Original Article

J Nepal Health Res Counc 2021 Jan-Mar;19(50): 148-53

DOI: https://doi.org/10.33314/jnhrc.v19i1.3373

Ethical Characteristics of Research Proposals Related to COVID-19 Pandemic in Nepal: A Retrospective Review

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ABSTRACT

Background: Public health emergency is vulnerable time where maintaining ethical principles is obligatory while doing research, on the other hand, it is the same time when breach in ethics is much likely whenever a researcher is unaware, unprepared or hastens to do research. The aim of this study was to assess ethical issues of the coronavirus disease 2019 (COVID-19) related research proposals submitted during the early stages of pandemic in Nepal.

Methods: Retrospective analysis of COVID-19 related research proposals and their informed consent document submitted to the ethical review board at Nepal Health Research Council was done for the study. The analysis was done as per the National Ethical Guidelines, Standard Operating Procedure for Health Research in Nepal and World Health Organization guidelines for infectious disease outbreak, 2016 under ethically relevant headings. Descriptive data were analyzed in SPSS v24.

Results: The major issues were observed in the informed consent documents where 55% were lacking principal investigator's contact information, 68% not having participant selection criteria, 70% without clear informed consent taking process, 57% without explanation of possible risks. Similarly, 68% of the interventional studies' consent form didn't mention possible adverse events and mitigation mechanisms.

Conclusions: Most of the research proposals related to COVID-19 were devoid of major ethical elements which took longer time for receiving approval and eventually delayed the opportunity for evidence generation in critical time. More attention is needed to increase awareness and to develop capacity of researchers, reviewers, ethics committees and relevant stakeholders at the time of health emergencies.

Keywords: COVID-19; ethics pandemic; research proposals

INTRODUCTION

During public health emergencies, it is important to generate quick evidence to contain the problem. However, in doing so, an inadequately prepared health system, quandary public, insufficient resources and underdeveloped regulatory mechanism may expose research participants to unethical handling and compromised safety.[1-3] In 2016, WHO published "Guidance for Managing Ethical Issues in Infectious Disease" to ensure scientific validity of research and participants' rights and safety during outbreaks. The guidance stated that during outbreaks, there is moral obligation to conduct timely scientific research and at the same time to develop mechanisms to ensure ethical values for research conduction.[4] NHRC, the apical research regulatory body functions to maintain highest ethical standard of health research in Nepal. NHRC has been publishing research ethics guidelines since 1995 with latest version in 2019. The objective of this study is to assess the ethical aspects of COVID-19 related research proposals submitted to ERB, NHRC.[5]

METHODS

A retrospective analysis of the proposals submitted to ERB, NHRC between the periods of February 09, 2020 to July 21, 2020 was conducted. All COVID-19 related proposals which were submitted in the online application system of the ERB were analyzed. The contents of proposals and informed consent documents were analyzed before inclusion of any reviewer's comments. However, for assessing the timeline of review and response, information after the comments were also utilized.

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NHRC, being a responsible body for regulation of health research in the county has established an independent ERB at NHRC and has accredited 52 Institutional Review Committees (IRC's) located at various health academic and research institutes and health facilities with a mandate to follow the 'Guidelines for IRC for Health Research in Nepal' in order to review, approve or disapprove, monitor and periodic report of the activities and progress of IRC to ERB at NHRC. The ERB, NHRC assesses any health related proposals submitted through its online platform, for ethical review before initiating the research in human participants. It follows a structured process of review of research proposals (Figure 1).[4]

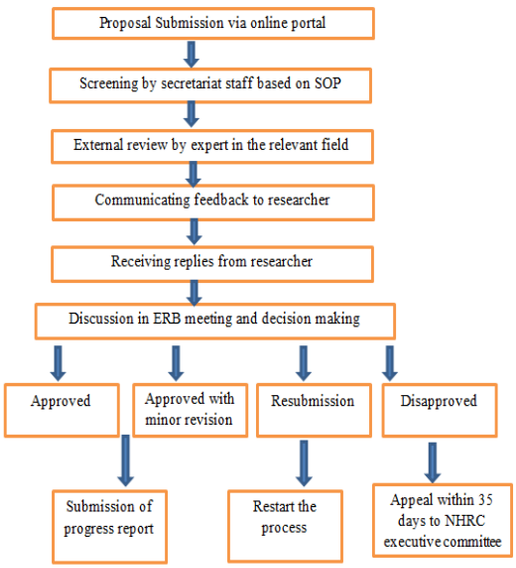

Figure 1.Flowchart showing review process of Ethical review board (ERB) of Nepal Health Research Council.

