**Eligibility criteria for COVID- 19 trials: key considerations during enrolment of vulnerable population**

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***Abstract***

*COVID-19 is one of the most difficult global challenges of recent times. Till date, more than 13 lakh people have succumbed to this pandemic. Efforts for developing effective therapies were initiated globally and some vaccines and repurposed drugs have increased the hopes of countering the pandemic. While several others are still in the process of development. However, clinical development of new drug in a pandemic comes with many ethical challenges. One of which is deciding the eligibility for enrolment. Eligibility criteria are ‘characteristics’ of participants to be enrolled and quite often, vulnerable population like pregnant and lactating women, those with co morbidities and ethnic minorities are excluded. However, vulnerability could also be situational and in a pandemic like COVID-19 where many are socially displaced identifying who is vulnerable is crucial. The present article discusses the key aspects to be considered while enrolling vulnerable population in COVID -19 trials.*

**Introduction**

COVID-19 is one of the most difficult global challenges of recent times. This disease was first reported in Wuhan, China in November 2019 [1] and today, it has affected more than 200 countries across the globe. As of November 2020, more than 50 million people have been infected and over 13 lakh have succumbed to the infection [2]. COVID-19 has had enormous social, economic and political implications. It has disrupted normal life, and socially displaced people forcing many into poverty. Therefore, an urgent need to develop effective therapy against this pandemic was felt. Recently, some vaccines and repurposed drugs have increased hopes of effectively countering the pandemic [3-5]. However, the efforts in development of better alternatives have not ceased. For example, a search of ‘all studies’ related to COVID-19 on *clinicaltrials.gov*, yielded 3977 results from the database as on 21 Nov 2020[6]. While these measures are appreciable, the testing of experimental therapies in a pandemic comes with many challenges. One of which is deciding the inclusion criteria for clinical studies.

Eligibility criteria are like ‘characteristics’ or ‘guidelines’ to decide the right candidate for a study [7]. One of the criterion while deciding eligibility is to identify the population in need or those who are more likely to benefit from the drug. Quite often, clinical trials exclude vulnerable population like pregnant and lactating women, children, those with co morbidities and ethnic minorities [8]. Conventionally, vulnerable means those who are ‘a disadvantaged segment of the community’ and their exclusion is based on some ‘anticipated harm’. However, the definition of this ‘disadvantage’ could vary from case to case. A pandemic like COVID-19 has socially displaced people and communities and has rendered many ‘vulnerable’. When the therapies for a disease are in developmental stage, access to the experimental drug through trials could be the only hope for some. Therefore, excluding certain sections of the population from enrolment purely on the basis of ‘anticipated risks’ needs some rethinking. Identifying who is vulnerable in a given situation and weighing the harms and benefits of their participation is crucial to define eligibility criteria. The present article discusses who is vulnerable and the key aspects that one must consider while enrolling them in a research for pandemic like COVID-19.

***Who is Vulnerable?***

The term ‘vulnerable‘is derived from the Latin noun ‘*Vulnur*’ which means ‘to wound’ [9]. A vulnerable person can thus be the one who is disadvantaged, or may be at a risk of greater harm relative to those who are not vulnerable. The need to enrol the ‘right’ or non-vulnerable population has been highlighted by several guidelines. For example, the Nuremberg code of 1947 clearly states that consent must be obtained from those who are in a position to give their consent [10]. Here, the ‘ability to give consent’ emphasizes the need that the concerned person is able to take decision without any bias or pressure. Similarly, the Declaration of Helsinki published by the World Medical association states that, ‘*some research populations are vulnerable and need special protection*’ [11]. This guideline clearly defined when to enrol a vulnerable population in a study. There is however ambiguity over who really is vulnerable? Traditionally, vulnerability as a term has been used for pregnant, lactating women, children, ethnic minorities, persons with disabilities, prisoners, mentally retarded and the refugees. The Belmont report of 1979, assumes the vulnerability in people for whom ‘*their own resources are not sufficient to participate prudentially in the process of being research subjects’* [12]. For example: a student of an investigator would be vulnerable if he or she meets the eligibility criteria of a study that the concerned investigator is undertaking. Whereas the same student may not be vulnerable in case he /she are associated with an investigator who was not his tutor. The concept of situational vulnerability has gained more acceptance and consideration in recent times. The Council for International Organization of Medical Sciences [CIOMS] guidelines for the first time stated that, vulnerability may not be associated with an entire group but could be at an individual level within the group [13]. Vulnerability can also be classified as extrinsic or intrinsic [14]. When external factors like financial difficulties, social inequality, or unemployment render a person vulnerable it is called extrinsic vulnerability. While, when illness or some physical or physiological condition makes a person vulnerable it is called intrinsic vulnerability. In case of COVID-19, the extrinsic factors could at time be more crucial in defining the vulnerability status of a participant.

