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Ethical Issues in Covid-19 Research.

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1. ABSTRACT

The aim of this narrative review is to discuss ethical issues related to Covid-19 research based on existing literature. This thesis introduces the relevance of the problem, aim and objectives, and the strategy of literature search. The discussion section begins with describing the responsiveness to the pandemic before presenting ethical issues concerning biomedical Covid-19 research. Further on, the ethical issues related to recruiting participants for research trials will be discussed, and lastly, the responsibility of Research Ethics Committee´s in Covid-19 research will be deliberated. The conclusion section (5) summarizes the key points of the discussion and suggestions for future directions in research ethics related to the Covid-19 pandemic.

2. SUMMARY

This narrative review of existing literature on ethical issues in Covid-19 research introduces the relevance of the problem, the aim and objectives, and the strategy of literature search. The discussion section begins with highlighting the responsiveness to

the pandemic before presenting the ethical issues encountered in biomedical Covid-19 research, specifically vaccine development. Further on, comparison of traditional trials and human challenge trials will be discussed. In the second section of the discussion, ethical issues on recruiting participants in Covid-19 research trials will be described including challenges of obtaining informed consent and enrolment of research subjects. The last section will discuss the responsibility of Research Ethics Committee´s during the Covid-19 pandemic including procedural aspects of granting approval on research. In the conclusion section (5), the key points from the discussion are summarized along with suggestions for future directions in research ethics related to the Covid-19 pandemic.

Keywords: ethical issues, Covid-19 research, vaccine development, human challenge studies, traditional clinical trials, ethical principles, informed consent, vulnerable populations, position of REC´s in Covid-19.

3. INTRODUCTION

3.1 Relevance of the problem

The topic of this thesis "Ethical Issues in Covid-19 Research", introduces the ethics, that is, an understanding of the nature of conflicts arising from moral imperatives and how best we may deal with them [1], in the context of research in the Covid-19 pandemic.

The novel coronavirus 2 (SARS-CoV-2) was discovered in an outbreak in Wuhan, China in December 2019. The World Health Organization (WHO) declared the outbreak a public health emergency of international concern on 30th January 2020, and a pandemic on 11th March 2020 [2]. This quickly led to pressure on researchers, regulators and policymakers which created challenges of how to make decisions quickly but safely in a time of uncertainty [3].

Research on pharmacological and non-pharmacological modalities, as well as establishing preventive measures, have been of out most importance during the pandemic as they aid for the rapid alleviation and disappearance of symptoms, limiting interpersonal transmission and amelioration of severe forms of Covid-19 infection, which is beneficial both locally and globally [4].

Challenges on planning and conducting research during Covid-19 have been evident after the implementation of preventive measures to limit the spread of the disease, such as national lockdowns, restrictions in traveling and attending large gatherings, necessity of mandatory face masks, social distancing and so on. Furthermore, fast-tracking vaccine development have created difficulties in carrying out ethically acceptable research as it may come into conflict with the key ethical principles laid out in the 1979 Belmont report, that the conduct of research at any time should focus on respect for persons, beneficence, and justice [5, 6, 7].

3.2 **Aim and objectives**

Aim:

The aim of this narrative review is to describe and understand ethical issues related to Covid-19 research based on literature from open resources, mostly from the periods 2020 to 2023. To achieve this, ethical challenges concerning development of vaccines, inclusion of participants in clinical trials, and the responsibility of Research Ethics Committee´s in Covid-19 research, will be discussed.

Objectives:

1. To describe ethical issues concerning biomedical Covid-19 research. The focus will be on vaccine development and comparison of traditional- and human challenge clinical trials.
2. To describe ethical challenges concerning participant recruitment for research in Covid-19. Specifically, ethical issues with obtaining informed consent and enrolment of research subjects.
3. To describe the responsibility of Research Ethics Committee´s in relation to Covid-19 research and challenges concerning approval of Covid-19 research.

3.3 **Strategy of literature search**

This is a narrative review, a survey of scholarly sources on “Ethical issues in Covid-19 research”. As the topic of this thesis is greatly wide, the intention is to identify and summarize the most relevant information which has previously been published; to provide more potential for individual insight. Hence, in this review, current knowledge regarding this topic is applied in a thematic structure, where relevant theories in the existing research are identified and described.

The relevant literature has mainly been selected from reviews published between year 2020 to 2023. The literature has been searched with keywords such as *"Covid 19, ethical issues, research"* on different databases, mainly Google Scholar and PubMed, where specific articles and reviews have been selected for the basis of this thesis. All references have been uploaded to the application "Zotero", where they have been thematically organized according to themes and topics, and finally added to this paper [8].

