A medic administers an injection to a volunteer in a COVID-19 vaccine trial in Jaipur, Rajasthan, on 18 December 2020. VISHAL BHATNAGAR/NURPHOTO/GETTY IMAGES

COVID-19

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In October 2020, a 40-year-old man in Chennai who had taken part in a clinical trial for the COVISHIELD vaccine, suddenly fell ill. The COVID-19 vaccine was developed by the Serum Institute of India in partnership with the Swedish-American company AstraZeneca and the University of Oxford. His doctor diagnosed him with encephalopathy, which describes a range of neurological disorders that alter brain function and structure. He slipped in and out of consciousness for four days. Even when he was awake, he was drowsy and disoriented. For a few days, he was unable to talk or recognise anyone around him. “One time he couldn’t even pronounce our children’s names,” his wife told me. On one of the days he was in hospital, a doctor told his wife that he was doing better. “I rushed

inside, hoping to see my husband sitting up and smiling at me," she said. "Instead, I found him lying on the bed and staring at the wall. He glanced at me for a second but couldn't recognise me."

The Serum Institute of India based in Pune is conducting trials of COVISHIELD at multiple sites across India. Researchers at the Ramachandra Higher Education and Research Hospital, the site in Chennai, gave the trial participant an injection on 1 October. He started showing neurological symptoms 10 days later. The trial participant, his wife and his doctor believe that the trial dose triggered his symptoms. But the Serum Institute of India said that his illness had nothing to do with the clinical trial. The trial participant and the Serum Institute of India exchanged legal notices. The episode has called into question the company's and the government's response in case of complaints about vaccine candidates and approved vaccines. It also highlights the lack of transparency in clinical trials in India and the shortcomings of their regulatory framework.

On 11 October, the trial participant woke up with a splitting headache and nausea. He slept for most of the day, but when he woke up again he displayed disturbing behavioral changes. He was angry, irritable and unaware of his surroundings. By late evening, he was hospitalized at the Ramachandra Higher Education and Research Hospital where he got the trial dose. He was sedated and put on intravenous fluids. The doctors conducting the trial treated him for 16 days.

The trial participant's wife told me that the doctors at the trial site and the principal investigator suggested that he might have a vitamin deficiency or an auto-immune disorder that could have caused the reaction. However, their investigations did not find a plausible cause or underlying condition that could trigger encephalopathy. "Whenever I asked what the issue with him might be, what was the cause, they would just tell me I should be happy my husband is recovering," she said.

On 26 October, his family requested the hospital discharge him. By then the man had regained basic cognitive skills and was able to interact with family members and the healthcare staff looking after him. He was also eating solid food without vomiting. However, he remained confused and unable to focus or recall what had occurred during most of his stay at the hospital. His wife told me that he was in the same condition for weeks after he was discharged, and so the family decided to consult another doctor. "The doctors at the trial site treated my husband but they didn't tell us what caused this sudden illness and he continued to suffer, so we had no option but to consult other neurologists, who were not connected to the trial," his wife said.

The family consulted Dr Zaheer Ahmed Sayeed, a neurologist at Apollo Hospital in Chennai. Sayeed ran a series of tests but could not find a cause for the neurological dysfunction. He noted "a neuro psychological assessment revealed borderline changes" in the man's brain function and structure. He wrote these observations down in a letter dated 21 November, which the trial participant's advocate shared with me. All this while, the trial participant and his family did not hear from the Serum Institute of India or the Central Drugs Standard Control Organisation, the government body that oversees clinical trials in India. "No one called us to check in or inform us of any action they had taken. We were left to fend for ourselves. We were concerned and angry and we wanted to speak out and bring this incident to public notice," the participant's wife said.

On 21 November, the participant and his family sent a legal notice to Balram Bhargava, the Director General ICMR; Adar Poonawalla, the CEO of the Serum Institute of India; Venugopal G Somani, the Drugs Controller General of India; Pascal Soriot, the CEO of AstraZeneca; Andrew Pollard, the chief investigator of the Oxford vaccine; and PV Vijayaraghavan, the vice chancellor of the Sri Ramachandra Higher Education and Research Hospital. On 29 November, the Serum Institute

of India issued a statement threatening to seek damages in excess of Rs 100 crores. They claimed that there was no correlation between the volunteer's medical condition and the vaccine.