Once a researcher submits research proposals via an online system, there is first screening by secretariat followed by the external review process by the experts in the relevant field. After that, researchers get feedback from reviewers who are supposed to address the comments (if any) given by the reviewers. Researchers should edit their proposal following the comments and then post it to the online portal. As soon as the researcher responds to all the comments, the 'Status' of the proposal is changed to 'ERB'. Once the proposal is found satisfactory then, the proposals are forwarded to the meeting either Expedited or Full Board based on the risk categorization. The Ethical Review Board which gives either approval, approval with minor revision, resubmission revision or declines the proposal based on the quality of proposal submitted. Normally, an application is reviewed twice a week by the group of experts in the committee. When the COVID-19 pandemic started, the ethical review process was expedited maintaining the standards as mentioned in the latest guideline of NHRC and following the SOP in each step. Proposals related to COVID-19 were identified each day and assigned for review as soon as possible following preliminary administrative and document check, as per the proposal submission checklist by the secretariat staff. Experts in relevant fields were assigned as reviewers of the respective proposals for quick review. Once the reviewer was satisfied with the technical and ethical contents of the submitted proposal, then the proposals were forwarded to expedite or full board review meeting based on the risk categorization. The regular review meetings (one expedite and one full board) are held twice a week or more as per the volume of proposals received for review which were increased during COVID-19 pandemic. From February 9th 2020 to July 21st 2020, 23 expedited and 11 full board meetings were conducted and with emphasis to COVID-19 related research. ERB full board as well as expedited committee meetings were conducted online along with a few in person meetings maintaining social distance as well as using universal public health measures to avoid possible transmission of the disease among the members. Priorities were given to COVID-19 related research, with some space for other research proposals requiring approval based on urgency. Most of the COVID-19 related research proposals were in 'less than minimal risk' or 'minimal risk", category, hence the proposals were preceded through a fast track process, without compromising quality in terms of essential components of a research proposal. Administrative, financial, technical, ethical and documents of the research proposals were assessed. From Informed Consent Document (ICD) , information from following headings were extracted: Introduction of the research, purpose of research, type of intervention, participant selection and voluntary participation, information on Investigative Product (IP) (if clinical trial), procedures and protocol, alternative procedures (if clinical trial), duration of study, risk and benefits associated with research, reimbursements if any, maintenance of confidentiality, sharing of results, independence of the participants through right to refuse or withdraw, alternatives to participation (if clinical trial) and contact details of the principal investigator (mobile, email, landline). In the certificate of consent form, signature or the thumb print of the participant or its Legally Authorized Representative (LAR), signature or thumb print of the witness and the researcher were also assessed. Default entries were excluded from the entry. Ethical approval for this study was taken from Nepal Health Research Council (Registration Number: 537, Year of registration 2020), where the authors were not

involved in any process of review. Ethical approval for retrieval of anonymized information/data was obtained from the ERB of NHRC, where the investigators did not participate in decision making during the proceeding. Conflicts of Interest for authors were declared while making the decision. Anonymity, confidentiality and uniformity of the data were maintained. Data were retrieved in the excel sheets, interpreted in SPSS version 24 and presented as Number and percentage.

RESULTS

Majority of study was observational (91.3%), followed by interventional study (4.3%) as shown in Table 1.

Table 1. Types of study design in research proposals.

Types of study	Number N (%) (n=138)
Observational study	126 (91.3)
Interventional study	6 (4.3)
Diagnostic	6 (4.3)

As illustrated in Table 2 majority of research proposals were related to social sciences (70.28 %) followed by clinical characterization and management 20 (14.44%) as per the global priority set by WHO.

Table 2. COVID-19 related research in Nepal as per the Global priorities set by World Health Organization[6]

S.N.	Areas	Total (%) (n=138)
1.	Virus: natural history, transmission and diagnostic	3 (2.17 %)
2.	Animal and environmental research on virus origin, management measures at the human-animal interface	0
3.	Epidemiological studies	11 (7.97 %)
4.	Clinical characterization and management	20 (14.44 %)
5.	Infection Prevention and control, including health care worker's protection	3 (2.17 %)
6.	Candidate therapeutics Research & Development	3 (2.17 %)
7.	Candidate vaccines Research & Development	0
8.	Ethical consideration for research	1 (0.72 %)
9.	Social sciences in outbreak response	97 (70.28 %)

As illustrated in Table 3, mean duration for approval was approximately 23.15 days and with a minimum time of 4 days and maximum of 57 days from the time of submission to final approval. Also, 52 (37.68 %) proposals were under review process. For proposals under review, non-response from the researcher was the most common reason for delay in processing in all the proposals 34 (68.00 %) as well in the interventional studies 3(60.00 %).

Table 3. Review status for COVID-19 research proposals.

