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Revisiting the clinical trial history and regulatory mechanisms in Nepal in the context of COVID-19 pandemic

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ABSTRACT

Presence of Nepal in global clinical trials has been visibly negligible despite the history of conducting large scaled randomized controlled trial on Hepatitis E vaccine decades ago. Majority of the problem is attributed to the lack of collaborative work, financial and human resource constrains. COVID-19 pandemics seems to have triggered urgency among the authorities of Nepal leading to a substantial increase in the number of clinical trials in collaboration with national and international organizations/institutions. Immediately after detection of the first COVID-19 case on 13 January 2020, the Ethical Review Board (ERB) of NHRC received several research proposals, subsequently leading to the approval of the first clinical trial for COVID-19 on 01 July 2020 to investigate potential of traditional Ayurveda based medicine for COVID treatment. Soon, number of other clinical trial proposals received approval and implemented in the country, however budgetary allocation from the Government of Nepal (GON) was prioritized for COVID-19 outrage management and vaccination coverage only. Collaborations with various international institutions played a significant role in the successful implementation of large-scale clinical trials in the country and further laid the path for future. In this review paper we present the recent developments in clinical trials in Nepal, budgetary allocation from the government and the mechanisms in place for regulation of clinical research in the country along with challenges and way forward.

1. Introduction

Clinical trials are prospective systematized searching of evidence to evaluate the efficacy of various biomedical or behavioral interventions using humans beings as subjects [1]. Any new drugs, biological samples, medical devices, surgical and radiological procedures and behavioral therapies receive approval in the market from regulatory authority of respective country only after successful completion of multiphase clinical trials [2]. International Council of Harmonization of technical requirement for pharmaceuticals for human use (ICH) Good Clinical Practice (GCP) defines clinical trials as "Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamics effects of an investigational product (s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy" [3]. Clinical trials help in the development of new treatments for diseases, their diagnosis, and help researchers know what does and doesn't work in humans that cannot be learned in-vitro. The results of clinical trials which are focused only on specific population or age groups cannot be generalized, because of the differences in genetics, ethnicity, immunity, culture, and disease burden [4].

The COVID-19 pandemic has created a significant impact on clinical trials worldwide. The pandemic has demanded for more rational and scientific evidence on the use of drugs and vaccines in the context of COVID-19. Various research on the development of new drugs and efficacy/safety of repurposed drugs are being conducted globally. Fast track Randomized Control Trials (RCTs) are increasingly being practiced, particularly in the context of COVID-19 to evaluate efficacy of drugs and vaccines. Analysis of 62, 252 clinical trials conducted in the United State during the pandemic shows that only 57% of the trials would be taking place if it were not for the COVID pandemic [5].

Despite massive increment in total number of registered trials, clinical trials conducted in various non-COVID dimensions of health are in

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decreasing trends in terms of number of trial as well as participant's recruitment. The impact of massive rise in COVID-19 trials led surgical trials, cancer treatment trial and few other small scaled trials to struggle for participant recruitment and to gain attention from regulatory authority, which was never the case prior to pandemic [6]. In the developing countries like Nepal, clinical trials are still in their infancy, as the majority of health research conducted within the country are descriptive in nature. Meanwhile, the pandemic has uplifted the health research culture in the country, especially sensitizing scientific community and health administrators to conduct clinical trials to generate evidences from people of Nepal. Compared to the pre-pandemic scenario, the awareness about the importance of clinical trials among the scientific community has increased and so has the number of clinical trials in Nepal. There are ongoing clinical trials on drugs, vaccines, Traditional medicinal formulations like Ayurveda etc. in Nepal with the inclusion of local population [7]. Interest of scientific communities to dive deep for evidence generation on this novel disease was further augmented by national regulatory obligations released by different countries. In most of the European countries, this accelerated approval procedure is considered as fast track procedure where different countries released their own guideline but in coherence with member countries within the European Economic Area (EEA) [8]. National Health Service (NHS) has defined criteria to apply under fast-track review as Vaccine, prophylactic early treatment, diagnostic or transmission study of COVID-19 and such study are mandated to publish their interim analysis report or final report within one year of approval. Such regulatory code led path for large scaled clinical research like world's largest clinical trial, Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial [9]. Nepal Health Research Council (NHRC), an apex body of research and evidence generation for health also has taken a major step by developing various guidelines dedicated to promote and regulate COVID-19 research activities in the country in ethical manner [10].

