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ETHICAL ISSUES AND ARGUMENTS FOR A LEARNING HEALTH CARE SYSTEM IN THE COVID-19 PANDEMIC

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Abstract: A newly identified infectious agent, SARS-CoV-2, has been the cause of the 2020's pandemic, finding medical practitioners and researchers around the world in need for answers and data to support a course of treatment for a great number of patients, at a time when no specific medicine is known. We aim to review data concerning COVID-19 clinical studies, from the beginning of the pandemic and discuss their ethical framework. Latest data from June 2020 revealed approximately 1200 interventional-recruiting adult subject studies. World Health Organization stated, among other recommendations for COVID-19 research, that individual informed consent is a fundamental ethical requirement for research, even that having an informed consent on paper raises the possibility of contamination risk or a quarantine breach. The ethical considerations of the evaluated studies will be discussed with the framework for the Learning Health Care System, showing that all seven obligations are applicable for the search of treatment for COVID-19. The strongest argument against a Learning Health Care System in outbreaks would be that unethical practices will be carried out in the name of public health or emergency response efforts. From the very beginning of this pandemic, information came from the medical practice, observations made by the physicians that were acting in the best interest of the patient and not necessarily declared researchers, so the line between practice and research became blurred.

Key words: Learning Health Care System, COVID-19, informed consent, ethics.

INTRODUCTION

The end of 2019 found China, specifically Wuhan, confronting with a cluster of patients with pneumonia of unknown origin [1]. Soon after, the beginning of 2020 has been marked all around the world with the deadly threat of the newly identified pathogen-SARS-CoV-2 [2]. On January 30th, 2020, The World Health Organization declared the outbreak a Public Health Emergency of International Concern and soon after a pandemic, on March 11th [3, 4]. As of June 13th, 2020, more than 7.69 million cases of COVID-19 have been reported in more than 188 countries and territories, over more than 426,000 deaths worldwide, but also more than 3.65 million people have recovered [5]. From the beginning of the pandemic until now, the specialized literature "has exploded", new, more and more detailed aspects, being brought to light by recent studies.

The COVID-19 scientific literature, regarded as a "study" body, raises ethical issues about respect for person, beneficence and justice, especially because of the time sensitive issue of this highly contagious pathogen and the impact it has had and is having on health systems around the world. Keeping in mind the previously stated ethical issues, in the face of the pandemic, the question is if there is time for strict research or the beneficence for a greater number of people is gained through a learning health care system when research is necessary even without a careful planning and prior approval. The principles of beneficence and justice govern the entire body of scientific work regarding the search for a COVID-19 treatment, nevertheless without diminishing the relevance of respect for person and non-maleficence. However, medical practitioners around the world found themselves the last few months in a situation where a great number of patients needed treatment, but that specific medicine was not known,

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when the safety of a drug was previously established, would not an action with a potential benefit be better than an inaction? And wouldn't it have been better that all data be recorded, retrieved and shared? It can be considered that in this situation, the "sharp distinction" between research and practice, created by research ethics and guidelines, becomes blurred [6].

METHODS

We have chosen to discuss the scientific literature regarding the emerging pathogen SARS-CoV-2 as a "study" conducted by the research community around the world, respectively identifying the infectious agent observational studies that described the clinical characteristics of the disease, interventional studies for treatment and/or prevention through vaccination.

We have reviewed data from the beginning of the pandemic to the present time, respectively when safety measures have begun to relax in Europe. World Health Organization, PubMed, ClinicalTrials.gov were searched from beginning until 12 June 2020. The search terms used in various combinations were: "chloroquine", "hydroxychloroquine", "CQ", "HCQ", "coronavirus disease-19", "COVID-19", "SARS-CoV-2". These search terms were adapted for use with specific filters for clinical trials and studies, if available, in regards to the ethical framework of the research.

RESULTS

What is particular for this new pathogen is the remarkably short time frame of the outbreak, from the first patient cluster in early December 2019 to the data in the latest World Health Organization (WHO) situation report, respectively 7 410 510 confirmed cases around the world with 418 294 deaths [7]. An illustration of the global impact and fatality in comparison with recent viral respiratory outbreaks can be found in Table 1.

A study submitted to Nature on January 7th 2020, had announced that through the metagenomic RNA sequencing of a sample of bronchoalveolar lavage fluid, from a patient with pneumonia of unknown origin, the authors had identified a new RNA virus strain from the family Coronaviridae, which was named at the time "WH-Human 1 coronavirus" [1], referred during this small time period also as "2019-nCoV" [8]. Just one of the examples of how rapidly changing information is in this pandemic is the fact that by the time the previously mentioned article appeared in the Journal, the virus had already received another name "SARS-CoV-2" (Severe Acute Respiratory Syndrome Coronavirus 2) [9] and the disease an official WHO name COVID-19 [10].

