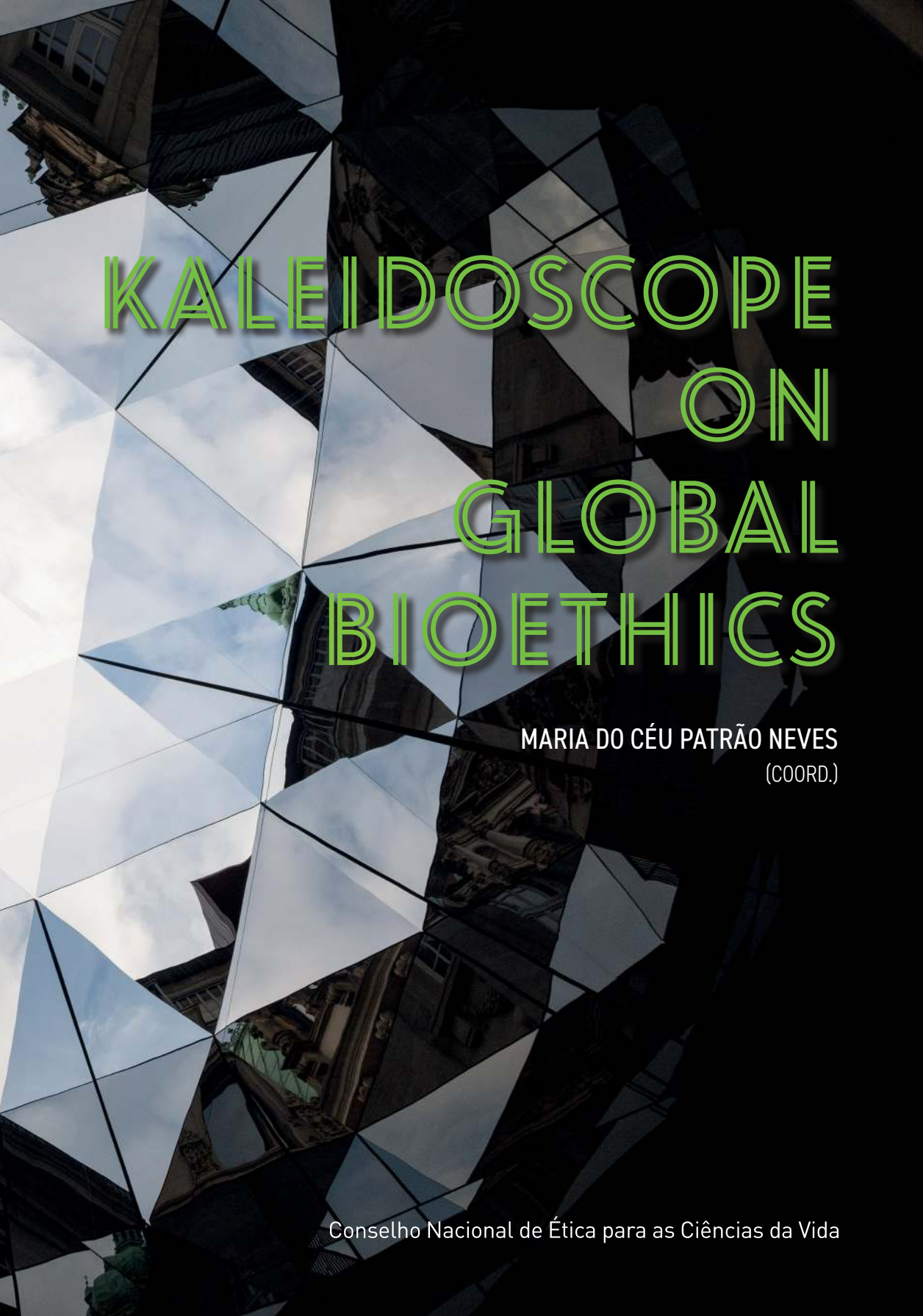

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Ethical Issues around Covid-19 Vaccine Research in India