Considering that the serious adverse reaction had raised several questions regarding the trial, members of the All India Drug Action Network—an independent network of non-government organisations working on access to medicines—wrote a letter expressing concern over the fact that SII had requested an emergency approval from the CDSCO on 6 December. The letter, dated 8 December, was addressed to the Indian Council of Medical Research, a co-sponsor of the COVISHIELD trial; Vinod K Paul, a member of Niti Ayog who heads the expert committee on COVID-19 vaccination; and Rajesh Bhushan, the health secretary and the apex authority for clinical trial regulations. It also condemned SII's decision to send a legal notice to the trial participant. "ICMR, being the co-sponsor of the trial, ought to have stopped such intimidation tactics by the company," the AIDAN members wrote.

In a press conference on 1 December, Bhushan said he could not comment on the matter claiming that it was sub judice, even though neither party had initiated legal proceedings. The next day, the wire service Press Trust of India reported (https://timesofindia.indiatimes.com/india/dcgi-finds-no-link-between-covid-vaccine-shot-and-adverse-reaction-in-chennai-volunteer-during-trial-sources/articleshow/79533499.cms)that Somani, who is the DCGI—the top official at the CDSCO responsible for approving clinical trials—, had ruled out any link between the severe adverse reaction and the trial dose of the COVISHIELD vaccine. The PTI reported that Somani's assessment was based on recommendations of an independent expert committee. Sandhya Srinivasan, a consulting editor for the *Indian Journal for Medical Ethics*, said, "With no transparency on how the adverse reaction was dealt with, and on how government authorities concluded there was no causal link, we are left with so many unanswered questions and ethical concerns."

All clinical trials to test for drugs, vaccines or medical devices prepare for possible adverse reactions. In most cases the reactions are mild and non-threatening. Participants in the COVISHIELD trials were told to expect minor reactions such as pain, swelling and redness at the injection site, fatigue, fever and chills. These mild to moderate adverse reactions usually dissipate within a few days. But every trial runs the risk of a participant suffering a severe adverse event or SAE. According to the CDSCO, an SAE is "associated with death, inpatient hospitalisation, prolongation of hospitalisation, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or is otherwise life threatening." Any such reaction observed in a patient enrolled in the trial is referred to as an SAE, even if it is yet to be established whether the SAE was caused by the trial itself.

In September, AstraZeneca revealed that a trial participant in the United Kingdom had experienced (https://www.thehindu.com/sci-tech/health/coronavirus-vaccine-trial-volunteer-had-neurological-symptoms-says-astrazeneca-ceo/article32565754.ece) neurological symptoms indicative of a rare but serious spinal disorder called transverse myelitis. The company halted the trial immediately while they investigated the matter and resumed it three days after, declaring that the participant's condition was unlikely to be connected with the vaccine candidate. In India, the Serum Institute of India continued its trial until

the DCGI sent (https://www.theweek.in/news/india/2020/09/09/oxford-covid-19-vaccine-dcgi-issues-show-cause-notice-to-serum-institute.html) them a show cause notice, asking them to halt its proceedings. After the DCGI's notice, the SII updated trial participants' consent forms with information on the adverse event for its new volunteers. The SII only resumed its trial once AstraZeneca resumed in the UK.

India has a poor record of responding to, treating and compensating clinical trial participants who have suffered serious adverse reactions. In 2017, Swasthya Adhikar Manch, a public health advocacy group, filed a Right to Information request, asking for data on severe adverse reactions in clinical trials. In November 2017, the health ministry responded (https://www.sundayguardianlive.com/news/11550-over-24000-clinical-trial-deaths-and-saes-india-ten-years)to the RTI revealing that 20,758 clinical trial participants suffered from serious adverse reactions between 2005 and 2016. The RTI response also revealed that 4,500 trial participants died from such reactions, but only 160 families received compensation from the pharmaceutical companies sponsoring the trials. Referring to the 160 families, Amulya Nidhi, the convenor of Swasthya Adhikar Manch, said, "We don't have any details on these people and which trial there were involved in, so we can't even be sure whether they were actually compensated and if they compensated fairly for their damages."

Five years earlier, in 2012, the Swasthya Adhikar Manch filed a petition in the Supreme Court, bringing to light the loopholes in India's clinical trial regulations. The PIL cited incidents where participants were given false information, where consent was taken forcibly and where participants suffered adverse reactions for which they were not provided medical care or adequate compensation. In its judgement, the Supreme Court ordered the central government to halt all medical trials until it amended existing regulations to ensure participant safety and stringent monitoring of clinical trials.

