**Title**

Expanded principles of ethics and its implementation during COVID-19 vaccine trials: A scoping evidence based research synthesis

**Authors**

1. Dr. Abhishek Royal, Department of Public Health, Faculty of Medicine, Public Health & Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.

Email: [abhishekroyal2010@gmail.com](mailto:abhishekroyal2010@gmail.com)

1. Dr. Vaibhav Kumar Faculty, Department of Public Health Dentistry, TPCT'S Terna Dental College, Navi Mumbai.

Email: [drvaibhav1989@gmail.com](mailto:drvaibhav1989@gmail.com)

1. Dr. Venetia Aranha, BDS, TPCT’s Terna Dental College, Navi Mumbai, Maharashtra-400706

Email: varanha97@gmail.com

1. Dr. Rajni Rajgarhia, Private Practitioner, Dental Profiles, Bellandur, Bengaluru – 560103

Email: rajninemani@gmail.com

1. Dr. Kedar Mehta, Assistant Professor, Community Medicine Dept., GMERS Medical College, Gotri, Vadodara, Gujarat – 390021

Email: [kedar\_mehta20@yahoo.co.in](mailto:kedar_mehta20@yahoo.co.in)

**Funding –** Nil

**Competing Interest** – Nil

**Conflict of Interest** - Nil

**Abstract**

The coronavirus disease-19 (COVID-19) pandemic, an unfortunate event has spread globally and caused a disastrous calamity. However, there remains an unknown reason about the pathology of the virus. Concerted measures are taken to stop the rapid spread of this deadly virus, and return back to normalcy.  Even after undertaking preventive measures such as maintaining social distancing, testing, and tracing, countries are struggling to contain the pandemic. Pandemic will suppress only when the herd immunity is developed, and we have an effective vaccine available in the market. Physicians, academicians, and different companies worldwide have expedited the testing to develop severe acute respiratory syndrome coronavirus-2 (SARS- COV-2) virus vaccine. This opens up a discussion of what norms to follow during the clinical trials while developing the vaccine. As of now, various companies like Moderna, Pfizer, University of Oxford, Astrazeneca and so on, have moved beyond the safety, efficacy and immunogenic studies. This review article consists of all four general ethical principles along with the 10 expanded principles in a structured approach. Additionally, the article delves into the different types of vaccines, their role, side effects, limitations, and advantages.

**Introduction**

The worldwide escalation in the cases of the coronavirus disease (COVID-19) throws light on the dire requirement for an efficacious, safe COVID-19 vaccine. In September 2020, the Advisory Committee on Immunization Practices put forth four main interim ethical principles, essential for development and implementation of recommendations for COVID-19 vaccine use, including maximisation of benefit for the patient, to do no harm, equality, justice and fairness. [1] The rapid spread of the pandemic necessitated an acceleration in obtaining a vaccine, this demand has become critical for all medical professionals and scientists even though it might include a more ‘relaxed’ approach in order to establish procedures. [2] Animal models are usually tested for evaluating a new drug through preclinical studies, followed by later stages where the testing is done on humans through clinical trials.[3] In order to expedite the process of developing the COVID-19 vaccine, a condition arose wherein no testing was done on animals.[4]

In addition, the Global Solidarity Trials began in February 2020, an initiative by the World Health Organisation (WHO) research forum in order to recommend evaluation for treatments in large and randomised trials on COVID-19 disease. [5] WHO began an international randomised trial that was simple and open-label on March 2020. It included in-hospital patients to assess the effects on in-hospital mortality of the four drugs. About 11,330 hospital patients were enrolled for this trial, from around 30 countries in six all WHO regions during March 22nd up to October 4th, 2020. [5]

Although there are differences, a few common value orientations including autonomy, beneficence, non-maleficence, justice and confidentiality have to be followed by medical professionals. [6,7] A strong emphasis on these ethical principles and the ability to negotiate differences may be advantageous not only to the patients but also the health care professionals. [8] This review article focuses on ethical considerations during the COVID-19 vaccine trials along with its expanded principles and the significance of them.