One of the objectives of the WHO reports that followed the January 30th 2020 declaration of the outbreak as a Public Health Emergency of International Concern (PHEIC) is "Address crucial unknowns regarding clinical severity, extent of transmission and infection, treatment options, and accelerate the development of diagnostics, therapeutics and vaccines" [17]. In the search for answers to these crucial unknowns, in a few months a great deal of scientific literature has been shared.

After identifying the infectious agent, another challenge for healthcare workers was identifying the source and epidemiology. For example, coronaviruses were known to be zoonosis, human diseases with animal reservoirs of the pathogen [18] and after finding a link in the cluster of initial patients to the Wuhan's Huanan Seafood Wholesale Market (a wholesale fish and live animal market selling different animal species

Table 1. Comparison between: Severe acute respiratory syndrome (SARS) caused by SARS-CoV-1, Middle East respiratory syndrome (MERS) caused by MERS-CoV and Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, adapted after Outbreak of a new coronavirus: what anaesthetists should know [16]

	SARS	MERS	COVID-19			
Timeline	November 2002 to July 2003	June 2012 to present	December 2019 to January 2020	December 2019 to present	Italy (January 30th2020[12] to present)	USA (January 20th 2020 to present) [14]
Confirmed cases	8096	2494	12 404	7,799,243 [11]	236,305 [13]	2,126,483 [15]
Fatality	744 (10%)	858 (37%)	259(~2%)	429,850 (~10%) [11]	34,223 (~16%) [13]	117,031 (~12%) [15]
Global impact	26 countries	27 countries	26 countries	188 countries		
Date of virus identification	April 2003	October 2012	January 7, 2020			

[1]), research suggested due to the strain resemblance that bats were with high probability the animals in question [1, 8, 19]. Other work supports a cross-species transmission and suggests that snakes are a probable virus reservoir for human infection [20, 21]. Thus, the scientific consensus remains that COVID-19 has a "natural origin" [22].

With the animal to human link researched, regarding human-to-human transmission it is primarily via small droplets produced by an infected person or contact with contaminated surfaces [23], with articles supporting the possibility of fecal-oral, kissing, intimate contact transmission [24, 25].

We have structured our results regarding the ethical framework the following way: observational studies (initial research after the identification of the pathogen) and interventional studies for COVID-19 – complete clinical studies for the most discussed drug hydroxychloroquine.

An article in the New England Journal of Medicine constructing a parallel with previous epidemics aims to provide a summary of study designs for researching the epidemiology of COVID-19, underlining that simple counts of the number of confirmed cases could be a misleading indicator for the epidemic's trajectory because they are limited by problems of access to care, laboratory testing, or when only patients with severe cases are tested [26]. To describe the clinical and laboratory features of the disease, several studies were undertaken in China during almost one month (Huang C, Wang Y, Li X, *et al*. [27]; Chen N, Zhou M, Dong X, *et al*.[28]; Li Q, Guan X, Wu P, *et al*. [29]; Song F, Shi N, Shan F, *et al*. [30]; Chen L, Liu HG, Liu W, *et al*. [31]; Wang D, Hu B, Hu C, *et al* [32].

In Table 2 we have underlined the claimed ethical framework for the previously mentioned studies, thus these were mostly retrospective studies, on small numbers of patients, for which the ethical approval of an Institutional Review Board (IRB) was sought and given with a certain leisure regarding informed consent (waived/ oral consent). All the subjects included in the studies were confirmed COVID-19 patients. A literature review regarding clinical characters showed that the studies previously mentioned indicated that the main clinical manifestations of COVID-19 were fever (90% or more), cough (around 75%) and dyspnea (up to 50%) and a small but significant subset had gastrointestinal symptoms [33].

The initial treatment course in the short period when scientists were figuring out what they were dealing with, in regards to the new pathogen and its clinical and laboratory characteristics, was advanced supportive respiratory treatment and symptomatic

Table 2. Ethical framework for observational studies

Study	Design	Ethical framework	Observation
A [27];	-Prospective data collection and analysys; -patients with laboratory-confirmed 2019-nCoV infection [27]; - data collection from electronic medical records using standardized forms.	- approval from National Health Commission of China - Hospital Ethics Commission	**-Waived informed consent (IC)**
B [28];	-retrospective, single-centre study; - patients diagnosed as having 2019-nCoV pneumonia [28]; - data from patients' medical records.	- Hospital Ethics Committee	**-IC obtained**
C [29];	- Data collection using standardized forms;	- approval by National Health Commission of the People's Republic of China as a „continuing public health outbreak investigation"[29]	**No IRB approval**
D [30];	-retrospective study. - data colection included: clinical, laboratory data and CT images.	- approval from the committee of Shanghai Public Health Clinical Center	**-IC not mentioned**
E [31];	- clinical data, laboratory and CT images.	English version not found	
F [32];	- consecutive patients with confirmed nonspecific interstitial pneumonia	-approval by the Hospital Institutional ethics board	**Oral consent**

