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LETTER TO THE EDITOR

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The negative impact of *ad hoc* committees for ethical evaluation: The case of COVID-19-related research in Ecuador

Ecuador, an Andean country located in northwestern South America, has not made research a priority. Its publication rate (25 docs/million inhabitants) is among the lowest in the Latin American region.[1] This might be partially due to a lack of a national policy on science and technology and government funding for research is low. During the COVID-19 pandemic crisis, funding has been further reduced, as seen in the government´s decision to cut state university budgets.[2] To facilitate health research, in 2006, the Ecuadorian Ministry of Health (EMoH) launched the national regulation for institutional review boards (IRBs) and, in 2015, there were already six fully accredited IRBs in the country.[3] In that year, the EMoH updated the national regulation for IBRs with the Ministerial Order 4889 which, in practice, outlined procedures around the formation of new IRBs and supervision of the existing ones.[4] The ethical evaluation has progressively become a standard requirement of both the authorities and the general Ecuadorian research community.[5] Currently, Ecuador has thirteen fully accredited IRBs anchored to either an Academic (~54% [7/13]) or a Hospital (46% [6/13]) institution.[6] Unfortunately, this progress in the national health research system came with a burden of overregulation by the EMoH. Thus, in Ecuador, according to the national regulation (Ministerial Order 4889), each observational study using biological samples– even if it involves just a collection of blood samples by venipuncture – must be analyzed as a full board study. This same minimal risk study approved by an accredited local IRB must then also pass a second evaluation process in the EMoH.[7] In this process, commented protocols are sent back to the local IRB to approve the suggested modifications through amendments. Due to this back and forth cycle, in Ecuador, it takes an average of between 4 and 6 months to gain final approval for a minimal risk study using biological samples. This overregulation environment has lengthened research initiatives and discouraged researchers and sponsors on the road.

Since the SARS-CoV-2 pandemic began last year in March 2020, more than 80 million cases have been reported worldwide.[8] Major health care bodies like the World Health Organization (WHO) and its regional branch, the Pan American Health Organization (PAHO) have called for alternative and flexible mechanisms and procedures for ethics review and oversight that best suited to the characteristics of each country.[9] For example, in the UK during COVID-19, the Medicines and Healthcare Products Regulatory Agency prioritized and processed clinical-trial applications within a week, and the Health Research Authority reduced the average ethical-review cycle from 60 to 10 days.[10] To efficiently respond to this pandemic emergency and to avoid delays and overwhelming the capacity of local IRBs, PAHO suggested the following evaluation strategies be considered by each national authority: i) Ad hoc committee, ii) National-level committee, iii) (Sub) Regional extra-territorial committee, iv) Provincial or sub-national committee, and v) Institutional-level committees.[11]

Ecuador has been one of the countries in South America most affected by COVID-19, with over 100,000 cases and 20,000 deaths in excess since February 2020.[12] This makes us a suitable community to implement or participate in a wide variety of COVID-19-related studies. Notwithstanding, very early in the pandemic, on April 16, 2020, the EMoH made an unprecedented decision to issue a transitory law, revoking authorization for local IRBs to review and approve any observational study related to COVID-19 that intends to use

[1]Confraria, H., & Vargas, F. (2019). Scientific systems in Latin America: performance, networks, and collaborations with industry. Journal of Technology Transfer. 44,874–915.

[2]Perez Ortega, R., & Wessel, L. (2020). 'We're losing an entire generation of scientists.' COVID-19's economic toll hits Latin America hard. Retrieved October 26, 2020, from https://www.sciencemag.org/news/2020/08/we-re-losing-entire-generation-scientists-covid-19-s-economic-toll-hits-latin-america

[3]Fors, M., Mercado, A., & Castro, K. (2015). Funcionamiento de los comités de ética de investigación en seres humanos en Ecuador. Revista Ecuatatoriana de Neurologia. 25(1-3), 10-16.

[4]Ramos, T.I., Castro, K., Escalante, L.S. & Vispo, N.S. (2017). Advances in clinical research in Ecuador. Therapeutic Innovation & Regulatory Science. 51, 307-313.