***Autonomy***

Autonomy is pivotal in bioethics. Autonomy simply implies respect for persons. It ensures that subjects are capable of making their decision which is recognised, respected and at the same time safeguarding the autonomy of the vulnerable by avoiding unnecessary decisions. This fundamental principle gave rise to informed consent which is now practised legally wherein qualified subjects or an authorised candidate is permitted to decide to part take in a study or not. Informed consent must subsume a well thought out process for achieving the goal of research and it is expected to be complied to. [9]

Moreover, some researchers concur that autonomy is extremely crucial and that there are situations where a person's own choice should be valued about their treatment although others might be in a better place to decide for the well-being of the patient. [10]

The question arises, on what basis informed consent is considered invalid? When researchers themselves give the wrong description of research either due to lack of knowledge or understanding? Is it done deliberately due to their false belief? Or are the volunteers misguided by researchers? The factors such as ignorance and uncertainty make it difficult to obtain a valid informed consent. Therefore, in the present scenario of understanding and knowledge, validity is of serious concern for the participant's consent to COVID-19 vaccine trials.[11]

The vaccine trials of COVID-19s’ informed consent forms are unavailable to the public due to reasons of privacy. [12] These informed consent forms are similar to the “Risks to participants'' part of the trial guidelines which have been given by Pfizer, Moderna and Johnson & Johnson in the vaccine trials for COVID-19. [13] These three vaccines represent the diverse vaccines that are being tested.

In addition, all of these three protocols include the risk of any diseases associated with or by administration of the vaccine. The mentioned risks in the consent form for Moderna vaccine are after allergy reaction at the site of injection, fainting, intrinsic negative effects and abnormalities of the laboratory. For Pfizer vaccine, risks mentioned are injection site response locally, and antagonist reactions systemically. Johnson & Johnson showed up risks such as phlebotomy and collection of nasal swab samples are present. Lastly, Moderna and Pfizer, cite the risk of prior proof of vaccine obtained disease improvement with Respiratory Syncytial Virus (RSV), dengue; also, feline corona virus for Pfizer whereas it is measles for Moderna. The side effects, limitation, mechanism of action and advantages of the various vaccines are mentioned in figure 1, figure 2, figure 3. The informed consent form must explicitly mention the protocol and related risks of worsened COVID-19 virus from the inefficiency of the vaccine up to death if any. [10]

***Beneficence***

Beneficence is of central value in ethics in medical trials. It states that researchers should do good for the patients enrolled in the study. It is a moral obligation, in which researchers do things for the benefit of participants by preventing them from any harm.

Beneficence can be subdivided into actual benefits and perceived benefits. In actual-benefit, patients may have an extra advantage for financial compensation or additional medical assistance. Actual-benefit rarely changed in COVID-19 clinical trials. However, perceived benefits have a foreseen medical outcome for a newfound treatment for the vaccine and, are likely to change.[14]

Moreover, WHO issued “Human challenge trials” to speed up the COVID-19 vaccine trials without undergoing phase III trials, where volunteers were deliberately infected to develop COVID-19 vaccine.[15] It questioned an important ethical principle which is, beneficence. Is it fair to infect people on purpose with deadly coronavirus infection, knowing the consequences? [16] Furthermore, it is tough to elucidate the durability of COVID-19 vaccine with phase I or phase II trials. Also, re-infection registered with SARS coronavirus. Without any evidence on the immune response to COVID-19 vaccine, verification on durability and “beneficence” is questionable. [17]

***Non maleficence***

Non maleficence is a principle that demands no subject should be harmed during the process of the study. This principle ensures that the study conducted and the design of the study must minimise any possibility of harm, given the chance of limited benefit for all those participating in the study. [18,19] The probability and severity of harm to the subjects should be addressed by risk mitigation. [9]

Potential maleficence can be broadly categorized into burden to the subject and risks to the participant. In usual instances, the volunteers partaking in clinical trials are subjected to risks that are unknown and serious adverse effects of the procedure. For a study participant, the additional risks might involve that the new treatment method is ineffective or the treatment may not be as good as the standard treatment that was being followed or may be a subject assigned in a group that did not receive any active treatment (control group participant). [14]