4. DISCUSSION

Responsiveness to the Covid-19 pandemic

The Covid-19 pandemic has created extensive interruption to clinical trial research globally, with thousands of trials (around 80%) of non-Covid-19 trials- being ceased or delayed because of the difficulties in continuing under lockdown conditions. Furthermore, the pandemic has seen an extraordinary reorientation in clinical trials research towards Covid-19, redirecting health-personnel away from other fields of studies. Consequently, prior to the pandemic, many patients participated in clinical trials as a last treatment option for cardiovascular conditions, progressive cancer, and other life-threatening conditions; in these patients, the discontinuation of their trials possesses risks to their prognosis and the eventual restart could come too late [9].

Not only has the pandemic disrupted non-Covid-19 clinical trials, but it has also had its effect on all biomedical research that is not directly related to Covid-19. Because of the contagious nature of the novel virus, laboratories have been closed, gatherings such as conferences have been cancelled, supply chains for equipment have been lost along with resources. At the same time, there have been financial losses within academic centers that have had widespread spillover effects on their research operations. Additionally, many researchers were pulled away from conducting and working on clinical trials to work in emergency medical care, especially during the first months of the pandemic in places where the pandemic threatened to overwhelm critical care resources [9].

We have seen some significant structural flaws in the response of the pandemic around the world, however, the clinical trial response to Covid-19 is in part encouraging. Ongoing trials in many cases shifted and made alternative plans in concurrence with

funders and institutions and new trials addressing Covid-19 were fast-tracked in which several existing inefficiencies were identified and streamlined [9].

4.1 **Ethical issues in Covid-19 biomedical research**

Development of vaccines

Vaccines are one of the most effective ways to protect people against infectious diseases and hence, actively promote better health and quality of life. It is shown that safe and effective prophylactic vaccines are significantly more cost-effective measures for public health than repeated application of drugs or other treatments [10]. Therefore, there are many beneficial reasons for the public sector to engage actively in vaccine research and to support the development of new vaccines.

On the other hand, vaccines have always been controversial and the reasons for these controversies include the concerns of safety and adverse effects, disturbing the natural order, persuading individuals to be vaccinated for the public good and the injustices of uneven access to the benefits of vaccines. These controversies raise considerable ethical challenges in the development, public health use and social acceptability of vaccines [11].

By July 2021, there were 184 Covid-19 vaccine candidates in pre-clinical development, 105 in clinical development, and 18 vaccines approved for emergency use by at least one regulatory authority. Understandably, some people were concerned about the speed of this accomplishment [12].

However, issues that come up when planning and conducting research during Covid-19 pandemic as with other pandemics, include the immediate necessity for speed of vaccine research as well as the inherent need for protection of research subjects, which is the greatest concern of research ethics. Usually, vaccine development takes on average a decade as the trial process consists of several steps which need to be conducted systematically and in a measurable pace [13].

The attempts to accelerate vaccine development are associated with efforts to streamline the process. Unfortunately, streamlining may have consequences for the

traditional ethics of vaccine research and development, especially the long-held principle of beneficence and non-maleficence [13].

As SARS-CoV-2 is a coronavirus, it shares similarities with SARS-CoV-1 (Severe Acute Respiratory Syndrome, SARS) and MERS-CoV (Middle East Respiratory Syndrome, MERS). Hence, prior work on SARS and MERS vaccines shortened time spent on pre-clinical assessment of Covid-19, and the target antigen was identified quickly [13].

Two months after the SARS-CoV-2 genome was sequenced and shared, the first phase I clinical trials began, in March 2020. Phase II clinical trials began before phase I ended. In many Covid-19 vaccine trials, phase I and phase II trials were combined to further speed up the progress. However, scientific design was not compromised as the dosage, safety and immunogenicity measures were evaluated. Phase III clinical trials also began before phase II trials were complete. There were even a few trials where phase II and phase III were combined [13].

Overlapping and combined phases of clinical trials, the urgency of a need for a safe and effective vaccine, international collaborative efforts, funding, and pre-planning in manufacturing, allowed vaccine development period to be reduced to about 10 months [13].

Ethical issues emerging from Covid-19 fast-track vaccine research and development include [14]:

- Safety concerns resulting from the accelerating of the research and development process and the use of new technologies.
- Issues related to the early licensing of vaccines and the ensuing impact on the design of trials.
- Challenges posed by the enrolment of study participants and issues regarding informed consent. *(Discussed in section 4.2).*

Safety concerns

There are several requirements that must be fulfilled by vaccine candidates, these include safety, efficacy, and quality. Because of the need to protect people

worldwide, public health ministers, head of states and the pharmaceutical industry have contributed large investments in vaccine research to fast-track the process. Additionally, it pushes governments and societies to a have high expectations for the new vaccines. The uppermost expectation, although with diverse interests, may influence the objective judgement which is required for candidate vaccine safety [14].