care [27, 28]. When the resemblance to other viruses that caused recent epidemics was detailed, several compounds were proposed for having therapeutic potential such as remdesivir, lopinavir/ritonavir and interferon beta [34]. As none of these drugs were approved treatments for COVID-19, no other efficient compounds were available, rapidly increasing number of cases and fatality, with a precedent established by Monitored Emergency Use of Unregistered and Investigational Interventions for the Ebola outbreak [35], the COVID-19 patients began receiving antiviral treatment.

One example of such a drug, that raised debate in research and practice during this period was Chloroquine for the Treatment of COVID-19. This is a drug used worldwide for more than 70 years, with an established clinical safety profile, for which review identified six relevant articles which showed that clinical research was justified as there were pre-clinical evidence for the effectiveness of chloroquine in treatment of COVID-19 and also reasonable evidence for safety from the long-time use in clinical practice [36]. The article also pointed out the ethical issues with this treatment, respectively is it experimental, thus requiring ethical trial approval or an off-label indication ethically justifiable the best available treatment.

At the beginning of the pandemic, the only completed study, which appeared on "clinicaltrials.gov" was regarding the use of hydroxychloroquine as treatment for COVID-19 infection, to cure and to limit transmission and to curb the spread of COVID-19 in the world. This was a small study, conducted only on 30 subjects, the including criteria being the confirmed viral pneumonia in adults, with several excluding criteria- primary in relation to previous diseases of the patient. One cannot help to consider this a form of overprotection for some and under protection for others; especially because it was known at that time that the virus affects older, sicker people in a severe way and they would have been the ones to benefit more [37].

At the moment, on "clinicaltrials.gov" there are 127 COVID-19 studies completed, most of them are from Europe-62 (France-21, Italy-12, UK-5), China-22, Turkey-14, and 12 from North America. Of these only 35 are interventional and mostly from China [38, 39].

Meanwhile, hydroxychloroquine has become one of the most publicized substances used in the treatment of COVID-19, so we analyzed data on the following studies that had, among the drugs used, hydroxychloroquine. We have found on "clinicaltrials.gov" two completed studies that used hydroxychloroquine, having 30, respectively 60 participants. Among the inclusion criteria it is listed symptomatic infection with COVID-19 and for exclusion criteria besides severe heart, kidney, brain, blood diseases or other important systemic diseases there are other criteria, such as participants with retinal disease, hearing loss or history of alcohol or drug addiction in the past 5 years [40, 41]. In Table 3 is underlined the claimed ethical framework for the two previously mentioned studies. Latest evidence has led to the decision communicated by WHO on 17 June 2020, respectively to stop the hydroxychloroquine (HCQ) arm of the Solidarity Trial for the search of an effective COVID-19 treatment [42]. The arguments for this action were based on evidence from the Solidarity trial, UK's Recovery trial and a Cochrane review of other evidence on hydroxychloroquine [42], thus illustrating the ongoing, constantly changing and controversial search for treatment in the face of an emerging pathogen even in the 21st century. What is relevant here, in terms of respect for person and beneficence, is the constant re-evaluation and monitoring of risks and benefits ratio, favouring the research subject not the quest for knowledge.

We are also pointing out that, at the beginning of this research-March 2020-on "clinicaltrials.gov" were 30 interventional-recruiting adult subjects- studies, the subsequent searches have revealed a number of 54 studies almost in one week and approximately 1200 interventional-recruiting adult subjects studies in June 2020[43] of which only 9 with the informed consent document available online [44]. However, this is for certain not an indicator of unethical research and it is just a problem of access to information.

The necessity of ethical supervision over the

Table 3. Ethical framework for two completed clinical studies [40, 41]

Study	Design	Ethical framework	Observation
H1 [40]	-Prospective study; -Treatment-naive patients with confirmed COVID-19	-approval from Ethics Committee of Shanghai Public Health Clinical Center	**-Written informed consent (IC)**
H2 [41]	-Prospective study;	-approval from the Ethics in Medical Research Committee of the Shahid Beheshti University of Medical Sciences	**-Informed consent form used**

entire research body should not be undermined thus an approval from an ethics committee/ board, such as IRBs, is essential as it will evaluate the proposed research protocol, safeguarding the ethical principles not solely in regards to the process of informed consent or study subject selection and should be accessible and prompt given the time sensitive scenario [45, 46].