***COVID-19 and Vulnerability***

The World Health Organization (WHO) has identified certain group of people to be ‘vulnerable’ or at high risk. This includes those who are over 60 years of age, have some underlying disease and have a compromised immune system [15]. The criteria laid down by WHO fits within the conventional norms which define a population as ‘vulnerable’ on the basis of ‘risks’ involved. COVID-19 has however created a scenario wherein millions of people have lost their jobs, livelihood, shelter and have slipped into poverty. Considering the impact of this pandemic, the scope of vulnerability would not be limited to only those who are diseased, or physically disadvantaged. Extrinsic vulnerability could be as greater an ethical challenge as intrinsic vulnerability. For example, a financially distressed person would be more willing to participate in trials with the lure of free treatment or remuneration [16]. They may fail to see the risks in the study and in such a scenario; researchers have an added responsibility to ensure that an ‘informed decision’ is taken during the consent process. Developing good interpersonal relations with the participants could help sensitize the participants to the nuances of the research. Identification of vulnerability of a participant based on extrinsic factors could be a challenge unless there is good dialogue between the investigator and participant. An editorial in Lancet highlighted this more sternly by stating that *‘If vulnerable groups are not properly identified, the consequences of this pandemic will be even more devastating* [17]’ A study by Ranjib *et al.* identified five different indices to define vulnerability in a COVID- 19 situation. These included socioeconomic, demographic, housing and hygiene, availability of healthcare and epidemiological factors. The matrices considered by them are dynamic and thus vulnerability may be a position not associated with a specific group of people [18]. The vulnerability index helps to identify the regions that have more of vulnerable population. Thus, while recruiting participants from such regions investigators could develop proper measures well in advance to ensure the safety and rights of the participants. The parameters required to calculate the index may however not be available for every region and it could be a limitation of this approach.

***COVID -19 and Risk and benefit assessment***

The term ‘risk’ refers to some harm or any event which can cause harm [19]. Benefit on the other hand could be ‘cure’ or ‘improvement in patient’s condition’. An ideal scenario would be when the benefits are maximum and harms are negligible. However, in practice ensuring that the balance is tilted in favour of the benefits could be a daunting task. This could be especially true for vulnerable population. Let us understand this challenge with an example. The STRIVE trial for Ebola virus began in Sierra Leone in 2015. This study was undertaken in five districts which were affected by the endemic. In this study, it was observed that women who were vaccinated with the Ebola vaccine candidate [rVSVΔG-ZEBOV-GP] had a higher chance of loss of pregnancy relative to those who were not vaccinated [20]. If one were to consider the outcomes of this trial, the risks were lowered by excluding pregnant women. Currently, many ongoing COVID-19 trials have explicitly mentioned pregnant and lactating women in their exclusion criteria [21]. However, in case of patients who do not respond to the standard of care or available treatment options, how ethical will it be to still continue to deny them the benefit of experimental treatment?

Consider another example, as per the existing data on coronavirus disease, COVID-19 patients with comorbidities have poorer clinical outcomes [21]. In a study of individuals with severe infection requiring hospitalization, it was observed that nearly half had the presence of some comorbidity [22]. Some of the most common causes associated with mortality were diabetes, hypertension and renal impairment [23, 24]. While there is merit in the argument that presence of comorbid conditions may cause harm, would it be ethical to deny access to experimental therapy when no other drug appears to offer benefit? Exclusion of patients with comorbidities is more for ‘logistical convenience’. Logistical convenience here indicates a reduction in medical provisions required to deal with the risk associated in participants with comorbidities. The challenge then is, and can the efficacy of the drug in healthy patients be extrapolated to those with comorbidities? The recommendations given by Depaula *et al.* for cancer trials during COVID-19 are particularly important to note here. They state that ‘*the risk of continuing the therapy must be carefully balanced with the risk of stopping or denying treatment that might extend life’* [25]. The fundamental issue that arises when one assumes potential benefit with a certain intervention is that the principal of ‘*clinical equipoise*‘ ceases to exist. Enrolment of those with comorbidities could be largely based on chance of some ‘incremental benefit’ with an intervention and therefore assumption of an equipoise may not hold true in such cases. The decision to choose the right study design is therefore critical when such fragile population is considered for trials. One of the common designs preferred for COVID- 19 trials is the adaptive study design [26]. This design systematically assigns patients to the treatment arm that is proven to be more beneficial. At present, in Europe certain ‘compassionate programs’ also allow access to experimental drugs that are not marketed to patients who do not have any other alternative treatment available. However, there cannot be a generalized recommendation on whether to include them or not because the evaluation of ‘risks’ and ‘benefits’ is a subjective criteria. The decision should therefore not be solely based on investigator’s discretion but also the participant’s willingness and careful evaluation of the data from the general population that has been tested.