For example, mRNA- and DNA- based vaccine technologies are being implemented in vaccine candidates. On one hand, concerns about mRNA vaccine safety have been identified with the most important risks being the possibility that they may generate responses that could lead to inflammation and autoimmune conditions in humans. On the other hand, the safety concerns of DNA-based vaccines involve the possibility that the targeting of DNA into the chromosomal DNA of the recipient will trigger mutagenic effects in the functional gene located in the insertion loci [7].

Prior to the pandemic, fast-tracking candidate drugs was relatively common, nevertheless, the development and approval of a vaccine has never been fast-tracked to this extent. This has led to that, by deviating from standard procedures, and potentially exposing individuals to an investigational vaccine while safety is still being assessed, the health of research participants could be put at risk.
As some Covid-19 vaccine trials were overlapped to shorten the duration of the development, less time was available to identify possible side effects, which might eventually emerge. Consequently, when vaccines are administered to the general population, safety-related concerns persist. The only way to mitigate the risks and provide an ethical justification for the early deployment of vaccines is by implementing a very careful post-marketing safety monitoring plan [14].

Before starting the vaccination campaigns, European Medicine Agency (EMA) and the national competent authorities established a detailed pharmacovigilance plan indicating all the monitoring activities to be carried out after the marketing of the vaccines. On a regular basis, EMA publishes a safety update on each authorized vaccine, providing information on newly observed side effects, as well as warnings and recommendations [14].

Issues in early licensing and study design

The main issues in early licensing and deployment of vaccines could compromise two ethical principles that guide clinical research- scientific validity, which is based on the tradeoff between risk and benefit, and social value, which depends on the short-term and long-term prevention of Covid-19. Moreover, early deployment could interfere with the acquisition of long-term data [14].

Additionally, early licensing of any single vaccine might complicate the evaluation of remaining vaccines; once a vaccine is licensed, new placebo-controlled randomized trials of other vaccines will not be ethically acceptable. According to the Declaration of Helsinki (2013) and to the CIOMS Guidelines (2016), the use of the placebo in the control arm of a trial is ethically acceptable only "when no proven intervention exists." When trials for COVID-19 vaccines first started, the therapeutic validity of the intervention under study was not determined yet; therefore, investigators could randomly assign participants to a placebo or intervention group. However, since the first vaccine was found to be safe and efficacious, though, in countries where such temporarily authorized vaccine was available, placebo-controlled trials could no longer be considered acceptable [14].

In response to this particular ethical issue, the World Health Organization (WHO) published a statement as such: "A candidate vaccine's attainment of emergency use designation does not, in itself, render that candidate the best proven intervention […] Accordingly, the continued use of placebos or active controls in the control arm of current or future trials testing other candidate vaccines […] should not be regarded as violating the Declaration of Helsinki, CIOMS, or WHO's previous guidance." This statement further emphasized that the use of a placebo control can be justified by the social value of the research, and therefore legitimized the conduct of blinded, placebo-controlled vaccine trials even in the context of a candidate vaccine being publicly accessible [14].

Moreover, there have been debates on considering alternative approaches, such as non-inferiority trials, where a candidate vaccine is compared to an already authorized vaccine, to demonstrate that the new vaccine is no worse than the comparator, or controlled human infection (CHI*)* trials, where a candidate vaccine,

after going through phase I safety and dosage trials, is administered to volunteers, who are then deliberately infected with the virus, in order to see how well the vaccine protects them [14].

Comparison of biomedical methodologies

Traditional clinical trials

Usually, a candidate vaccine must go through several phases of clinical trials before it can be licensed. Before a candidate vaccine enters clinical trials, it undergoes pre-clinical assessment, where the target antigen is identified, and the vaccine safety and efficacy are tested in laboratory and animal models [13].

In phase I clinical trials, typically 20-100 otherwise healthy volunteers who haven't been exposed to the disease is being studied. These studies are used to determine whether there are adverse reactions with increasing doses and, if possible, to gain early information about how fast the vaccine induces an immune response in participants [13].

In phase II clinical trials, in the absence of safety concerns from phase I studies, phase II studies include more people, where various dosages are tested on hundreds of people with typically varying health statuses and from different demographic groups, in randomized-controlled studies. These studies provide additional safety information on common short-term side effects and risks, the relationship between the dose administered and the immune response and provide initial information regarding the effectiveness of the vaccine in its ability to generate an immune response. These vaccine studies typically also include a control group consisting of people who may receive a placebo for the purpose of comparison [15].