[5]Fors, M, Mercado, A., & Castro, K. op. cit. note 3; Ramos, T.I., Castro, K., Escalante, L.S., & Vispo, N.S. op. cit. note 4.

[6]Ministerio de Salud Publica del Ecuador. (2019). Retrieved September 4, 2020, from https://www.salud.gob.ec/wp-content/uploads/2019/04/Lista-de-CEISH-vigentes-abril-2019.pdf.

[7]Fornasini, M., Sisa, I., Baldeón, M. (2019). Las políticas públicas y su influencia en las buenas prácticas de bioética en investigación clínica. Practica Familiar Rural. 4(3), 101-105.

[8]Johns Hopkins University. (2020). Coronavirus COVID-19 Global Cases by Johns Hopkins CSSE. Retrieved January 5, 2021, from https://agers.es/coronavirus-covid-19-global-cases-by-johns-hopkins-csse/

[9]Pan American Health Organization. (2020). Guidance and strategies to streamline ethics review and oversight of COVID-19- related research. PAHO/HSS/BIO/Covid-19/20-0004

[10]Mather, N. (2020). How we accelerated clinical trials in the age of COVID-19. Nature. 584,:326.

[11]Johns Hopkins University. op. cit. note 8.

[12]Registro Civil Ecuador. (2020). Cifras mortalidad 2020 (mortality 2020). Retrieved August 18, 2020, from https://www.registrocivil.gob.ec/cifras/

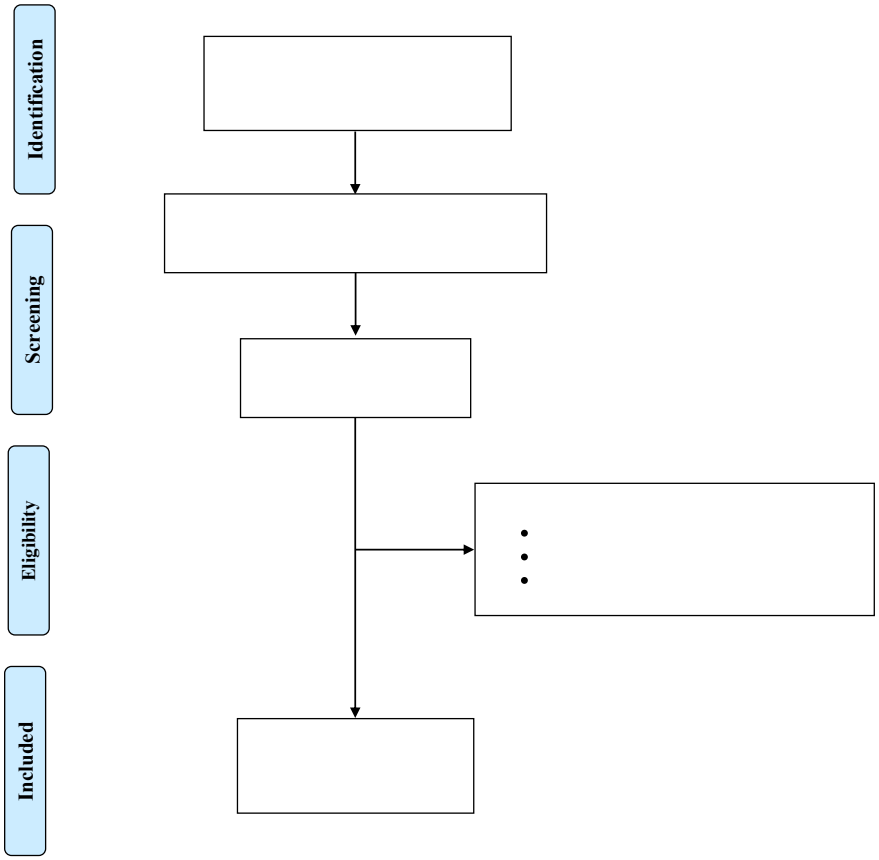

FIGURE 1 PRISMA flowchart [Colour figure can be viewed at wileyonlinelibrary.com]

either biological samples or confidential data (e.g. medical records, imaging records, and any laboratory/procedures results).[13] Under this law, potential research initiatives need approval from an *ad hoc* "Ethics Committee for the Expedited Review of COVID-19 investigations" that belongs to the national authority.[14] This *ad hoc* committee was constituted of seven members where five are health care workers, one is from the civil society, and the last member is a delegate with legal expertise.[15] The stated aim of the committee was to minimize bureaucracy and to speed up the approval process. The group committed to analyzing these proposals in no more than five days.[16] Notably, the committee members work without any compensation for their time.