1.1. Regulatory and ethical procedure for conducting clinical trials in Nepal

Nepal Health Research Council (NHRC) is the national apical body for conducting as well as regulating health research in Nepal. NHRC has conducted various health related researches including clinical trial by collaborating with national and international institutions/organizations. Besides that, if any other institutions in the country or researchers want to conduct their health research project, NHRC provides them necessary trainings and monitoring support. The regulatory and ethical support provided from NHRC are not limited to research on mainstream contemporary medical system but also on traditional health systems such as Ayurveda. The Current Applicable National guideline developed by NHRC provides a stepwise procedural guide to conduct clinical trials in the context of Nepal. Designed in coherence with international practices, researchers can navigate their path of conducting a clinical trial with these guidelines where roles, responsibilities and obligations of each stakeholder of clinical trials are detailed [11]. Similarly, the Department of Drug Administration (DDA), national regulatory body of Nepal, acts as a licensing authority to conduct any human trials on new drugs. Any individual or institution with the idea of conducting clinical trials in Nepali population has to submit their documents to DDA, after due regulatory checks, license will be assured for the same and the trial will be considered as valid within the country [12]. Prior to DDA approvals, the person/institution shall obtain permission from the Ethical Review Board (ERB) of NHRC. The ERB requires the clinical trial protocol along with the investigator's profile, clinical trial agreement letter, budget and risk/benefits to the participants involved in the trial. The clinical trial should be conducted as per the principle of Good Clinical Practice (GCP) and other applicable regulatory requirements. Both NHRC and DDA are acting bodies of ministry of Health and Population Nepal (MoHP). Both are autonomous in their decision making process but necessary guidance through policy formation, organization and co-ordination functions are performed by MoHP [13].

Recently, NHRC has extended its function of record keeping via the Clinical Trial Registry in Nepal (NCTR). Registry was developed as a subcommittee of nine members in 2018 which includes representatives of WHO, MoHP, Department of Drug Administration (DDA), NHRC executives, secretariat and staff [11]. NHRC has developed a national guideline for strengthening evidence generation on COVID-19 with prime aim to define priority research areas in COVID-19 related research and guidance to capacity building as well as public dissemination of the findings [14]. Similarly, National ethical guideline for health research has been released in 2022 to make clinical trials and other research activities more ethical and vigorous so that competency of national scientist can contribute world by generating key evidences specially in situations like COVID-19 [10].

2. Materials and methods

We have gathered information on recently approved clinical trials in Nepal from November 2019 till January 2022 from Ethical Review Board (ERB), NHRC by making an official request. Furthermore, data has been collected from various web search on 'google', 'NCBI', 'web of science' 'clinicaltrials.gov' etc. All the relevant articles and data was analyzed and verified official website information whenever possible and final data has been included in this article.

2.1. Historical aspects of clinical trial in Nepal

First clinical trial was conducted in Nepal by U.S. army and GlaxoSmithKline to evaluate safety and efficacy of the hepatitis E vaccine in July 2001. It was officially titled as 'phase II, prospective, Randomized, double-blind, placebo controlled, field efficacy trial of candidate hepatitis E vaccine in Nepal'; the study protocol was approved and monitored by both U.S. army as well as committee from Nepal Health Research Council [15]. First community trial was conducted in Nepal to understand the efficacy of Vitamin A supplementation in reducing preschool child mortality. Study was conducted in 1989 by applying a well-designed placebo controlled blinded structure among 28 thousand preschool children in Terai region of Nepal for which study protocol was approved from NHRC as well as Joint committee on clinical investigation at John Hopkins University school of Medicine, Baltimore, USA [16].

2.2. Clinical trials after COVID-19

2.2.1. July 2020–December 2020

First COVID-19 case was reported in Nepal on 13 January 2020 and took couple of months to incline on daily positive reports [17]. After upsurge of COVID-19 cases, clinical trials on various drugs and vaccines started to boom in Nepalese context. In the initial days of the pandemic i.e, during the first wave, the Nepal Health Research Council (NHRC) took an initiative to observe efficacy of traditional Ayurvedic formulation - Yastimadhu decoction by conducting a trial named 'Clinical evaluation of YASH-T decoction in management of mild to moderate COVID-19 cases: Open label controlled trial'. After due approval on 1st July 2020 from ERB NHRC, the trial was conducted on six different hospitals throughout Nepal including National Ayurveda Research and Training Center (NARTC), COVID-19 isolation centers and zonal hospitals. The study has completed its recruitment and currently data analysis is ongoing.