In phase III clinical trials, the vaccine is generally administered to thousands of people and the study generates critical information on effectiveness and additional important safety data. This phase includes additional information about immune response and compares those who receive the vaccine to those who receive a control, such as a placebo, to see whether the vaccine reduces the incidence of

disease in the ones that have received the vaccine. These studies may also provide identification of less common side effects [13].

After collecting data, regulatory bodies assess vaccine safety and effectiveness before the vaccine is licensed. Usually, going through all of these phases takes up to a decade because of delays caused by writing grant applications, obtaining regulatory approval for trials, negotiating with manufacturers, and recruiting trial participants. [16].

Human challenge trials

Human challenge studies involve deliberately infecting research participants with a disease-causing agent. One benefit of this type of research is that it can result in extensive public health benefits by providing important scientific data regarding host–pathogen interactions and the transmissibility of pathogens. Another benefit to these studies is that it can hasten vaccine development because they often require a smaller number of participants, the duration is shorter, and less expensive than other kinds of studies. Thus, it can enable the efficient selection of vaccine candidates for further investigation in larger studies such as field trials or for monitored emergency use with the ongoing collection of safety and efficacy data [7].

These studies have been done with many pathogens prior to the pandemic, including low virulence coronavirus strains and pandemic influenza virus H1N1. Historically, challenge studies have been shown to generally have a good safety record; nevertheless, there have been cases of serious harms, such as myocarditis among influenza challenge study participants. Human challenge studies have also previously been used to develop vaccines against malaria, typhoid, and cholera, which are diseases with established treatment, therefore, subjects who suffered from deleterious effects after experimentation could be rescued by the already existing treatment. But the application of human challenge studies in Covid-19 is a very different story as there is no standard treatment for this new and highly contagious disease, which creates a problematic risk-benefit ratio [7].

Generally, human challenge studies are ethically sensitive and raise controversial and unresolved issues in research ethics because some study designs can be perceived to involve high levels of risk for healthy volunteers, risks to third parties, and high levels of uncertainty regarding the consequences of infection, especially with novel or neglected pathogens [17]. Despite these ethical controversies, there have been thousands of volunteers from 162 countries who affirmed their enthusiasm to be participants in controlled human infection trials as the need for a vaccine is prevalent in people´s minds and equally necessary from the public health perspective [7].

The ethical justification of Covid-19 human challenge studies would in part be possible if the potential benefits for public health or for participants, outweigh the expected risks. Potential benefits to public health include those arising from the acceleration of vaccine development, the development of more effective vaccines, and the improvement of relevant scientific knowledge that can inform public health practice, for example results regarding protection or the risks of transmission from asymptomatic individuals [17].

Selecting participants at low risk of severe disease (e.g., healthy young adults) would reduce the risk to participants. However, this strategy is suboptimal as the results might not enable accurate estimates of vaccine efficacy in individuals at higher risk of disease (e.g., older people >60 years and those with comorbidities). Though, eventually, if a vaccine for Covid-19 is approved for use, this strategy might at least enable the effective vaccination of individuals at lower risk to indirectly protect those at higher risk [17].

Potential direct benefits to participants

There are several potential direct benefits of being infected with SARS-CoV-2 during human challenge studies. Firstly, participants are exposed to lower infection-related risk than if they are infected in the community, due to early diagnosis and medical care. Secondly, the direct benefit of participants gaining immunity against future infection in a high background risk. Lastly, they might also benefit if they receive an experimental vaccine that results in being effective.

Eventually, participants immunity, whether resulting from challenge infection or an experimental vaccine, might also benefit third parties. Especially if health-care workers are recruited to participate in the studies, because this immunity might prevent health-care workers from becoming infected and subsequently infecting others [17].

Risks to participants

Participants in Covid-19 human challenge studies might face risks both associated with the challenge infection and, in some cases, the experimental vaccine. These risks could be minimized, for example by limiting participation in initial studies to healthy young adults and provide high-quality medical care, including intensive care, if required [17].

Many young adults infected with SARS-CoV-2 are asymptomatic, however, some infections might cause more severe disease. There might be rare severe outcomes (e.g., respiratory failure requiring ventilation) or lasting harms (e.g., long-term respiratory deficits) among participants in human challenge studies. Such risks might be considered acceptable if Covid-19 human challenge studies have considerable expected benefits, and the risks do not entail a major net increase in risk (considering background risks of infection), and there is long-term follow-up of participants and full compensation for any research-related harms. Thus, Covid-19 challenge studies might be ethically acceptable (especially when participants already face a high background probability of infection), even in the absence curative treatment [17].