To provide quantitative evidence regarding this situation, we used PubMed and Scopus electronic databases to conduct a systematic review of Ecuadorian publications only related to COVID-19 from April 17th to October 26th. The implemented search terms were the same in both databases: *"2019 novel coronavirus disease"*, *"COVID19"*, *"COVID-19 pandemic"*, *"SARS-CoV-2 infection"*, *"COVID-19 virus disease"*, *"2019 novel coronavirus infection"*, *"2019-nCoV infection"*, *"coronavirus disease 2019"*, *"coronavirus disease-19"*, *"2019-nCoV disease"* and *"COVID-19 virus infection"*. Overall, we identified 137 publications but only 72 (52.6% [72/137]) remained for the final analysis (Figure 1). Across the analyzed period, we were able to identify only ten observational COVID-19-related publications that used either biological samples or confidential data (Table 1).[17] During the manual assess-

[13]Ministerio de Salud Pública. (2020). Aprobación de investigaciones en salud. Retrieved October 26, 2020, from https://www.salud.gob.ec/autorizacion-de-investigaciones-en-salud/

[14]ACESS. (2020). Acuerdo ministerial 00003-2020. Retrieved October 26, 2020, from: http://www.calidadsalud.gob.ec/wp-content/uploads/2020/04/ACUERDO-MINISTERIAL-00003-2020-REGLAMENTO-PARA-EL-DESARROLLO-DE-INVESTIGACIONES-EN-SALUD-DURANTE-LA-EMERGENCIA.pdf

[15]Registro Civil Ecuador. op.cit. note 12.

[16]Johns Hopkins University. op. cit. note 8; Registro Civil Ecuador. op.cit. note 12

[17]Del Brutto, O.H., Costa, A.F., Mera, R.M., et al. (2020). SARS-CoV-2-related mortality in a rural Latin American population. International Journal of Infectious Diseases. 99, 226-228; Del Brutto, O.H., Costa, A.F., Mera, R.M., et al. (2020). Household Clustering of SARS-CoV-2 in Community Settings: A Study from Rural Ecuador. American Journal of Tropical Medicine and Hygiene. 103(3), 1207-1210; Del Brutto, O.H., Mera, R.M., Recalde, B.Y., Costa, A.F. (2020). Social Determinants of Health and Risk of SARS-CoV-2 Infection in Community-Dwelling Older Adults Living in a Rural Latin American Setting. Journal of Community Health. 15, 1–6; Del Brutto, O.H., Costa, A.F., Recalde, B.Y., Mera, R.M. (2020). Frailty and SARS-CoV-2 infection. A population-based study in a highly endemic village. Journal of Neurology Science. 418, 117136; Marquez. S., Prado-Vivar, B., Guadalupe, J.J., et al. (2020). Genome sequencing of the first SARS-CoV-2 reported from patients with COVID-19 in Ecuador. medRxiv [Preprint]. https://doi.org/10.1101/2020.06.11.20128330; Del Brutto, O.H., Costa, A.F., Mera, R.M., et al. (2020). SARS-CoV-2 in rural Latin America. A population-based study in coastal Ecuador. Clinical Infectious Diseases. 27:ciaa1055. https://doi.org/10.1093/cid/ciaa1055; Del Brutto, O.H., Costa, A.F., Mera, R.M., et al. (2020). Late incidence of SARS-CoV-2 infection in a highly-endemic remote rural village. A prospective population-based cohort study. Pathogens and Global Health https://doi.org/10.1080/20477724.2020.1826152; Freire-Pasquel, B., Vega-Mariño, P., Velez, A., et al. (2020). "One health" inspired SARS-CoV-2 surveillance: The Galapagos islands experience. One Health. https://doi.org/10.1016/j.onehlt.2020.100185; Santamaria, M.G., Riscal, D.B., Beddings, I., et al. (2020). COVID-19: What iodine maps from perfusion CT can reveal—A prospective cohort study. Critical Care. 24(1), 619; Márquez, S., Prado-Vivar, B., Guadalupe, J.J., et al. (2020). Metagenome of a bronchoalveolar lavage fluid sample from a confirmed COVID-19 case in Quito, Ecuador, obtained using Oxford Nanopore MinION technology. Microbiology Resource Announcements. 9(41):e00996-20.