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Covid-19 pandemic has led to enormous morbidity and mortality in many parts of the world including in India. In order to combat the disease and save lives, the world saw an unprecedented race against time for finding the right therapeutics and novel candidate vaccines that would impart protection from infection, disease or transmission (1). Vaccine development has historically been time consuming often requiring decades of research before reaching the public. However due to the urgency imposed by the pandemic, huge funding available, new technologies made available, vaccine research was fast tracked across the world and including in India. Laboratories worked in a time bound manner; involving inactivated/ recombinant/ live attenuated / protein/ or RNA/ DNA based vaccines. However, the accelerated research was seen with a lens as evidence to generate safety and efficacy data is considered to be time consuming (2).

The Indian Council of Medical Research (ICMR), New Delhi, is the apex body in India for the formulation, coordination and promotion of biomedical research and is one of the oldest medical research bodies in the world. It has not only attempted to address the growing demands of scientific advances in biomedical research, but also involved in developing ethical guidance and policy to guide the conduct of biomedical and health research in India. The first National Policy on ethics was created way back in 1980 which was revised and converted to a more detailed guidance in 2000 and further revised in 2006 and 2017. In April 2020, ICMR came up with its latest guidelines to help ethics committees review research during the pandemic. ICMR has set up a Bioethics Unit to serve as an ethics advisory unit and to guide development and timely updation of national ethical guidelines, policies, reports, other supplementary documents and tools in order to address ethical aspects of biomedical and health research. It also serves as the secretariat for the Central Ethics Committee on Human Research (CECHR) and carry out ethics review of nationally important complex issues. Further it builds capacity of ethical review in institutions across the country and creates networks in the areas of ethics related to biomedical research. Further

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ethics committee now require a registration with the National Authorities as an essential requirement.

The ICMR Ethical Guidelines, 2017 discuss the ethical requirements for undertaking any biomedical and health research including vaccines trials are now mandated under law to be followed for any Biomedical and health research in India (3). Further the ICMR National Guidelines for Ethics Committees, 2020 released during Covid-19 Pandemic provided direction to ethics committees regarding updated requirements for research carried out during this period (4). Further Clinical Trials are regulated under the New Drugs and Clinical Trial Rules, 2019 which provide the ethical requirements for conducting a trial (5). All of these documents highlight the need to uphold ethical values and ensure participant protection. There are some landmark decisions contained in these documents which are very unique to India, such as, the requirement to have an external person (non-affiliated) to serve as the Chairperson for an ethics committee. This provision ensures that the ethics committee members are in a position to voice their concerns without any fear of higher institutional authority and function independently. Secondly it is legally binding in India to provide medical management in case a research participant suffers from an injury, even if causality is undetermined. Further the regulatory agency has provided a timeline for reporting of serious adverse events, causality assessment and provided a formula for calculation of compensation to be paid in case the injury is found to be related to participation in research. Therefore, every research undertaken must plan to make budgetary provisions to take care of these costs and seek insurance policies before implementation.

In the beginning, the world was totally unprepared to handle the Covid-19 pandemic. The disease was novel, and there was incomplete information, inadequate preparedness to conduct robust science, reluctance to support research in fast-track mode, lack of public trust, allegations about probable compromises on the quality of research, doubts about heightened risks to the research participants, etc. (6). These challenges imposed serious ethical dilemmas in undertaking Covid-19 vaccine research in the country related to scientific, political, social and ethical issues. This paper attempts to highlight some of these ethical challenges in undertaking Vaccine research involving humans.