Risks related to experimental vaccines

Vaccines are usually associated with very low risks. However, experimental vaccines, in some cases, might increase the severity of disease among those who are subsequently infected. Unfortunately, such outcomes have been witnessed in previous vaccine research, e.g., in vaccines against respiratory syncytial virus and dengue virus, in some cases resulting in small numbers of deaths among participants. This might also apply to coronavirus vaccines as vaccine-enhanced disease has been detected in animal challenge studies [17].

Risks to third parties

Regardless of if either high-risk strains or low-risk strains being used to infect research participants, there would be strong ethical justification for infection control measures. This include strict use of protective equipment by research staff and isolating participants to prevent transmission of infection to third parties. The reason why even low-risk strains might sometimes warrant strict infection control is due to potential mutations of the virus [17].

To compare traditional clinical trials to human challenge trials, there is clearly more controversies regarding the latter as it poses participants of greater risks. Essentially, in a traditional phase I trial, new drugs or vaccines are tested in healthy volunteers to determine the safety of the investigational product; the subjects are only given the drug or the vaccine that is being studied, they are never intentionally administered the disease-causing agent. In the case of human challenge trials, the healthy volunteers are deliberately infected with a disease-causing agent so that the researchers can study the host-pathogen interactions [18].

While human challenge trials have been used in vaccine development before, it has been performed when there is already an available and established standard treatment. This treatment would then be given to the healthy volunteer if they were to become seriously ill as a result of intentional infection. Contrary, when human challenge studies were proposed for Covid-19 vaccine development, there was still no effective treatment, which raised several ethical issues [18].

In addition to risks of human challenge studies in Covid-19 research, infection with a novel virus might be associated with high levels of uncertainty and unexpected adverse events might occur. However, levels of uncertainty regarding so-called “familiar pathogens” are often higher than they seem, this might increase the scientific benefits of human challenge studies as such studies might reveal important new findings that can help to reduce risk to future participants in larger studies or improve clinical and public health practice [18].

4.2 **Ethical issues in recruiting participants for Covid-19 research**

Obtaining informed consent

Individual informed consent is a crucial ethical requirement for research. The process of obtaining informed consent involves [19]:

- That the investigator discloses all relevant information about the nature, purpose, methods, risks, potential benefits, and alternatives available of the clinical trial, to the potential participant.
- That the potential participant understands the information provided and understands its relevance to his or her personal clinical situation.
- That the potential participant have the capacity or ability to make decisions after understanding the information provided by the investigator and voluntarily decide to participate in clinical trial without coercion.

Prospective research participants must be able to weigh the risks and benefits of participation, however, this can be particularly challenging in a public health emergency such as with the Covid-19 pandemic due uncertain risks [19].

Challenges for investigators

One of the elements for informed consent is the description of any measurable risks to the subject, an estimate of their possibility, and a description of how to prevent or minimize them. Usually, all research involving investigational therapies bear unknown risks. However, there are typically animal models and earlier clinical trials done in the same or similar disease populations that might provide valid scientific data of potential risks. In the case of Covid-19, almost no research have been conducted which sets it apart from other areas of study. Due to such uncertainty, researchers might encounter challenges in efficiently highlighting potential risks and benefits for the participants. Moreover, individuals usually make their decisions on participation in trials based on the way information is presented to them verbally, rather than reading a written consent form. However, because of clinicians' time constraints during the pandemic, they may limit the ability to sufficiently provide this need for patients, further compromising their informed consent [19].

Challenges for patient-participant

The patients understanding of the information provided depends on clear disclosure from investigators. Therefore, many of the obstacles that make it challenging for researchers to meet these disclosure obligations in the context of Covid-19, also interferes with patient comprehension and robust informed consent [19].

Risk of clouded decision-making

When a patient suffering from a serious infection is requested to participate in a clinical trial, his vulnerability is likely to cloud his voluntariness. Such patients, e.g., those treated in intensive critical care (ICU), receiving high flow oxygen or on mechanical ventilator, would foremost be worried about complications of disease and death. In such patients, their decision-making capacity is impaired due to the severity of their illness, hence making them vulnerable. Difficulties in understanding information about the experimental nature of clinical trial, benefits and risks of the investigational drug, and the concept of randomization-chance, comes in conflict with adequately giving informed consent. In such vulnerable patients, the decision may be influenced by high expectation of benefits and/or low understanding of risks of participation in a clinical drug trial and experimental treatment. This situation is further made complex by challenges of language of consent and literacy level, and communication by physicians wearing full personal protective equipment [19].

