya Pradesh
19. Shri Basant Kurre, Commissioner Bhopal Gas Tragedy Relief & Rehabilitation, Govt of Madhya Pradesh
20. Shri. Avinash Lavania, Collector Bhopal District, Govt of Madhya Pradesh

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[1] https://ethics.ncdirindia.org/asset/pdf/ICMR_National_Ethical_Guidelines.pdf

[2] http://www.icmr.gov.in/pdf/covid/techdoc/EC_Guidance_COVID19_06052020.pdf

[3] https://timesofindia.indiatimes.com/city/bhopal/covaxin-trials-volunteers-being-administered-second- dose/articleshow/80122237.cms

[4] https://theprint.in/health/bharat-biotech-thousands-of-volunteers-short-for-ongoing-covaxin-phase-3-trials/573250/

[5] https://www.freepressjournal.in/bhopal/madhya-pradesh-gandhi-medical-college-keeps-fingers-crossedas-icmr-bharat-yet-to-give-nod

[6] https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/common_download.jsp?num_id_pk=MTMwMg==

[7] https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/common_download.jsp?num_id_pk=MTMwMQ== ; https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/common_download.jsp?num_id_pk=MTMwMA==