Scientific Validity

Research has to be scientifically robust. It was a critical time when research was being fast tracked, and there was no time to invest in ensuring details in well written vaccine trial protocols or the informed consent forms, or looking at

site preparations and infrastructure to support the research. The scientific challenges encountered during the period were very challenging, for research ethics committees referred to in this paper as ethics committee. These ethics committees reviewing research protocols had a difficult time determining if the clinical trials with new vaccines be continued when a successful candidate vaccine was approved and was available. Similarly, there were concerns, if blinded placebo control trials should be continued or whether there was a need to switch to open label studies. There were discussions about using adaptive trial designs or the stepped wedge cross over designs, which being novel methodologies were not well understood by many. There was incomplete information, gaps in the review processes as well as funding mechanisms. Compromises in scientific review especially in respect of vaccine studies cannot be acceptable as it has wide implications on the implementation of the vaccination program and public trust. There was demand for improved transparency in the review and approval processes at the highest level. Every Vaccine trial is required to be registered on the Clinical Trial Registry of India Platform which is an online platform accessible to all (7). This brought in some transparency, but still left room for many more questions about reporting of research results, accuracy and research integrity. The principle of utility means that the best values may be provided to the people despite situations and the benefits to be accrued need to be maximised. The indigenously prepared vaccines were found to be safe, efficacious, cost effective, and beneficial as required routine cold chain already available across India. Vaccine rollout in a clinical trial mode without completion of Phase 3 did raise lot of concerns around scientific deliberations and proactive approaches and better transparency would have helped in reducing vaccine hesitancy. A decision was taken to provide the vaccines free of cost so that there would be no financial burden on the public and any economic harm can be avoided. Considering the fact that the covid-19 morbidity and mortality was higher amongst elderly or those with co-morbidities, and therefore in order to save more lives, this group was identified to receive vaccine in the initial phase. There was an incomplete knowledge set available in view of prior experience, incomplete information about scientific validity, long term effects, values and incomplete evidence for public health decisions. Therefore, ethics committees needed a lot more deliberations, to come to consensus to make difficult decisions while undertaking benefit risk assessments. It was well realised that the challenges need to be tackled in public interest, without making any compromises on the core ethical values for a greater good for the society, to approve new methods and technologies, in a fast-track mode.

Informed Consent Process

An informed consent process is integral to provide due information before receiving a voluntary agreement from the participant for any given research. The information has to be communicated in the simplest of manner to explain the details of the study, the risk and benefits, procedures to be followed and other relevant information and decisions be taken without any undue pressure or coercion. ICMR National Guidelines for Ethics Committees, 2020 released during the pandemic have suggested that novel methodologies can be adopted by researchers to facilitate informed consent process during the lockdowns. The importance of utilizing audio/ visual aids or electronic tools to seek consent with appropriate documentation has been highlighted (4). As soon as vaccine trials were announced, several vaccine study sites reported that many volunteers turned up in the hope to be amongst the first ones to receive protection from the deadly disease. Therapeutic misconception was high and vaccines (though experimental) were seen as a magic portion to save lives. There was lack of clarity in the public understanding of experimental vs approved vaccines, since many of the vaccine were granted an emergency use authorization (EUA) even before the trials were completed and results published. Recent reports have suggested that India's Covid-19 Vaccination Program saved millions of lives (8). But on the other hand, at other sites, there were concerns related to obtaining and documenting informed consent (9). It is time that scientific community makes better investments to make informed consent truly voluntary where participants or their communities are engaged in a meaningful manner and there are measures to build trust between the stakeholders. An online e-program was developed namely, Covid Vaccine Intelligence Network (Co-WIN) application for improved access to information, availability of vaccination sites, booking appointments, and generating vaccination certificates. The vaccination was voluntary and protected individual autonomy to an extent to decide and have a choice to choose the center as per available vaccine. Further even during the roll out of vaccination in the very initial phase, it was made voluntary to come forward for vaccination and receive the same after a written informed consent process. Further fact sheets were disseminated and those who received vaccines were closely followed up over the telephone for any adverse events. These measures were taken in order to protect autonomy and rights of the people and protect them from any undue harm. In addition, a landmark decision was taken in India to make budgetary provisions to pay compensation in case of any harm caused due to vaccination in the initial phases of its implementation and roll out (10).