TABLE 1 Ecuadorian COVID-19-related publications using biological samples or medical records and IRB approval, 2020

Papers	Month revised	Month accepted	Biological sample	Confidential data[a]
SARS-CoV-2-related mortality in a rural Latin American population[22]	July 2nd	August 2nd	No	Yes
Household clustering of SARS-CoV-2 in community settings: A study from rural Ecuador[23]	June 16th	July 29th	Yes	Yes
Social Determinants of Health and Risk of SARS-CoV-2 Infection in Community-Dwelling Older Adults Living in a Rural Latin American Setting[24]	N/A	July 15th	Yes	Yes
Frailty and SARS-CoV-2 infection. A population-based study in a highly endemic village[25]	August 10th	September 8th	Yes	Yes
Genome sequencing of the first SARS-CoV-2 reported from patients with COVID-19 in Ecuador[26b]	N/A	N/A	Yes	Yes
SARS-CoV-2 in rural Latin America. A population-based study in coastal Ecuador[27]	June 17th	July 21th	Yes	Yes
Late incidence of SARS-CoV-2 infection in a highly endemic remote rural village. A prospective population-based cohort study[28]	N/A	September 29th	Yes	Yes
"One health" inspired SARS-CoV-2 surveillance: The Galapagos Islands experience[29]	August 30th	October 12th	Yes	Yes
COVID-19: What iodine maps from perfusion CT can reveal--A prospective cohort study[30]	July 24th	October 6th	No	Yes
Metagenome of a bronchoalveolar lavage fluid sample from a confirmed COVID-19 case in Quito, Ecuador, obtained using Oxford Nanopore MinION technology[31]	September 8th	September 21th	Yes	Yes

N/A denotes information not available.

[a]Encompasses information regarding medical records, laboratory results, imaging records, and any other diagnostic or procedure result.

[b]Preprint manuscript registered at medR$_x$iv and posted June 14.

ment of each, including the methods section and the ethics disclosure section, we were not able to confirm that any of these ten published studies had been ethically reviewed by the *ad hoc* committee.

Six out of the ten studies belong to a single research group that used their own institutional IRB, one of the thirteen IRBs previously approved. One published study, using confidential data, was part of a multicenter study and did not obtain a local IRB approval but, instead, used a foreign IRB evaluation to be run. One of the published studies that used biological samples did not state whether they had obtained approval from an IRB or even consent from the study participants to use their laboratory results. Considering the standard requirements of scholarly journals, we find these results difficult to explain. Also, local IRBs are not permitted to revise research proposals seeking to performed population and/or epidemiological studies using aggregate data because these studies will use health records data retrieved from local health care centers. Considering the delays produced by the previous approval process for minimal risk studies, we were not surprised to note that the newly implemented *ad hoc* committee system quickly collapsed. Based on our own and other colleagues' experience submitting COVID-19 research proposals to the *ad hoc* committee, we have estimated a median (interquartile range) time of 45 (30-60) days to receive a first response to the submitted protocols. In most of the cases, the approval decision is still pending after the committee required major changes to the submitted protocols. Moreover, according to the guidelines of this new approval process,[18] there is only one opportunity to resubmit a protocol that received comments from the committee; if approval is not granted directly on the second submission, the proposal will be archived with no further option. Perhaps due to this burden, Ecuadorian researchers have opted to conduct and publish COVID-19-related studies that use biological samples and/or confidential data without the required formal ethical review process; instead, most have obtained only a local or foreign IRB approval as shown previously.[19] Based on our findings and our local experience,

[22]Del Brutto, O.H., Costa, A.F., Mera, R.M., et al. op. cit. note 17.