In the COVID-19 vaccine trial, there are two significant ways where the participant might be subjected to potential risk. Firstly, the risk of developing SARS‐CoV‐2 because of increased exposure to others. Secondly, a drug that is still under investigation could increase the likelihood of contracting SARS‐CoV‐2 or might even worsen the symptoms and outcomes of COVID-19. Risk of virus contraction can be due to three reasons: 1) at the time of the trial, presence of asymptotic virus carriers. 2) the reproduction number of an effective virus. 3) to reduce the risk of contamination, strategies implemented by trail-specific risk mitigation.The SARS‐CoV‐2 being transmitted by an asymptotic carrier is still being debated. [14]

The direct transmission of virus can be protected by following norms like social distancing, regular sanitization protocols, utilisation of personal protective kits and screening of SARS‐CoV‐2 before confining a patient. In cases where an individual is infected, compartmentalization should be done to prevent spread of virus to the population at large. This can be done by separation of regular care from trials, isolation of infected individuals, utilising different areas of the clinic for class confinement or performing home visits. These methods aid in mitigating the risks and can be scaled up or down based on the population under study and the dynamic of the virus to increase non-maleficence without being a burden on the subjects. [14]

Careful consideration must be given to vulnerable participants with life threatening conditions as they are highly susceptible to infection when partaking in the study during the pandemic. Thus, the added benefit should be thoroughly weighed against the potential factors that can cause harm for COVID-19 morbidity and mortality. [14]

The strategies for risk mitigation should be identified and carried out during the pandemic. Apart from being infected with SARS‐CoV‐2, complications of the virus for the particular study population should be carefully examined and evaluated. Geriatric patients and any person with debilitating diseases like hypertension, diabetes mellitus, chronic lung disease, cardiovascular diseases and kidney diseases are at higher risk of severe COVID-19 disease. There also might be a requirement of ICU admittance and mortality. [14]

The risk analysis on investigational compound should be carried out highlighting the added risks of SARS‐CoV‐2 and has to be updated to every study record file until the COVID-19 pandemic persists, as these are given by the present EMA (European medicine agency) and FDA (Food and drug administration) COVID-19 guidelines. [14]

Finally, the pandemic's impact on the burden for the study subjects should be taken into consideration. The side effects that are expected, discomfort and anxiety related to participation in the study or study procedures, study restrictions, challenges related to travelling to the clinic, investment of time and findings related to the status of health of the patient all include in the burden for the study participants. The strategies of risk mitigation as discussed like social distancing further increase the burden on the participant. Lack of certainty related to trial continuation can lead to anxiety in patients during a new outbreak of the viral infection, for example, in oncology patients. [14] Thus, only necessary strategies for risk mitigation should be carried out in order to decrease the burden on study participants and should be immediately put to an end when redundant and not automatically maintained till the end of trial. [14]

***Justice***

Lastly Justice, a principle of bioethics, acts on fair judgement. It is sub-categorized into 1) distributive justice 2) justice-related to right of the subject 3) legal justice. [14]

Distributive justice states that there should be fair delivery of limited resources to people at large. Due to high demand, and less production in an unprecedented situation like the COVID-19 pandemic which makes the distribution difficult or sometimes impossible. The foremost role of the vaccine is to lower the infection and minimize the spread in the community. During the vaccine distribution, people at high risk should be prioritized first. Proponents claim that herd community with a denser population, poor citizens and lack of medical facilities should get the vaccine delivered before others. In local areas; immunocompromised, comorbidity, old age and poor patients should be prioritized whereas globally; the underdeveloped and developing countries that lack in sanitization, have scarce availability of food and water, that are at greater risk of health hazards should be pondered. Although the distribution of COVID-19 vaccine in the developing countries seems difficult, it is not impossible. [20,21] When the COVID-19 pandemic began, there was an increase in the influx of patients in the healthcare system globally. As a result, other non acute healthcare activities including clinical trials were postponed. The shortage of medical staff, equipment, protective equipment, test kits and intensive care units due to the COVID-19 pandemic soon led to the cessation of clinical trials. Therefore, when allocating limited resources, a method should be used that provides the maximum benefit to all patients, be it COVID-19 or other diseases.[14]