When challenges of obtaining consent are met during an emergency, the investigator may consider option of waiving or deferring the consent process. However, the principle of waiver of consent requires strict justification. Ethics committee can authorize research without requiring informed consent from participants if (1) the research would not be feasible or practicable to carry out without the waiver; and (2) the research has important social value; and (3) the research poses no more than minimal risks to participants. The waiver is usually implementable in emergency-care settings, when patients are not capable of giving informed consent, in cases of seizures, sepsis, shock, severe traumatic brain injuries and so on. However, there are some clear issues to ethically justify a waiver of consent in Covid-19 clinical trials as benefits of investigational products

are uncertain and the risks of adverse reactions of investigational products are present, which comes into conflict with principles of beneficence and non-maleficence. Therefore, to grant this type of consent, the research must always be approved by the relevant Research Ethics Committee [19].

Legally authorized representatives

Another option to obtain informed consent when a patient lacks capacity, is from a family member or relative acting as the patient's legally acceptable representative (LAR). In trials conducted with individuals that are incompetent for a limited period of time e.g., hospitalized intubated patients, a deferred consent must be sought; when legal representative is available, their written consent must be followed by the participant´s written consent to remain in the trial once he or she can provide it. However, the investigator needs to be aware of potential issues with consenting the surrogates as 1) the LAR themselves may have their decision making capacity impaired due to the emotional and/or psychological stress of having a loved one admitted to an ICU, 2) the potential disqualification of the patient if/when they regain decision making capacity if they decline to give informed consent and, although less likely, 3) the possibility of reprimand or disciplinary action if the investigator is found to be responsible for research misconduct, specifically coercion or undue inducement [20, 21].

In some cases, for example in Randomized Evaluation of Covid-19 Therapy (RECOVERY) clinical trial, for patients who lacked capacity to consent due to severe disease, and for whom an LAR was not available, randomization could be done with consent provided by a treating physician, who was independent of the investigator conducting the clinical trial, and who would act as the legally designated representative. Consent would be obtained from the patient's LAR or directly from the patient if they recover at the earliest opportunity [21].

Inclusion of participants in research trials

In Covid-19 vaccine development, there is a need of multi-centered research involving participants from various countries. With such type of research, the safety, tolerability, and efficacy of the vaccines would be obtained from different geographic areas, and ethnicities. To fulfil this requirement, the involvement of

countries with limited resources and underdeveloped infrastructure may be of concern as people included become even more vulnerable as research subjects from the ethical and humane perspective. Another concern in this type of research is the availability of an adequate health facility and system to ensure the trial subjects and their families and/or communities to have access to treatment and proper care in case of serious adverse events related to the trial outcomes [7].

In vaccine development, research subjects are sometimes segmented into target groups, which is related to the host distribution of the target disease, for example by gender, age, and specific population in the endemic area. Moreover, a vaccine clinical trial is usually initiated in adult subjects and later continued to more vulnerable subjects such as young children, the elderly, and women. The exclusion of vulnerable groups may diminish trial validity because of selection bias, so they should not be excluded without reasonable scientific and ethical justification, such as an unfavorable benefit-risk ratio [7].

Medical research with a vulnerable group is only justified if the research is sensible to the health priorities of this particular group and the research cannot be carried out in a non-vulnerable group. Additionally, the subjects should benefit from the knowledge, practices or interventions that result from the research [22].

Early evidence shows that some segments of the population are at higher risk either of contracting Covid-19 or being more susceptible to severe consequences of Covid-19 including hospitalization and death. Unfortunately, some of these groups have not been well reached by traditional research design and delivery mechanisms, leading to concerns that some of the groups most vulnerable to the impact of Covid-19 are under-represented in research studies [23].

Any developed vaccine is, by definition, intended for administration to the global population. Yet, the study population of Covid-19 vaccine trials is comparatively much smaller and does not optimally represent the diversity of the intended target population. This issue is exacerbated by vaccines' fast-tracked trials, whose reduced sample size have made it even more difficult to take all demographic groups into appropriate consideration. This hinders the generalizability of the

resulting safety and efficacy data, with under-represented groups being the ones more exposed to unexpected harms [23].

To compensate for this issue, from a justice-based perspective, researchers should design study protocols to allow recruitment through a wide range of routes. Without a good scientific reason, recruitment should not be limited to hospitals, primary care practices or care institutions, but should be enabled through all these routes including those appropriate to reach under-served groups, as they are the most likely to benefit from the candidate vaccine. In the case of Covid-19 vaccine research, these under-served groups consist of those at highest risk for infection, serious morbidity, or mortality, namely, older adults, as well as socio-economically deprived populations, including ethnic minorities [14, 23].