***Adequacy of data for defining benefit or harm***

The basis of any decision in context to a clinical trial is the existing evidence pertaining to that drug. Let us have a quick look at certain numbers; between the years 1960 to 2013, only 1.29% of the total participants enrolled in trials were pregnant women [27]. Also, an examination of data on studies of heart failure by Cherubini *et al.* in the WHO’s clinical trial registry found that out of 251 trials, more than a quarter had excluded patients based on age [28]. These are just a few cases which indicate how little information on evaluations in these vulnerable populations exists. In 2018, the Food and Drug Administration (FDA) released a regulation which clearly states that studies on pregnant women must be carried only if the ‘*nonclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted’ and* the guideline also emphasized the need to generate data regarding the same [29]. It also recommends that the risk to the fetus be less than minimal risk. However, the guideline has not defined what would be considered as an ‘adequate data’ to conduct a study in pregnant women. Literature reports on treatment of pregnant women infected with COVID-19 indicates that the symptoms and manifestations do not differ from the general population. However, there is very limited evidence on how effective a therapy is in severe cases of infection and in the first trimester of pregnancy [30]. In case of COVID- 19, some reports indicate that there is no vertical transmission of the infection from a mother to the child [31]. At the same time, reports of placental injury in pregnant women have also surfaced [32]. Thus, the evidence on harm to the fetus due to COVID- 19 is ambiguous. In addition to these, the psychological distress to the pregnant female due to quarantine cannot be denied [33]. In case of another vulnerable population, i.e elderly [34], FDA in a guidance document has clearly stated that ‘*to achieve an unbiased estimate of treatment effect in the general population, sponsors should develop a strategy to enrol diverse populations, including different age groups that are consistent with the intended use population* [35]’. However, despite of this, the elderly are quite often excluded from the trials. The International Conference on Harmonization [ICH] guideline released in 1994 stated that in case of drugs or vaccines tested in younger population, the purpose of exclusion for elderly must be clearly defined [36]. As per existing literature, it has been found that the mortality rate is high among the elderly for COVID-19 [37]. In such a scenario, identifying therapies that could improve the outcomes would be necessary. Data based on the evaluation of such therapies in the elderly could be a better guide for clinical decisions rather than the one extrapolated from an otherwise healthy adult population.

***Social Milieu and challenges***

The need to show respect to various social and ethnic groups was more strongly felt after the unfortunate event of the Tuskegee syphilis study [38]. The Belmont report introduced in the aftermath of this incident clearly stated that there is a need to safeguard the rights and interests of racial minorities during enrolment in trials [12]. The concept of showing ‘respect’ means participants from diverse social backgrounds should be treated as per the principles of distributive justice and not manipulated for participation. These principles state that no one should be denied the opportunity to participate if found eligible and willing. Yet, at times limited health literacy, misconceptions related to the pandemic and subsequent ‘*stigmatization*‘may create challenges. In case of COVID- 19, as per WHO, the common reasons for stigma include, lack of awareness and fear resulting out of the ignorance about the disease [39]. In developing countries the issue of social stigmatization could be more prominently seen. For example in India, the families of the patients who succumbed to the disease refused to accept the bodies and perform last rites [40]) Also migrant workers who arrived from different regions were selectively targeted and singled out by community members even after they had completed the quarantine period [40] People who witness such octracism or have themselves faced it are quite likely to overlook the risks in a research study in anticipation of ‘cure’. This could be a major challenge and it is essential for researchers to be sensitive to the cultural concerns that might arise.

Sometimes the fear of social stigma may dictate a participant’s decision to participate. This ‘fear’ may clout their ability to see the risks in a study clearly. Let us understand this with an example, during the outbreak of Zika virus which began in Yap, Micronesia in 2007. During this public health emergency, many pregnant women who were affected had children born with congenital anomalies. Thus, the prospect of giving birth to a child with the disease was associated with significant psychological distress and patients often faced social ostracism [41]]. In a study conducted by Samuel *et al.* in New York City regarding the knowledge, attitude and perception related to Zika Virus infection, it was reported that 46% pregnant women had a fear of stigmatization from the society in case they contracted the disease [42]]. If we evaluate this situation, it is quite possible that many participants would prefer to undertake the ‘risk’ of taking the experimental vaccine rather than getting the disease and facing ostracism. This is an ethical concern where, the decision to participate in a trial for an experimental therapy could be driven more by the fear of social stigma rather than understanding of the research. There is need to show greater sensitivity in such cases and one useful strategy could be counselling the family members and making them actively involved as stakeholders in the research rather than as mere participants.

**Final Thoughts**

The world at present is grappling with a difficult challenge called COVID- 19. While clinical development of drugs to counter this challenge is an important step, ensuring that it is done ethically is more important. In this pursuit, defining who is vulnerable and identifying the challenges with these population is critical. The process of safeguarding the rights of these participants does not necessarily imply denying them participation on assumption of risks.

However, while redefining the eligibility criteria with an ‘all inclusive’ approach , one needs to establish quality safety mechanisms and this will need concerted efforts from all key stakeholders including the investigator, ethics committees, sponsor and the participant.

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