The right of subjects includes protection from misconduct or negligence, medical care provision, compensation for damage, medical confidentiality, privacy of data and its protection, right to participate freely in the study trial and right of withdrawal whenever during the clinical trial. [14]

Legal justice refers to respect to a morally acceptable law. Although clinical trials are standardized, it was only during the coronavirus pandemic that auxiliary instructions were disclosed by European medical agency (EMA) [14], US Food and drug administration (FDA) [14] and many health authorities.[14] These new instructions need time, analysis to be implemented and is open to discussion. It was over challenging initially due to the coronavirus urgency.[14] Thus, the instructions are required to maintain an open-ended discussion between hospital site, sponsor and ethics committee for application in a clinical trial. Unless guidelines for data integrity and subject safety are followed, mutual decisions can be acceptable. It is observed that at times sponsors take an aberrant path to continue trials for potentially fatal conditions where a trial needs to be put on hold. In this situation, it is necessary to record any decisions taken explicitly and their justification if there is any deflection because of the COVID-19 pandemic. [14]

***Expanded Principles of ethics***

|  |  |
| --- | --- |
| **Principles** | **Ethical consideration in COVID-19 research Trials** |
| Principle of essentiality | It must be reviewed by an independent and responsible person who, after careful consideration, must decide that research can ease humankind.[22] |
| Principle of voluntariness, informed consent and community agreement | People participating must be briefed about the right to refrain or withdraw from the study at all times. Principle of voluntariness, informed consent applies to the entire society and each individual where the study requires treating anyone in the society.[22] |
| Principle of non-exploitation | The participants should be completely informed of all potential risks that may occur during research. Also, each participant should be compensated by any insurance or other means for any expected or unexpected risks and provide therapeutic and comprehensive post-operative aftercare.[22] |
| Principle of privacy and confidentiality | The database and identity of the participants should be kept confidential to prevent any form of suffering and inequity.[22] |
| Principle of precaution and risk minimisation | Risk minimisation can be promoted by selecting patients who are both young and healthy, and by giving them priority access to top-notch medical facility during the trial. Current, SARS CoV-2 Controlled Human Infection (S-CHI) includes additional risk minimisation rule and improved consent processes aimed at fostering participants, accepting possible dangers. [23] |
| Principle of professional competence | Healthcare workers should fully understand both the practical and moral rationale for authorising COVID-19 vaccine.[25] |
| Principle of accountability and transparency | The principle of transparency is enforced across the entireness of vaccine allocation decision making process. This principle, decision making process and design of COVID-19 vaccine allotment must be evidence-based, explicit, comprehensible and publicly available.[24] |
| Principle of maximization of public interest and of distributive justice | The distribution of the COVID-19 vaccine should promote equity by knowingly ensuring that everyone has an equal chance of being vaccinated, both in the groups recommended at the start of vaccination and when the vaccine is available instantly. [24] |
| Principle of public domain | The research result must be in the public domain and provide access to any production facility that promises to operate under strict international control.[26] |
| Principle of totality of responsibility | This principle states that the research should be rightfully observed and must be subjected to review consistently along with the medicinal action being taken at each point. [22] |

**Conclusion**

Currently the world is undergoing the development of the COVID-19 vaccine with trepidation. During the vaccine phase trials, a host of ethical dilemmas are bound to arise while the strong financial incentives, political interests and urgency develops a pressure to forge rapidly ahead. To resolve these dilemmas that gradually arise it is necessary to discuss these ethical principles well in advance. [27] The critical challenges faced not only by the public but also the research and the scientific community, and this is one of the main reasons why a safe and efficacious vaccine needs to be developed urgently in order to stop the rapid spread, complications and death arising from it. It is extremely essential now, in these times to follow the ethical guidelines that clinical research needs and also stringent control, supervision measures. [28]