Vaccine Research in Pregnant Women, Children, Vulnerable Persons

Traditionally clinical trials exclude persons or group who are determined to have diminished autonomy and are vulnerable. The same practice was followed for Covid-19 vaccines trials, where the pregnant women and children were excluded from participation in the initial phases of vaccine research/ trials, due to safety related concerns. The principle of Non-Maleficence or to 'do no harm' requires that the pregnant and lactating mothers or children be excluded from clinical trials in order to protect them from harm that was possible due to experimental vaccines. While other public health researchers have concerns that when the vaccine was approved and become available to general public, it could still not be administrated to pregnant women and children across all ages, since, the safety and effectiveness of the vaccines remained to be tested in these groups. It was noted that unvaccinated children were reservoirs and passively transmitting the infection to others around them. Therefore, the vaccine remained inaccessible to pregnant women and children for a long time and they were denied of their right to receive the benefits of vaccination early on (11). The unresolved debate on whether vaccine trials need to be carried out concurrently in adults and children continues. Children have been excluded citing concerns of safety, and there is need for more discussion to understand the conditions and requirements that would encourage timely research in children with the due safeguards and monitoring (12). Use of experimental vaccines in children or in women during pregnancy provides the prospect of imparting protection for both mother and child, however this can be debated as there have been only a limited number of studies documenting the efficacy and safety of vaccines leading to an ethical dilemma in assessing the benefits and risks. The principle of equity requires one to set priorities to provide equitable access to all without discrimination. The high-risk groups were prioritised in the vaccination drives and access to vaccine was for all without any discrimination between rich or poor, socially marginalised, tribal or other vulnerable population group.

Safety Reporting

Vaccine trials require very vigorous adverse event or serious adverse event reporting and monitoring. However, in case of Covid-19 vaccine trials, there was very limited safety data available. During this period emergency use approvals were granted even before all phases of the trials were completed and, therefore understanding the safety aspects of vaccines was particularly challenging. Thus, the risk related to experimental vaccination was largely unknown. Further there

was no understanding about the long-term effects, duration of protection, and especially related to high-risk groups or vulnerable persons or those with co-morbidities, geriatric population, pregnant women or children. In addition, there was a risk of contracting infection, if the vaccine turned out to be ineffective. In order to overcome these challenges a meticulous procedure for follow up was created and further, a series of webinars, online as well as physical trainings were arranged for the healthcare work force on various aspects of safety reporting down to the block level health care workers. Adequate healthcare infrastructure was further created for delivering care and undertaking safety reporting. Co-WIN application had in built provisions to ask the recipients about any adverse event and to report the same. Skilled manpower and suitable logistic delivery platforms were available to ensure fulfillment of the principle of beneficence and protection of persons. The trials reported that the risks or discomforts were mostly mild, such as fever or pain or those that were related to anxiety, and resolved in 3-4 days (13). India has a strong Adverse Event Following Immunization (AEFI) monitoring mechanism in place. However, there was flooding of speculations and misleading claims, information on social media creating the scare of adverse events, leading to fears and vaccine hesitancy (14).

Psychological health and safety of Health Care Workers

Covid-19 affected the mental health of people in a significant way. They were exposed and vulnerable to various socio-economic changes, has fear related to vaccination and its long term affects. The ICMR Ethical Guideline discusses the need to focus on mental health issues and psychological needs of both people and the researchers during the pandemic. The guidelines discuss about the importance of ensuring respect, empathy, compassion, to those who become positive with infection and guidance to institutions to make provisions for emotional support and wellbeing. The health care workforce dealing with highly infectious material required appropriate protection gear as well as training on handling, storing or sharing the highly infectious samples across labs. The National Guidelines for ethics committees reviewing research during the Covid-19 pandemic released in April 2020 discuss about the need for self-protection, use of PPE kits as well as appropriate waste disposal for wellbeing (4). Despite the initial hesitation, the momentum of vaccination caught up and enormous efforts were made by government agencies to educate and communicate information which led to positive outcomes and overall, an improvement in the mental health status (15).