On 09 Sep 2020 Nepal Intensive Care Research foundation received approval for their proposal to conduct 'REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia'. The Study is still ongoing on four different sites including Nepal Medicity Hospital, HAMS Hospital, Grande International Hospital and Tribhuvan University Teaching Hospital. On 20 Dec 2020, NHRC got approval to conduct a study named 'Efficacy of

Favipiravir in treatment of mild & moderate COVID-19 infection in Nepal: a multi-center, randomized, open-labelled, phase III clinical trial' to conduct study on twelve different hospitals inside Nepal. This study also has completed its participant recruitment and currently the data analysis phase is ongoing.

2.2.2. January 2021–June 2021

Immediately on 27 January 2021, Nepal Health Research Council (NHRC) received an approval for world's largest clinical trial named 'Randomised Evaluation of Covid-19 Therapy (RECOVERY) Trial' in collaboration with Oxford University Clinical Research Unit Nepal (OUCRU-NP) Nepal and OUCRU Vietnam. With the objective of observing all-cause mortality within 28 days of randomization, trial was implemented initially in Shukraraj Tropical and Infectious Disease Hospital (STIDH) and Armed Police Force Hospital (APF). Being an adaptive study design, the study has tested various treatment arms on Aspirin, Colchicine in comparison to usual standard care, then high dose corticosteroid and recently Empagliflozin comparing its effectiveness against usual standard care and sites has been extended further to Nepal Police Hospital, HAMS Hospital and Pokhara Academy of Health Sciences. After successful completion of initial 600 approved participant recruitments, the RECOVERY trial has received approval for an additional 600 participants on all the sites.

Following an initial approval on 8th April 2021, COVID-19 sub-study on Village Integrated Worker Trial is being carried out in Chitwan and Nawalparasi districts of Nepal. Population health research institute also stepped forward amid pandemic to conduct a study named 'Anti-Coronavirus Therapies (ACT) to prevent progression of COVID-19: Randomized trials' and received approval on 02 Jun 2021 for sites B.P. Koirala Institute of Health Sciences, Dharan, Nepal, Koshi Zonal Hospital, Biratnagar, Birat Medical College & Teaching Hospital, Biratnagar, Chitwan Medical College, Chitwan, Karnali Provincial Hospital, Surkhet, Sahid Gangalal National Heart Center, Kathmandu, Mechi Zonal Hospital, Bhadrapur among 100 participants. Study is currently in the participant recruitment phase. Trial is still ongoing with various drug candidates – Colchicine, Acetyl salicylic acid and ribaroxaban.

2.2.3. July 2021–December 2021

A randomized controlled community trial titled "Equip training in Problem Management Plus to Improve Non-Specialist Competencies for Responding to COVID-19 Psychological distress" got approved on 14th July 2021 is being conducted in Kathmandu district from June 10, 2021 to June 30, 2022.

Amongst many registered vaccine candidates, only two study receive approval on 08 Sep 2021. International vaccine institute received approval for conducting a study named 'A parallel-group, Phase III, multi-stage, modified double-blind, multi-armed study to assess the efficacy, safety, and immunogenicity of two SARS-CoV-2 Adjuvanted Recombinant Protein Vaccines (monovalent and bivalent) for prevention against COVID-19'. This study is currently being conducted in Dhulikhel hospital, Dolakha community, TUTH, Kathmandu and Nepalgunj and will be continued till the end of 2022. On the same day another vaccine study also received approval proposed jointly by Yuxi Walvax Biotechnology Co., Ltd./Deurali-Janta Pharmaceuticals Pvt. Ltd. to conduct A Global, Multi-center, Randomized, Double-Blind, Placebo-controlled, Phase III Clinical Study to Evaluate the Protective Efficacy, Safety and Immunogenicity of SARS-CoV-2 Messenger Ribonucleic Acid (mRNA) Vaccine in Population Aged 18 Years and Older on B.P. Koirala Institute of Health Sciences, Dharan. Study will be continued till February 2023. Later on the NHRC collaborated with the George Institute for Global Health, Australia to conduct a trial named 'Australasian COVID-19 Trial (ASCOT) Adaptive Platform Trial' and received an approval on 22 Sep 2021 to conduct a study on TU Teaching Hospital and Bir hospital. Being an adaptive design, trials have been implemented with drugs on various domains such as antiviral domain, therapeutic antibody domain, anticoagulation domain, and other domain. Nafamostat has been added as a new treatment arm in addition to low/intermediate molecular weight anticoagulants (enoxaparin) on different dosages as per the patient's body weight (Fig. 1).