The Ethics committee (EC) / Institutional Review Boards (IRB) play a central role in monitoring and reviewing the clinical research protocol. As we are facing the pandemic, the ECs and the IRBs must closely monitor the study conducted and an accurate evaluation must be done to guarantee the vigilance of patient’s safety along with the procedures that are brought about in the most meticulous manner. [28]

**References**

1. Bell BP, Romero JR, Lee GM. Scientific and Ethical Principles Underlying Recommendations From the Advisory Committee on Immunization Practices for COVID-19 Vaccination Implementation. JAMA. 2020 Nov 24;324(20):2025-2026.

2. Tsatsakis A, Petrakis D, Nikolouzakis TK, Docea AO, Calina D, Vinceti M, Goumenou M, Kostoff RN, Mamoulakis C, Aschner M, Hernández AF. COVID-19, an opportunity to reevaluate the correlation between long-term effects of anthropogenic pollutants on viral epidemic/pandemic events and prevalence. Food Chem Toxicol. 2020;141:111418.

3. Docea AO, Gofita E, Calina D, Zaharie SI, Valcea DI, Mitrut P. Autoimmune disorders due to double antiviral therapy with Peginterferon and ribavirin in patients with hepatitis C virus infection. Farmacia. 2020;64:605–611.

4. Lakdawala SS, Menachery VD. The search for a COVID-19 animal model. Science. 2020;368:942–943.

5. World Health Organization. A coordi- nated global research roadmap: 2019 novel coronavirus. March 2020 (https://www.who.int/blueprint/priority-diseases/keyaction/Coronavirus\_Roadmap\_V9 blueprint and Covid-19 (https://www.who .pdf ?ua=1)..

6. Rancich AM, Perez ML, Morales C, Gelpi RJ. Beneficence, justice and lifelong learning expressed in medical oaths. *J Contin Educ Health Prof.*2005;25:211-220 [[PubMed](https://www.ncbi.nlm.nih.gov/pubmed/16173070)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=J+Contin+Educ+Health+Prof.&title=Beneficence,+justice+and+lifelong+learning+expressed+in+medical+oaths&author=AM+Rancich&author=ML+Perez&author=C+Morales&author=RJ+Gelpi&volume=25&publication_year=2005&pages=211-220&pmid=16173070&)]

7. Orr RD, Pang N, Pellegrino ED, Siegler M. Use of the Hippocratic Oath: a review of twentieth century practice and a content analysis of oaths administered in medical schools in the U.S. and Canada in 1993. *J Clin Ethics*. 1997;8(4):377-388

8. Stewart Gabel. Ethics and Values in Clinical Practice: Whom Do They Help? Mayo Clin Proc. 2011 May; 86(5): 421–424.

9. Taofeek K. Owonikoko. Upholding the Principles of Autonomy, Beneficence, and Justice in Phase I Clinical Trials. Oncologist. 2013 Mar; 18(3): 242–244.

10. Jukka Varelius. The value of autonomy in medical ethics. Med Health Care Philos. 2006 Dec; 9(3): 377–388.

11. Keren A, Lev O. Uncertainty, error and informed consent to challenge trials of COVID-19 vaccines: response to Steel *et al*. J Med Ethics. 2020 Dec;46(12):813-814. doi: 10.1136/medethics-2020-106793. Epub 2020 Sep 8.

12. Cardozo T, Veazey R. Informed consent disclosure to vaccine trial subjects of risk of COVID-19 vaccines worsening clinical disease. Int J Clin Pract. 2020 Oct 28:e13795.

13.  McNamara D. Three Major COVID Vaccine Developers Release Detailed Trial Protocols.Available from: [https://wwwmedscapecom/viewarticle/937845. 2020](https://wwwmedscapecom/viewarticle/937845.%202020).