4.3 **Responsibility of Research Ethics Committee´s in Covid-19 research**

Research Ethics Committee´s (RECs) have an essential duty in ensuring the ethical standards and scientific integrity of research involving human subjects. The ethics committee must ensure that the rights of research participants are protected, by assuring that individuals are provided with acceptable and easily understood information and ensuring appropriate strategies to protect participants from potential consequences of the research. [24]. Therefore, the pressure being exerted on medical research during the pandemic must not lead to research or testing of pharmaceuticals on humans without complying with ethical standards applicable to medical research [25].

Getting approval from Research Ethics Committee´s

There were several challenges encountered by RECs during the Covid-19 research review. Ethical issues were associated with the review of complex adaptive trial designs, standard of care, placebo use in vaccine studies, post-trial access, and benefit sharing. Another common ethical concern was potential social value and harms of Covid-19 related research [26].

Most RECs members have debated on the extreme vulnerability of individuals and communities during Covid-19 related research in which stigmatization and prejudice were frequently identified as social harms. The high potential for

therapeutic misconception associated with research was also deliberated on. Many RECs members highlighted that the fear of severe illness or death from Covid-19, increased the risk of therapeutic misconception [26].

Another major ethical challenge in the review of Covid-19 related research was the issues of informed consent. Challenges included procedural and pragmatic aspects of obtaining socially distanced consent. RECs also questioned the adequacy of informed consent due to e.g., significant fear and desperation that could improperly influence decisions to participate in research during the Covid-19 pandemic. Moreover, have been divergent views from RECs on when consent waivers or delayed consent were permissible [26].

RECs chairs and members have highlighted the significant overlap between research ethics and public health equity issues. A consistent example include the prioritization of Covid-19 related research during the national lockdown and the halting of non-Covid-19 related research, including therapeutic clinical trials, HIV and TB research etc. Critical social sciences and educational research was not prioritized, and many RECs members expressed awareness that this may have contributed to increased health-related inequities and structural social harms [26].

RECs have the responsibility to carry out ethics reviews rapidly and approve research protocols that adhere to ethical standards after a rigorous analysis. The ethical acceptability of research can vary throughout its duration. For example, a study can cease to have social value if the question it aims at answering has been answered by another study with high quality evidence. A study can cease to have a favorable risk/benefit ratio if the study intervention is found to be riskier than initially thought, or if an effective treatment has already been found for the condition studied. A consent process could also cease to be adequate if it does not inform potential participants about alternative treatments that are now available and were not available before. Therefore, once a study begins, RECs should oversee its development up until its conclusion [27].

The standard regulations for ethical review by RECs tends to often be too time-consuming to enable full research protocols to be prepared and reviewed at the

onset of a disaster, such as in the context of the Covid-19 pandemic. In such cases, RECs can contribute with accelerating and simplifying protocols and procedures by conducting an initial rapid review of study protocols and continue oversight if studies raise significant ethical concerns. However, these adaptive procedures should not be executed at the expense of safety, especially that of the research participants [28].

The European Commission, the European Medicines Agency and national Head of Medicines Agencies published "Guidance on the Management of Clinical Trials during the Covid-19 pandemic" (2020) for sponsors on how to manage the conduct of clinical trials and how to address questions of safety, risk assessment, and informed consent. The recognized ethical principles of autonomy, beneficence, non-maleficence, and justice must always be respected; therefore, the following rules are to be applied [25]:

> "REC´s should give clear priority to the assessment of submitted studies that are linked to the prevention or treatment of Covid-19 and related illnesses. The assessment of trials on other serious diseases with no satisfactory treatment option should also be prioritized" [25].

> "The free and informed consent procedure must remain in accordance with European and national regulations. It is recognized that national regulations and their application may differ across Europe" [25].

> "In the pandemic situation, the traditional meeting of ethics committees cannot necessarily be organized in the usual, often face-to-face manner. Therefore, the RECs should adopt new working methods, such as secure video conferencing, that are appropriate to the situation, and respect the new rules of conduct concerning the pandemic" [25].

> "It should be possible for RECs to hold extraordinary meetings outside the regular cycle to discuss research protocols relating to treatment, prevention or diagnosis of infections caused by SARS-CoV-2" [25].

> "Responsible RECs must be composed of experts with the appropriate expertise. Regarding the assessment of trials concerning Covid-19, relevant experience and expertise must also be ensured within the Research Ethics Committee" [25].
>
> "Digital communication technologies can speed up administrative procedures. However, the information and communication technology used must be designed in such a way that GDPR-compliant transmission of data is guaranteed" [25].
>
> "In the course of the study, the recording of undesired events and effects and their forwarding and evaluation must also be guaranteed by the investigator. The responsible REC must also be involved accordingly in pending decisions and modifications, e.g., of the protocol in the event of subsequent changes. It is advisable to document all deviations from the inspection plan that are attributable to the pandemic situation. All participants, including the RECs should be informed, without delay, of any changes that are relevant to them during the clinical trial. Where appropriate, a new informed consent may be required" [25].