3. Clinical trials and health budget allocation after COVID-19 (LMIC/HIC) - Comparative analysis

. By the budget announcement of 2021, India has allocated US $ 31,030 million in the health sector which is 137% higher than that of the previous year. COVID vaccination program was solely invested with US $ 4850 million in 2021 alone. The majority of the budget was focused on establishing and strengthening of critical care hospitals, diagnostics, health and wellness centers and strengthening public health via the National Center for disease control (NCDC) [18,19]. For health research alone, government of India has allocated 2,663 crores from its budget in fiscal year 2021/2022, which is 26.8% higher than compared to previous fiscal year (2020–2021). whereas in 2020, budget under same heading was only 8.58% higher from previous fiscal year.. This budgetary figure clearly demonstrate that priority of government has been shifted to health research significantly, especially after the hit of COVID-19 pandemic. Also for the first time, government of India provided finance commission grants of 13,192 Crores in health research in 2021 [20]. With a total expenditure of 7.2 trillion yuan in health, China increased total expenditure by about 11% in 2020 compared to last year. Similarly, health expenditure in proportion to gross domestic product (GDP) has reached to 7.1% in 2020 from 6.67% in 2019 [21]. China has adopted wide caliber public health expenditure (WPHE), which means focus of government will be not only on prevention and management of disease but also on broader aspects of healthcare systems such as medical care services, health institutions and health insurance [22]. China had already shifted its pivot on strengthening the healthcare system after releasing a health plan named 'healthy china 2030' in 2016. By then the number of national Clinical Trials centers were 30; with the plan of expanding that number to 100 by 2021 with prime focus of conducting interventional clinical trials and public dissemination via leading journals [23].

Nepal has spent 42.13 billion Nepali rupees managing COVID-19 outrages, which is nearly half of the total budget allocated to the health sector Via COVID-19 active response and expenditure support (CARES) program. The expense is solely occupied for COVID management but not on other aspects of health [24,25]. Total health budget allocation in FY 2020/2021 via the ministry of health and population and other ministries has reached 115.1 billion, out of which 90.6 billion has been specified as a health budget. Highest share of the health budget is with the ministry of Health and population (67%), then local governments (28%) and with provincial governments (5%). The major chunk of the health budget has been allocated for physical infrastructure development, wages and salaries and few mandatory health programs run by the government such as maternal and child health [26]. Federal, provincial and local governments have received budgets in the form of conditional health grants. The budget has been distributed on all three levels under 20 different clusters, health research and surveys being one among them. With the share of 0.2% of total health budget allocated to health, 199 million rupees has been provided to the federal government but provincial and local governments are in budget deprivation i under this section. This budget allocation is 110% higher than that of FY 2019/20. In FY 2020 alone 500 different research projects have been approved by the Nepal Health Research Council [27].

United States of America - For Fiscal Year 2022, $ 131.8 billion has been proposed for the department of health and human services. With a total of $51,953 million, NIH has received 21% incremental budgets than fiscal year 2021 ($42,936 million). Similarly, $41,685 million was allocated in FY 2019 and there was only a 3% budget increment in 2021. This allocated budget has been planned to achieve long term healthcare goals along with dynamic situational handling brought by COVID-19 and its future [28].