[23]Del Brutto, O.H., Costa, A.F., Mera, R.M., et al. op. cit. note 17.

[24]Del Brutto, O.H., Mera, R.M., Recalde, B.Y., Costa, A.F. op. cit. note 17.

[25]Del Brutto, O.H., Costa, A.F., Recalde, B.Y., Mera, R.M. op. cit. note 17.

[26]Marquez. S., Prado-Vivar, B., Guadalupe, J.J., et al. op. cit. note 17.

[27]Del Brutto, O.H., Costa, A.F., Mera, R.M., et al. op. cit. note 17.

[28]Del Brutto, O.H., Costa, A.F., Mera, R.M., et al. op. cit. note 17.

[29]Freire-Pasquel, B., Vega-Mariño, P., Velez, A., et al. op. cit. note 17.

[30]Santamaria, M.G., Riscal, D.B., Beddings, I., et al. op. cit. note 17.

[31]Márquez, S., Prado-Vivar, B., Guadalupe, J.J., et al. op. cit. note 17.

[18]Registro Civil Ecuador. op. cit. note 12.

[19]Del Brutto, O.H., Costa, A.F., Mera, R.M., et al. op. cit. note 17; Del Brutto, O.H., Costa, A.F., Mera, R.M., et al. op. cit. note 17; Del Brutto, O.H., Mera, R.M., Recalde, B.Y., Costa, A.F. op. cit. note 17; Del Brutto, O.H., Costa, A.F., Recalde, B.Y., Mera, R.M. op. cit. note 17; Marquez. S., Prado-Vivar, B., Guadalupe, J.J., et al. op. cit. note 17; Del Brutto, O.H., Costa, A.F., Mera, R.M., et al. op. cit. note 17; Del Brutto, O.H., Costa, A.F., Mera, R.M., et al. op. cit. note 17; Freire-Pasquel, B., Vega-Mariño, P., Velez, A., et al. op. cit. note 17; Santamaria, M.G., Riscal, D.B., Beddings, I., et al. op. cit. note 17; Márquez, S., Prado-Vivar, B., Guadalupe, J.J., et al. op. cit. note 17.

we believe that the creation of the *ad hoc* committee for ethical review of COVID-19-related research using biological samples and/or confidential data in Ecuador has become a barrier to the performance of local research due to its lengthy review times. Such delays reported elsewhere have been assessed as impediments to research.[20]

The decision to implement the *ad hoc* committee system in Ecuador would have made sense only if IRBs were not already established here (as was the case in some other countries).[21] We believe that the most appropriate strategy to support COVID-19-related research using biological samples and/or confidential data would have been to select and appoint the most experienced, functional, and robust committees from among the existing Ecuadorian IRBs to conduct the ethics reviews and to oversee approved protocols.

We are aware that not all research protocols should be approved immediately; however, in this pandemic, the rapid generation of knowledge is imperative if we are to defend ourselves against the SARS-CoV-2. Ethical evaluation should be done as quickly as possible so that studies can proceed on time, both during a pandemic and in more usual times.

Unfortunately, what happened in Ecuador shows the negative impact of creating an *ad hoc* committee to overregulate research. The mission of ethical review boards and committees is to protect the rights and welfare of research subjects; however, extensive delays in approval of research protocols caused by unnecessary bureaucracy and centralization are themselves unethical. The practice of bioethics demands (even more during a pandemic time) that we rethink the processes, adapt the existing procedures and search for suitable alternatives – all to reduce obstacles to conducting research. In summary, six months after its creation, the *ad hoc* "Ethics Committee for the Expedited Review of COVID-19 investigations" has not fulfilled its main objective but has severely impeded the execution of COVID-19-related studies using biological samples and/or confidential data in Ecuador. We wish to bring this to the attention of our EMoH authorities to provide the minimal facilities for research activities or, at least, to not create barriers to it; we hope that this might not be the case in other countries.

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[21]Kirigia, J.M., Wanbebe, C., Baba-Moussa, A. (2005). Status of national research bioethics committees in the WHO African region. BMC Medical Ethics. 6:10.