Between 2013 and 2019, the government issued a slew of amendments to existing laws and rules in an attempt to eliminate these loopholes. The most extensive and detailed of these new regulations was the New Drugs and Clinical Trials rules of 2019 (https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/NewDrugs_CTRules_2019.pdf). It introduced compensation laws and provided details on how to determine whether an adverse reaction was related to the trial or not. It also laid out a compensation mechanism, making sponsors—the organisations paying for or conducting the trial—accountable for providing compensation if the injury or death of a participant is considered related to the experimental drug or vaccine. The major overhaul of regulation did not put an end to unethical trial practices, Nidhi said. "Every year, we are fighting a new case where volunteers were exploited and were never compensated for the damages they suffered," he added.

As recently as 2018, Glenmark Pharmaceuticals came under scrutiny for unethical practices while recruiting 19 trial participants to test a drug for osteoarthritis pain in Churu district in Rajasthan. According to a report in *The Wire*, the trial participants were told (https://thewire.in/health/who-is-responsible-for-the-jaipur-clinical-trial-controversy) they were going to a medical camp, where they would receive a day's employment, remuneration, alcohol, food and a chance to watch an Indian Premier League cricket match. By the end of the day, the men were taken to Malpani Multispeciality Hospital where they were given dinner and the medicine under trial. The next day, a few of the trial participants suffered adverse reactions such as pain, drowsiness and fever. A few others suffered long term consequences, complaining of chest pain and constant fatigue, which made them incapable of engaging in physical labour to earn their daily wages. Eventually, the CDSCO intervened and the trial was halted. However, the participants were not offered medical treatment. "Our regulators clearly cannot be depended upon to safeguard the rights of trial participants," Nidhi said, while commenting on the episode.

On paper, there are checks and balances in place with regulatory bodies working together to monitor trials. Apart from the principal investigator and sponsor, an SAE is reported to the ethics committee of the hospital, the DCGI and a data safety monitoring board. If the DCGI has the power to set up another independent committee to investigate adverse events, which was done in the case of the Chennai trial participant as well.

"There are no audits, there is no way of knowing whether all processes are being followed correctly," Nidhi said. "It's only when we blow the whistle on an unethical practice do they notice, otherwise how are we to know what truly happened with the participants who suffer adverse reactions?"

Anand Grover, a Supreme Court lawyer who served as the United Nations Special Rapporteur on the Right to Health between 2008 and 2014, pointed to the potential conflict of interests between regulators and independent committees charged with monitoring the clinical trial. For example, the sponsor constitutes the data safety monitoring board, which is supposed to be an independent committee, is. The method of electing this independent expert committee is also not transparent. "The members of ethics committees, the data safety monitoring board, the subject expert are drawn from the same pool of people, researchers and scientists. It is, as it were, an old boys club. If the closed club makes these

decisions, there is a danger of compromising the integrity of the process," Grover said.

Grover pointed out that in the absence of a strong regulatory mechanism, the 2019 clinical trial rules are not enough to ensure the health and safety of trial participants. "The rules inter alia mandated compulsory registration of ethics committees and compensation to be paid in case clinical related injury or death, but no transparency was brought about," he said. "So, we really don't have a clear idea whether things are working or not, except for anecdotal data."

Experts told me that the rules leave room for interpretation in deciding whether a participant who suffers an SAE is eligible for treatment and compensation. Some sections of the rules suggest that a participant is eligible for treatment and compensation only if the SAE is "related to the clinical trial," while others seem to suggest that a participant is eligible for treatment and compensation for any SAE which occurs "during the clinical trial."

Chapter six of the rules, which is about compensation, has one section which gives criteria for establishing whether an SAE is related to the trial, and another which lays out a procedure for compensation "in case of an injury or death during clinical trial." Adding to this confusion, a clause under the section laying out this procedure, says: "the sponsor or its representative shall pay the compensation in case the serious adverse event of death is related to clinical trial or the bioavailability or bioequivalence study."

"Legally, every different iteration on the matter of compensation, will imply a different meaning," Murali Neelakantan, an advocate who served as global general counsel for the pharmaceutical company Cipla, said. "There is a difference between 'trial related injury' and 'injury occurring to the subject during the clinical trial.' But the way they are used in the rules causes uncertainty."