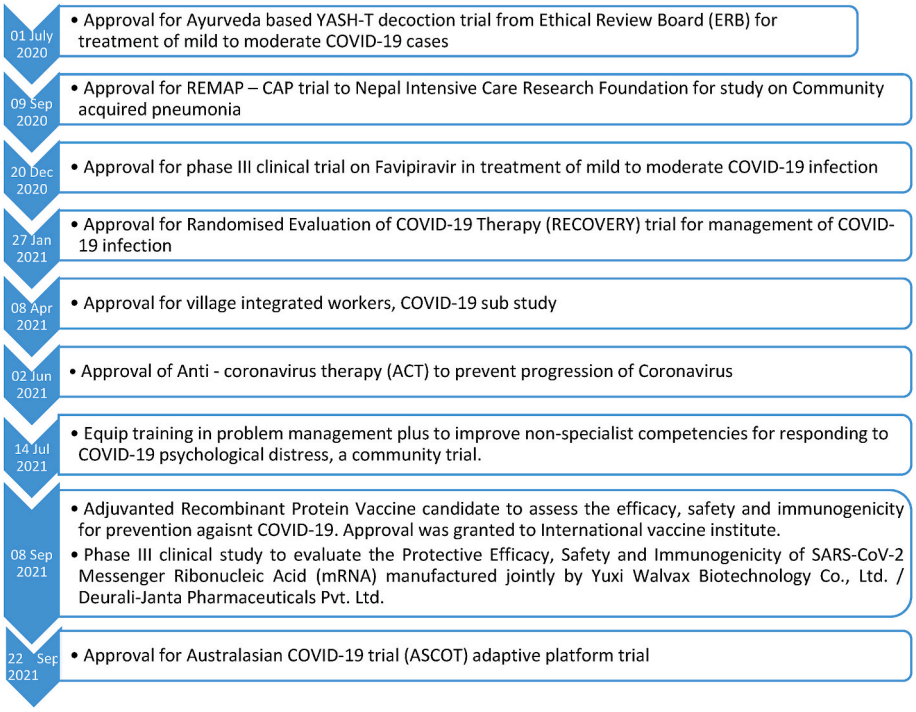

Fig. 1. Pictorial depiction of clinical and community trials approved after COVID-19 Pandemic in Nepal.

United Kingdom - The UK has planned to spend £ 11.35 billion for research and development (R&D) via the department of business, energy and industrial strategy (BEIS) in fiscal year 2021/22. With the priority of recovery from COVID-19, the budget will be spent on innovation, net zero, spaces and so on. Medical Council of UK, major stakeholder of medical research will alone receive £ 791 million, £ 98 million for vaccine manufacturing and innovation grants as well. There is substantial amount allocated for medical research charities as well [29].

4. Ethical, economical and other challenges for conducting clinical trials in Nepal

Conducting clinical trials is a sophisticated process which demands a lot of time, money, discipline and human resource. In the context of Nepal, lack of qualified manpower working on clinical trials is a major limitation. The process of clinical trials requires continuous documentation beginning from the initial screening phase, informed consent, recruitment/randomization of the participants, data entry and recording, data monitoring and every steps performed during the study and that should comply with the principle of GCP. In the principle of clinical trial documentation, whatever is not documented is not done. The incompleteness in documentation can lead to errors in analysis and wrong conclusions on outcome generation. Developing countries like Nepal have a minimal experience in conducting clinical trials due to lack of research capacity and limited resources [30]. During a workshop on clinical trial and systematic review, it has been found that most clinicians and health care workers in the country are unaware of scientific and procedural distinction of clinical trials from observational studies such as cohort study and they are also unaware of international ethical guidelines such as declaration of Helsinki. This fact was sufficient to ignite the culture of clinical research along with developing appropriate skills and awareness that the complex clinical trial process demands [31].

In clinical trials where complex biomedical samples are used, data must be generated from accredited central laboratory within or outside the country where all the bio-samples can be transferred after initial testing at local laboratory. Though there is inherent dichotomy in clinical trial globally whether to set up such laboratories or to rely on locally available data generated by study sites laboratory [32]. Since there are only 19 laboratory registered under category A and out of which four are embedded in hospitals already, Nepal does not have upper hands in such issue due to lack of standardized central laboratory [33]. Similarly, timely clearance of research proposal from national ethical body ERB and institutional review committees (IRCs) is also an issue to implement trials on allocated timeline. There are total of 52 Institutional review committees (IRCs) currently functional in the country who are assisting ERB by acting as first point of contact for any researcher to submit their documents. There is lacking of skilled human resources in IRCs who understands clinical trial and have necessary competency to approve or disapprove proposed study on timely manner.