Review Status	Approval and Processing status for all research proposals (n=138)	Approval and processing status for Interventional study (n=6)
Approved (days)	86 (62.31%)	1 (16.6%)
Under review	52 (37.68%)	5 (83.33%)
Reasons for delay for proposals under review	Non-response from the researcher: 34 (68.00 %)	Non-response from the researcher: 3 (60.00 %)
	Expert review: 18 (32.00 %)	Expert review: 2 (40.00 %)
Time from submission to first review request of all proposals (days) (n=138)	1.42±1.99 [95% CI*]	4.00±5.32 [95% CI]
Review time from submission to acceptance for approved proposals (days) (n=86)	23.15±12.52 [95% CI]	40

**CI: Confidence Interval*

Table 4. Different heading of methodology for research proposal.

Different headings	Headings absent or unclear for all research proposals (%) (n=138)	Headings absent or unclear for interventional studies (%) (n=6)
Sample size	27 (19.6)	1 (16.7)
Sampling	8 (5.8)	0
Inclusion criteria	48 (34.8)	0
Exclusion criteria	61 (44.2)	1 (16.7)
Data collection tools	3 (2.2)	0
Statistical analysis plan	3 (2.2)	0

In the information sheet of the majority of the submitted proposals, there is lack of information about the introduction, rationale/purpose and type of study, selection of participants and choice of voluntary participation (Table 5). There is also lack of communication regarding procedure/protocols of research, risk, and benefit to the participant. The information sheet also lacks information about the

duration of study, participants' involvement (in terms of time taken, specimen collection like taking blood, urine, sputum, etc.) and reimbursements to participants. In interventional studies, the majority lacked explaining possible risk and their mitigation measures including insurance or indemnity (66.7 %), duration of study (66.7 %), result / benefit sharing (66.7 %), and providing alternatives to the participant (83.3 %). Similarly, there was no space for signature or thumb print of witness (50%) as well as signature of researcher (16.7%) whereas those in observational studies were not analyzed because most of the observational studies were done via online platforms and verbal consent or consent via electronic media were obtained.

Table 5. Information sheet of informed consent documents.

Headings	Absent or unclear for all research proposals (%) (n=138)	Absent or unclear in interventional studies (%) (n=6)
Introduction of the study	46 (31.88)	0
Purpose of the study	42 (30.43)	0
Type of study design	69 (50.00)	0
Participation selection	94 (68.11)	1 (16.7)
Choice of Voluntary participation	46 (33.33)	2 (33.3)
Protocol information	90 (70.28)	2 (33.3)
Information in drug*		1 (16.7)
Unfamiliar procedures*		4 (66.7)
Side effects*		4 (66.7)
Risks	78 (56.52)	0
Benefits	82 (59.42)	0
Duration of study	95 (68.84)	4 (66.7)
Reimbursements	123 (89.13)	4 (66.7)
Confidentiality	33 (23.91)	1(16.7)
Result sharing	110 (79.71)	4 (66.7)
Refuse or withdrawal	53 (38.40)	2 (33.33)
Alternatives to participant (if applicable) *	-	5 (83.3)
Details contact information of Principal Investigator	76 (55.07)	3 (50.0)

**Drug trials or therapeutic procedures (n=6)*

DISCUSSION

Research forms the important aspect of healthcare response not only at the time of outbreak but also as a guide to develop evidence for future epidemics.[5,7] A state of moral obligation puts the health researcher, funders, healthcare workers, ethical boards, epidemiologist into ethical dilemmas while fast tracking the finding as a part of timely public health response. National research governance system should be aware of the development of the situation during the infectious disease outbreak and make provisions to ensure the advanced and accelerated ethical review without compromising any of the significant protections that ethics is obligated to provide with a goal that the findings are rapidly adapted for the given context.[5] There should also be corroboration that research activities will not drain the critical health related resources and the interventions are likely to be safe and effective.[5] Researcher involved also has a moral obligation to share preliminary results ensuring its quality to participants of the study, public health officials and relevant stakeholders.[5] However, the issues of capacity buildings improved literacy and participation of the community on research and building competency of regulatory agencies were the barriers for ethical governance during Ebola epidemics in local income countries.[7]

Delaying ethical approval is a loss of meaningful opportunity for research in epidemic responses which can happen in low income countries due to lack of infrastructure, trained experts in the Ethics Committee.[8] Studies done in West Africa at the time of Ebola took an average of 35 days with initial review request time of 12.4 days.[9] Similarly, ethical average time during the outbreak situation in one of the hospitals of Henan Province took 2.13 for initial review.[10] Our study took an initial review time of 1.42 days with 23.25 days on average for final verdict on ethical clearance. Only one interventional study was approved in 40 days duration while time from submission to first review was 4.00±5.32 days. Other 5 studies are still awaiting final clearance. This highlights that the process of peer reviewing of research proposals lacks trained manpower for expediting the process which can be in part of the researcher or the peer reviewer or both who have evaluated the manuscript. They should devour the guidelines and SOPs including 'National guidelines for strengthening evidence generation on

COVID-19' published by NHRC before submitting their research proposals for ethical review and should be actively responding to the comments of reviewers. Similarly, members and secretariat staff of the ethics committee should be updated and oriented to ethical issues of research during public health emergencies.