According to guidelines by the Council for International Organizations of Medical Sciences (CIOMS), research in disease outbreaks should ideally be arranged ahead. Essentially, health officials and RECs should set forward interventions to establish applicable, feasible, and adjustable structures for ethical review and maintenance. For instance, RECs could pre-screen study protocols to aid ethical review in a situation of crisis, and researchers as well as sponsors could plan on data- and sample-sharing that RECs can review in advance [28].

5. CONCLUSION

(1) Firstly, the vaccine development and clinical trial response to Covid-19 has been encouraging throughout the pandemic. Trials related to Covid-19 were fast tracked and several existing inefficiencies were identified and streamlined, allowing vaccine development duration to be compressed to less than a year from the onset of the pandemic. As there have been numerous challenges encountered during

Covid-19 research and development including safety concerns, early licensing of vaccines, challenges posed by enrolment of study participants and issues regarding informed consent, adapting to existing guidelines have helped overcome these challenges to an extent. The ethical issues encountered in Covid-19 research have given many lessons to be brought into the future for similar events.

(2) Secondly, it is of outmost importance that research studies are intended to yield scientifically convincing results by all stakeholders under challenging and rapidly evolving conditions such as in the Covid-19 pandemic. The priority of the research should always be to consider the health of the ones suffering, and to always make sure that participants are chosen fairly, and that there is reasonable justification when populations are targeted or excluded. Furthermore, the risks and benefits of experimental interventions must always be assessed continuously during the development. Usually, when conducting clinical trials of investigational therapy for a pandemic or a disease outbreak in general, ethical challenges that come forth include obtaining voluntary informed consent from vulnerable participants. As researchers are in a rush to discover treatments for a serious medical condition such as Covid-19, all relevant stakeholders should remember that the rights, safety, and well-being of the trial participants are the most important considerations and should be above the interests of science and society. Additionally, with attention to research results, any effective interventions developed, or knowledge yielded, must be made available, distributed, and shared amongst the populations.

(3) Finally, challenges encountered by RECs in Covid-19 research included the ethical issues associated with the review of complex adaptive trial designs, standard of care, placebo use in vaccine studies, post-trial access, benefit sharing, and potential social value and harms of Covid-19 related research. Ethical concerns during Covid-19 research reviews also included therapeutic misconceptions by vulnerable subjects as well as the issues on informed consent in due to e.g., significant fear of Covid-19 that could improperly influence decisions to participate in research. There have also been diverse views from RECs on when consent waivers or delayed consent were acceptable.

Usually, ethical review by RECs to ensure that full research protocols are prepared and reviewed at the onset of a disaster, is too time-consuming. In such cases, RECs contributes with adapting by accelerating and simplifying protocols and procedures by conducting an initial rapid review of study protocols and continue oversight if studies raise significant ethical concerns. In addition, to prevent these adaptive procedures to be executed at the expense of safety, CIOMS (2020) have outlined a set of guidelines on how to manage the conduct of clinical trials and how to address safety, risk assessment, and informed consent.

It is important to address that the ones responsible for upholding ethical principles in research is not only ethics review committees, but also other relevant stakeholders such as researchers, funders/sponsors, regulatory agencies, research institutions, and so on. Therefore, research should be based both locally and internationally in which partners should collaborate and join to prioritize the issues and challenges they are faced with during a pandemic. For example, by regulating research projects that will best assess those challenges e.g., how to conduct research, how to recruit participants, and how to ensure that the research benefits the participants and the communities. In doing this, the health care systems too, may learn from research results themselves, so that they may be better prepared for future pandemics.

(4) In conclusion, as it has been shown, the Covid-19 pandemic has brought forth many challenges in the context of research, but it has also been an accelerated learning process. The rush in designing and launching clinical trials for Covid-19 research has shown us aspects in which clinical trials may be improved, streamlined, or modernized in ways to benefit everyone included in research such as the patients/participants, researchers, and all other relevant stakeholders. The lessons that have been yielded throughout the pandemic should be incorporated into future research to ensure higher quality in accordance with existing ethical guidelines. To fast-forward the progress, taking what we have learned into leadership, preparation and planning must be applied in research before the next pandemic. To build knowledge, it is a necessity to collaborate globally and take lessons from one location and sharing and applying it to the next. To enable this, it

is important to continue recording symptoms, collect adverse safety data etc. all of which should be applied to research methodologies in the service of public health.

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