Though Nepal has made a significant improvement in the field of clinical trials in recent years, most of them have been supported by foreign institutions and sponsors. Despite regular training and capacity strengthening programs, there is no or very less trainings on protocol development, international ethical practice and clinical trial designing, which in the long run will be a limiting factor to conduct such trials independently with local resources and capacity [34]. Since clinical trials are sophisticated and complex in terms of design, implementation and data recordings, it's possible that research teams will not appropriately conduct studies following meticulous ethical standards, especially in resource limited countries where healthcare professionals are already overburdened with the clinical practice. Nandini has expressed further skepticism of participants confidentiality in such a scenario if clinical trials are extended from drug and therapeutics up to contemporary study paradigm such as genetics, precision medicines and oncology [35]. Protocol deviation is a frequently encountered problem in trials regardless of research settings. We can overcome those events without substantial effort because the impact it will create on integrity of collected data may not be significant. But Protocol violation can be of serious threat; without a dedicated research team with necessary knowledge and competency, it would be grueling to maintain data integrity [36]. Countries like Nepal, where clinical trials are being conducted with limited human resources can face such challenges frequently.

4.1. Strengths of Nepal and way forward in evidence generation

Nepal has already demonstrated its ability as a country to implement clinical trials even during the pandemic time by recruiting the highest number of participants after the United Kingdom in RECOVERY international Trial, world's largest ongoing clinical trial on COVID-19. Study was conducted on adaptive design which adds more complexities to it, especially in regulatory perspectives [37]. The Indian Council of Medical research (ICMR), an apex body being actively participated on basic medical research, prevention of communicable and non-communicable disease, reproductive, child health and nutrition and drug development researches in India has signed a memorandum of Understanding (MOU) with Nepal Health Research Council on 04 January 2021 with the prime objective of collaborative research, capacity building and development of regulatory principles applicable to Nepal as well as India. Area of joint collaboration will vary from cross-border health issues, Ayurveda and traditional medicine, tropical diseases, clinical trial registries, research ethics and many more [38]. Similarly, In order to enhance capacity building, synergistic collaborations with the international institutions and exposure of Nepalese scientists to innovative vaccinology research, an MOU has been signed by NHRC with the international vaccine institute (IVI) on 12 March 2021. Working in partnership with such institutions is expected to build research capacity in the country and to impact the public health of Nepal [39].

To initiate and strengthen the capacity of clinical trials in Nepal, early steps are expected at the policy level. The knowledge and experience gap of competent health care professionals in clinical trials can be bridged by giving training and orienting them with theoretical and practical sessions of clinical trials. Stakeholders from Nepal Government, sponsors and CRO need to collaborate for working together and capacity enhancement so that the same team can work in any clinical trial in the future as well. The Government of Nepal can act as a liaison between interested stakeholders for research funding and establishment and implementation of clinical trial units. A national clinical research unit seems a major necessity of the time being to enhance the situation of clinical trials in Nepal. Muhamad et al. suggested that Nepal can develop a research database of its own and further strengthen research institutes functional throughout the nation. In order to conduct clinical research with better quality, national organizations like Nepal Health Research Council (NHRC) should step up and strictly regulate all the studies throughout the country.

5. Conclusion

In Nepal, despite high budget allocation on health, its share on health research/evidence generation is seemingly feeble. Despite many limitations and resources constrains, research activities funded by private institutions, companies and those in collaboration with international institutions have risen significantly on recent times specially after COVID-19. In order to regulate various trials involved with multiple parties, currently applicable national guideline developed in 2005 seems to be outdated in scenarios where there is rapid upsurge of clinical trials in multidisciplinary fields of medicine. Specified guidelines applicable for clinical trials on COVID-19 and any other possible health emergency should be developed differently as practiced by many nations in recent times. International collaboration such as IVI and ICMR will develop research capacity and lead to independent strengthening of activity in the future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

List of abbreviations

ASCOT	Australasian COVID-19 Trial
BEIS	Business, Energy and Industrial Strategy
DDA	Department of Drug Administration
EEA	European Economic Area
ERB	Ethical Review Board
GCP	Good Clinical Practice
GDP	Gross Domestic Product
GON	Government of Nepal
HIC	High Income Countries
ICH	International Conference on Harmonization
ICMR	Indian Council of Medical Research
IRC	Institutional Review Committee
IVI	International Vaccine Institute
LMIC	Low and Middle Income Countries
MoHP	Ministry of Health and Population
MOU	Memorandum of Understanding
NCBI	National Center for Biotechnology Information
NCDC	National Center for disease control
NCTR	Nepal Clinical Trial Registry
NHRC	Nepal Health Research Council
NHS	National Health Service
NPR	Nepali Rupees
RECOVERY	Randomized Evaluation of COVID-19 Therapy
REMAP-CAP	Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia
WHO	World Health Organization
WPHE	Wide Caliber Public Health Expenditure

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