Among the proposals included in this study, majority were observational study whereas only 6 were interventional studies. Two interventional studies were related to Ayurvedic drug trials. Even clinical trials mostly failed in providing information on drugs or the procedures and its side effects, sharing results, as well as providing choice for alternative measures. Most studies did not mention clearly about inclusions (35 %) and exclusion criteria (44%) and clarity on sample size calculations (20%). It is also reported from china that stringent criteria for evaluating interventional study, has reported relaxing inclusion and exclusion criteria and evidence based basis for sample size for pandemic responsiveness. However our study completely lacks even the basis for this heading, which highlights the awareness level of the researcher.[10] In this study, it is difficult to differentiate whether the figures are high mainly due to pandemic situation or due to inadequate knowledge or competency in the part of researcher or insufficient resources of ethical committees which is likely to be exaggerated in crisis situation of a lower middle income country like Nepal.

There is a lack of information to the participants of research in all areas particularly in explanation regarding type and duration of study, details of procedures, risks and benefits. Provision for result sharing which is an important ethical issue for beneficial decision making for public health response during pandemic situations is overlooked almost completely (80%) in all studies and 67 % in interventional studies. This clearly highlights researcher's inadequate level of knowledge on the preparedness of research during a pandemic including not being aware of updated research guidelines and SOPs. Similarly, another reason could be researcher's unfamiliarity with the information technology particularly while submitting proposals to the online portal of ERB, NHRC where the researcher fails to follow the SOPs.

Issues such as failure of timely submission of acceptance letters from the study site, donor agreement letter, Informed Consent Document (ICD), ethical review processing fee also leads to impedance in the research procedure. Absence of documentation of signature regarding participant or its nearest guardian, witness and researcher involved in data collection especially for interventional studies raise a serious ethical issue regarding the proper and ethical collection of data. It is likely that the researcher either neglect or are completely unaware of the ethical values during research[11] or the data might be collected with coercion and documents manipulated during the outbreak situation. For research during the outbreak of contagious disease, verbal consent or consent via electronic media are preferred as this reduces risk of contact and disease transmission between researcher and participants. [12] This seems to be followed by most of the researchers (especially those for observational studies) whose proposals were included in our study. This prevails as a barrier to proper ethical research which is likely to escalate in outbreak situations. Even during usual situations researchers in low income set-up face issues of resource allocation, dilemmas in decision making, respecting autonomy of participants reflecting lack of teaching, discussions and support mechanism on ethical issues.[13] This also generates speculation in our context to whether researches done during pandemic situation are done primarily for public health benefits or a hidden opportunity for academic accomplishments.[14]

Health research in lower middle income countries like Nepal are often sponsored due to limited local funding and conducted as collaborative assemblages of national and international non-governmental organizations.[15] These situations can often have influence on policies and the programs which even call for the need for protecting public health interest and justice during outbreak situations in low- and middle-income countries.

The study didn't assess the scientific basis of the different headings which was submitted. It also didn't follow up what happened truly at the time of conduction of research.

This study was conducted during early phase of COVID-19 pandemic which was also the peak time of pandemic in our country. Our evidence would be stronger if we had done comparative study with the research proposals during normal (non-COVID-19) time. But due to time and resource constraints, it was not possible to conduct such study which is the limitation of this study.

CONCLUSIONS

Most of the ethical components were absent or not clearly written in proposals content and informed consent documents at the time of online submission even for the interventional studies. Mean time for approval of COVID research proposals was within 3-4 weeks through expedited review process. Most of the proposals were sent for the first review request within a few days even

for interventional study after preliminary check. Lack of timely response from the investigator side was the commonest reason for delay. Similarly, timely processing of a high volume of proposals by a limited number of secretariat staff as well as unavailability of subject experts sometimes was also a challenge for the ERB during a pandemic situation. Whenever a proposal lacks major ethical elements or there are technical issues related, then it takes longer time for approval which means there is a loss of opportunity in timely generation of evidence which can be costly to the researcher, participants or the nation as a whole. Although the fast-tracking and proper governance for ethical research during pandemic were managed by an ethical committee during a pandemic situation, lack of awareness on responsible conduct of the research which was likely to breach ethical values for appropriate public health response. Therefore, more attention is needed to increase awareness and develop the capacity of researchers, reviewers, ethics committees as well as of relevant stakeholders at the time of health emergencies.

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