A recent editorial (https://link.springer.com/article/10.1007/s40264-020-01018-y) in the journal *Drug Safety* lays out factors that regulators should consider while establishing links between vaccines being tested and SAEs in participants. The editorial includes a checklist of questions for regulators, which include: Is there evidence for other causes? Is there a known causal association with the vaccine or vaccination? Is there strong evidence against a causal association? The editorial also asks regulators to look for other qualifying factors such as previous history of similar events, pre-existing health conditions of the participant, other medications and potential risk factors; before deciding whether an SAE is indeed linked to the vaccine trial.

The 2019 rules do not provide a template of questions that regulators should attempt to answer before making adecision. Instead, they provide seven criteria for the "Consideration of injury or death or permanent disability to be related to clinical trial or bioavailability and bioequivalence study." The criteria do not say that a serious adverse event can be considered as related to the trial when investigators cannot find any other cause. They also do not mention a course of action when there is no conclusive outcome.

Sayeed, the trial participant's neurologist, wrote in his letter that "in the absence of any other diagnosable modalities, the neurological function suffered by [the participant] subsequent to his vaccination relates to immunogenicity of COVISHIELD COVID-19 vaccine." According to him, the absence of any other determinable cause implied that the serious adverse event was indeed related to the trial. R Rajaram, an advocate who helped the family draft the legal notice, said, "The participant's family have also consulted with a rheumatologist who cannot find any other cause for the encephalopathy but the trial itself."

The source of funding for compensation is important, because it determines who is accountable to the trial participant. Dividing the source of funding between different stakeholders such as regulators and

sponsors, ensures better accountability. Some countries, such as Japan, finance (https://ijme.in/articles/an-idea-whose-time-has-come-compensation-for-vaccine-related-injuries-and-death-in-india/?galley=pdf) their compensation programs through a combination of government treasuries. European countries like Finland, Norway and Sweden tax the manufacturers for compensation funding. In India, only the sponsor is responsible for compensation. India does not have a law mandating insurance coverage for trial participants.

"When private players are made responsible for funding, the government can easily abdicate their duty towards the harmed volunteer," Nidhi said. He told me that private companies often leave the country after completing their trials. "Often these sponsors were (https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0234925) unregistered and the government could not even chase them, leaving participants with no recourse to fight for compensation," he said.

Insurance coverage for trial volunteers will allow patients to receive compensation without fault being attributed to the sponsor, principal investigator, or the trial site and will encourage doctors to focus on the best possible patient, Neelakantan, the advocate earlier with Cipla, said. "Sponsors will not have to worry about patient compensation claims and they will have a better estimate of the cost of clinical trials," he added.

The Chennai man's experience has shown that despite the efforts to update clinical trial regulations in India, there are still many loopholes that leave trial participants without adequate information about their health. I called the principal investigator of the COVISHIELD trial in Chennai but he did not comment on the case. I emailed Somani, the DCGI, to ask why an independent committee was set up to look into the matter, and who were the members of the committee but did not get a response. It is not known if the committee has prepared a report on the matter. "Think about it," Srinivasan from the *Indian Journal for Medical*

Ethics said, "A healthy adult volunteers their body for scientific progress and if they get harmed in the process, you leave them in the dark."

On 3 January 2021, the DCGI approved (https://pib.gov.in/PressReleseDetail.aspx?PRID=1685761) the COVISHIELD vaccine for "restricted use in emergency situation." He also approved Covaxin, developed by the Hyderabad-based company Bharat Biotech in collaboration with ICMR, which is still recruiting participants for its phase 3 trial. *The Caravan* had earlier reported (https://caravanmagazine.in/health/in-bhopal-covaxin-trial-volunteers-allege-irregularities-in-recruitment-and-treatment) on irregularities at a Covaxin phase three trial site.

In late November 2020, more than a month after he was discharged, the trial participant struggled to operate his laptop. He was unable to take up new projects for his consulting firm. His children who are seven and 12 years old were unnerved by their father's changed demeanour. "It is changing; every day is a little better, but of course it has left a permanent scar on all of us," his wife said to me. She recalled the day she saw him lying vacantly in the hospital bed and said that was the moment she gave up on support or empathy from the people conducting the trial. "It was horrifying, but it did not appear to affect the doctor," she said. "It has not affected anyone—the investigators, the company or the government. It's as if what my husband and my family went through is inconsequential."

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