14. Vissers MFJM, Cohen AF, Van Gerven JMA, Groeneveld GJ. The impact of the global COVID-19 pandemic on the conduct of clinical trials: Return to normalcy by considering the practical impact of a structured ethical analysis. Br J Clin Pharmacol. 2020 Jul 15.

15. Eyal N, Lipsitch M, Smith PG. Human Challenge Studies to Accelerate Coronavirus Vaccine Licensure. J Infect Dis. 2020 May 11;221(11):1752-1756.

16. Katib A. Research ethics challenges during the COVID-19 pandemic: what should and what should not be done. jidhealth [Internet]. 19Sep.2020 [cited 25Feb.2021];3(Special1):185-7. Available from: https://www.jidhealth.com/index.php/jidhealth/article/view/49

17.Vashishtha, Vipin M; Kumar, Puneet. Emergency use authorisation of Covid-19 vaccines: An ethical conundrum. Indian Journal of Medical Ethics, [Internet.], v. VI, n. 1, p.[cited nov. 2020] ISSN 0975-5691. Available from: https://ijme.in/articles/emergency-use-authorisation-of-covid-19-vaccines-an-ethical-conundrum. Updated: 25 Feb. 2021.

18. Horstmann E, McCabe MS, Grochow L, et al. Risks and benefits of phase 1 oncology trials, 1991 through 2002. N Engl J Med. 2005;352:895–904.

19.  Roberts TG, Jr, Goulart BH, Squitieri L, et al. Trends in the risks and benefits to patients with cancer participating in phase 1 clinical trials. JAMA. 2004;292:2130–2140.

20.Liu Y, Salwi S, Drolet BC. Multivalue ethical framework for fair global allocation of a COVID-19 vaccine. J Med Ethics. 2020 Aug;46(8):499-501.

21. Carter s. Over Half of Americans Delay or Don’t Get Health Care Because They Can’t Afford It- These 3 Treatments Get Put Off Most, [updated 29 Nov 2018] Available from: [cnbc.com/2018/11/29/over-half-of-americans-delay-health-care-becasue-they-cant-afford-it.html/](http://cnbc.com/2018/11/29/over-half-of-americans-delay-health-care-becasue-they-cant-afford-it.html/)

22. Avasthi A, Ghosh A, Sarkar S, Grover S. Ethics in medical research: General principles with special reference to psychiatry research. Indian J Psychiatry. 2013 Jan;55(1):86-91

23   Jamrozik E, Selgelid MJ. COVID-19 human challenge studies: ethical issues. Lancet Infect Dis. 2020 Aug;20(8):e198-e203.

24. McClung N, Chamberland M, Kinlaw K, Bowen Matthew D, Wallace M, Bell BP, Lee GM, Talbot HK, Romero JR, Oliver SE, Dooling K. The Advisory Committee on Immunization Practices' Ethical Principles for Allocating Initial Supplies of COVID-19 Vaccine - United States, 2020. MMWR Morb Mortal Wkly Rep. 2020 Nov 27;69(47):1782-1786.

25. Kass N. An ethics framework for public health. Am J Public Health. 2001;91:1776–1782

 26. Yunus, M., Donaldson, C., & Perron, J-L. (2020). COVID-19 vaccines a global common good. The Lancet Healthy Longevity, 1(1), e6- e8.

27. Monrad JT. Ethical considerations for epidemic vaccine trials. J Med Ethics. 2020 Jul;46(7):465-469. doi: 10.1136/medethics-2020-106235. Epub 2020 May 15.

28. Sebastián Ospina Henao , Alejandro Marín Mora, Fanny Chan Solano, María L. Ávila-Aguero. Bioethical Implications in Vaccine Development, a COVID-19 Challenge. Cureus. 2020 Sep; 12(9): e10530.

29. Chung YH, Beiss V, Fiering SN, Steinmetz NF. COVID-19 Vaccine Frontrunners and Their Nanotechnology Design. ACS Nano. 2020 Oct 27;14(10):12522-12537.

30. Kaur SP, Gupta V. COVID-19 Vaccine: A comprehensive status report. Virus Res. 2020 Oct 15;288:198114.

****

****

****