Transparency and Accountability

Knowing that vaccines usually take years to develop, with the accelerated research, there was a perception that the vaccine may not be safe or effective. The regulatory processes for approval came under close scrutiny. Public demanded complete transparency in the decision-making processes. There was demand to post the names of all members of the expert committees involved in policy and decision making, requirements to declare conflicts of interest, posting of minutes of meetings in the public domain and follow-up action plans to be available on website for easy access to all. The public rightfully wants all stakeholders to be responsible and accountable. ICMR acted on this and launched a vaccine portal, which is a website collating all available and updated information about Covid-19. This was in order to provide transparency in the R&D process and to serve as a repository of all information related to vaccine development in India (16). These steps were important in building societal trust. However, much more efforts are needed to improve transparency. The regulatory decisions are often taken in closed doors meetings should also involve public as an important stakeholder in the deliberations and decision making. To ensure the principle of accountability and fairness, all efforts were made to find improved ways to communicate in a timely and objective matter, presenting available data or evidence to keep the public informed with honesty and make all efforts to communicate in the most simplistic manner for understanding. These initiatives are important in reducing vaccine hesitancy and improving confidence for decisions being taken at the policy level.

Importance of Communication

There was a realization how communication needs to take the center stage in order to cater to the needs of the communities. At different time periods, the disease forced the public to experience an emotional turmoil, such as 'fear', 'anger', 'depression', 'desperation' and 'anxiety'. These emotions could rather have been, 'satisfaction', 'confidence' or 'hope' if, there had been better communication. Often the communication received is partly skewed, or presents a one-sided perspective, or fake news driven by political motives, or sensationalized by media. News channels running 24x7 fueled this fire and created stories over factual information. WHO labelled the epidemic of misinformation causing confusion as an 'Infodemic' as it travels much faster leading to risk taking behaviors (17). There was a felt need to engage better with communities and people directly and for media to act more responsibly. Further the scientists need to learn to communicate

better and share information in a timely manner. India has high speed internet connectivity to the remotest part of the country which needs to be better utilized for sharing right information in a timely manner. Research needs a lot of investments and to have the capacity of not only dealing with the crisis situations but also having in place appropriate methods to inform and communicate better with the stakeholders so that right information and perspectives can be presented and understood. Truthfulness, honesty and empathy are critically important principles for an effective and ethical communication. Message content to be shared for public consumption must be understandable in lay language, honest and open. However, there were major challenges in form of rumors or scary information to create panic among the public. The Government of India left no stone unturned and held weekly Press Information Bureau (PIB) meetings and provided timely updates along with data presented as power point presentations/ graphs etc. which was live telecasted on national television to keep the public informed. Further the websites provided the guidelines, training modules, videos, etc. on their websites for easy access to the public. Various social media platforms in both electronic and print mode were utilized to broadcast and inform the public. Regarding fake news and warn the public from time to time. These measures were found to be useful and helped to reduce misunderstandings, unnecessary conflicts and helped to improve communication. Further a Communication Strategy was prepared by the Ministry of Health and Family Welfare, Govt of India which provided a detailed direction to these efforts (18).

Governance of Research

ICMR Ethical guidelines have suggested preemptive preparation for undertaking research in emergency situation such as these COVID-19 pandemic. Ethics preparedness can help in the conduct of research with improved outcomes while safeguarding the people (19). The government set up website to provide updated information on every new initiative. Several 'Make in India' and 'Atma Nirbhar Bharat' (which means self-reliance) initiatives were supported by the government to overcome the challenges through innovation and self-reliance to meet the priority needs of the country (20). The regulatory agencies further made every effort to streamline review processes with expert committees to ensure timeliness of reviews so that the vaccine trials could be promptly initiated without much delay for regulatory review. The regulation also contains clauses that allow emergency use authorization (EUA) in order to facilitate expedited vaccine development under exceptional conditions.

In India, a new drug approved outside the country can be given a waiver from conduct of clinical trial if there is an emergency such as an epidemic or disaster or for patients suffering from rare diseases for which treatments are not available on a case-to-case basis. Therefore, in such rare instances, unapproved drugs which are not available in Indian markets can be imported in small quantities by a medical institution for treatment related to life-threatening diseases or those with for unmet medical needs in India. Hence, there is a defined regulatory framework for import or manufacture of unapproved new drugs for compassionate use (21) However, there was a lack of understanding on regulation amongst not only practitioners but researcher as well. Initially only the two indigenously developed vaccines received the regulatory approval and were made available to the public as they were temperature stable not requiring very low temperature cold chain. Vaccine studies were not done in many other vaccines which required stricter cold chain support and would be unaffordable and inaccessible in the remote areas (22). Various Government agencies and departments set up Research consortiums, and National Task Force Studies in order to develop an integrated process for an effective vaccine to combat Covid-19. Support was extended to industry, academia, scientists and institutions to join hand Further India joined hands with the world in ACT Accelerator, CEPI, joined hands with neighboring countries for building science diplomacy for technological advancement and acceleration of indigenous vaccine development efforts. Multipronged approaches and efforts need to ensure vaccine manufacture and supply within the country and to low- and middle-income neighbouring countries dependent on India for the vaccine such as Nepal, Bhutan, Myanmar, Bangladesh, Maldives, Seychelles, Mauritius on a gratis basis. India emerged as global leader in advocating against vaccine nationalism and providing vaccines to different countries. India supplied COVID-19 related medical assistance, since the beginning of COVID-19 pandemic and under the Vaccine Maitri Programme supplied 723.435 lakh doses of COVID vaccine to about 94 countries (23). The underlying values for this work relate to the Principle of distributive justice ensuring fair selections and allocations of the available but limited resources, while involving and engaging with the diverse members from the community. Further these initiatives have helped India in its resolve towards the principle of equity and access to people. In the fight against the COVID-19 pandemic during the second wave, support in the form of COVID related equipment and medicines were received from more than 50 countries. These included supplies from foreign governments, private companies, Indian associations abroad, etc. (24).

Conclusion

The importance of implementing the principles of ethics came to the fore as India fought against Covid-19 infections. For the first time it was seen that there was a global requirement to prepare a safe and efficacious vaccine that could be administrated to all age groups right for new born to children, young and old adults, pregnant or nursing women and even geriatric population or those with co-morbidities. The various initiatives taken to combat Covid-19 underlined the bioethics principles to an extent, and taken in the best interest of public however more robust and open discussions around values and principles in ethics would have improved these responses further.

The vaccines trials conducted in India had their own set of challenges and issues and there are many lessons learnt during this time. However, being a large country with socio-economic, political, religious and cultural diversity, the efforts needed more ethical deliberations to ensure fairness. The political parties used the pandemic as an opportunity for self-promotion and fault finding for others leading to confusion and lack of public trust. There were concerns related to inclusion and accessibility to benefits for everyone, and especially those residing in remote areas or those who belonged to certain communities such as tribal population groups with limited access and awareness. The policies and decisions at the highest level were guided by transparent and fair procedures however there is much room to improve this further. Lessons have been learnt to ensure autonomy of persons and having better community engagement programs, better communications and preparation of advocacy material before enrollment of participants. Further handling of conflicts of interests, being transparent and accountable require appropriate disclosure since they raise serious questions on the outcomes of research and questions regarding integrity of findings. More and more participatory approaches and collaborations are required in order to undertake better research studies. It is now clear that there can be no compromises on the quality of science, rights or safety of participants even in an emergency situation. The meetings can be expedited, the procedures can be fast tracked, however, in no way the rights, safety and wellbeing of the participants can be compromised. The researchers need to work towards reducing bias and restoring public trust. The core ethical principles addressing issues and concerns raised in research around vaccines revolved around the principles of autonomy, beneficence, non-maleficence, justice including distributive justice and also around the ethical values of ensuring equity, fairness, utility, transparency, accountability, affordability and easy access. A safe and efficacious vaccine development and implementation involves both hard science as well as soft science focusing on ethical aspects to ensure processes leading to a good vaccine.

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