DISCUSSIONS

Kass and Goodman proposed a framework for the Learning Health Care System (LHCS) that stipulating seven obligations: "1) to respect the rights and dignity of patients; 2) to respect the clinical judgment of clinicians; 3) to provide optimal care to each patient; 4) to avoid imposing non-clinical risks and burdens on patients; 5) to reduce health inequalities among conduct responsible activities that foster learning from clinical care and clinical information; and 7) to contribute to the common purpose of improving the quality and value of clinical care and health care systems" [47]. The rigorous framework for research, where research provides guidelines and regulations, first of all aims to protect patients and volunteers engaged in research from any "exploitation, abuse, or unnecessary and unjustified risks" [6, 48]. WHO has summarized and published the "Ethical standards for research during public health emergencies: Distilling existing guidance to support COVID-19 R&D" [49], beginning with underlining the need to conduct research during public health emergencies and that the ethical standards must be met in all actions, meaning that all research should have scientific validity, social value, reasonable risk-benefit ratio, fair and voluntary participation, collaborative partnership, independent review, equal moral respect for participants and affected communities [45]. In supporting the LHCS for treatment search in global emergencies, particularly COVID-19, we have discussed each obligation of the framework presented by Kass and Goodman [47].

1) "to respect the rights and dignity of patients" [47], thus respecting autonomy, having as a tool the valid informed consent of the patient/subject is a common feature for both research and practice. The strict current research oversight system followed a scandal-ridden period in which people were included in research and exposed to considerable risk without their knowledge or consent [50]. In the face of this pandemic, some patients might be unconscious and the next of kin in distress, either in isolation or quarantine, thus obtaining written IC even if it is time consuming and could be considered as an increase in the risk of exposure of several individuals to the pathogen agent would still safeguard the rights and dignity of patients. Having an informed consent on paper from an infected patient will be a contamination risk for the researcher and having the informed consent from the families in isolation will be a breach of quarantine, thus some variations that would facilitate the actions as oral or a form of technology based process could help bypass these issues, supported also by WHO recommendations for COVID-19 research that state "Individual informed consent is a fundamental ethical requirement for research. Prospective research participants must be able to weigh the risks and benefits of participation. This can be particularly challenging in a public health emergency because of uncertain risks and the perception that any research-related intervention must be 'better than nothing'. Consequently, researchers and review bodies have an obligation to ensure that research activities do not proceed unless there is a reasonable scientific basis to believe that the study intervention is likely to be safe and efficacious and that risks to participants have been minimized to the extent reasonably possible." [49].

2) "to respect the clinical judgment of clinicians" [47], for most patients that fell ill with COVID-19, the clinical judgment of their doctor was the only element that benefited them, adjusting a course of action from guidelines of similar disease, brought benefit to the life of the patient in contrast to not doing anything.

3) "to provide optimal care to each patient" [47], first of all as Kass and Goodman stated the "impact of a learning activity on net clinical benefit is specific to the particulars of the activity and the related clinical context, but it is morally essential that such assessments be made in a learning health care context" [47], thus "optimal" in the case of COVID-19 where we have no known course of treatment as evidence-based guidelines and changing recommendation, is actually trying a drug for which the efficacy was established on a "reasonable" scientific basis.

4) "to avoid imposing nonclinical risks and burdens on patients" [47], with the exception of a small number of studies accepting healthy volunteers, phase 1 studies for vaccines, all other interventional research does not imply nonclinical risks and burdens on study subjects, as it is performed in a situation where research is medical practice, having no other evidence-based course of action.

5) "to reduce health inequalities among populations" [47], as the virus spread all over the world, in Romania as well, it does not seem to choose whom it

infects (there was an apparent sensibility in the elderly) why does research have to choose who benefits and who does not? This pandemic is not a problem of a cluster of patients but of all humanity and all health systems not just research groups.

6) "to conduct responsible activities that foster learning from clinical care and clinical information".

7) "to contribute to the common purpose of improving the quality and value of clinical care and health care systems" [47], these are the main arguments that support a LHCS in the search of treatment for COVID-19. Responsible medical activities in medical practice for the benefit of each patient that would and should foster learning and contribute to the common purpose of improving clinical care and health care systems. We find here the relevance of a balancing act between the need to protect and respect individual participants and the social value to improve care quality [48]. Furthermore, this scenario has found the physicians and medical researchers accepting that the universal ethical standards of research may be adapted to particular circumstances and contexts. The rigor of research ethics in this situation, even when we are discussing research on human subjects will not help but bent in the need of "Better evidence about what helps or doesn't help during an emergency is needed in order to improve the response to global health emergencies. Research conducted during an emergency itself plays a crucial role in obtaining this evidence, and helps support the immediate response, as well as learning for the future" [51] as it is the report that aims to identify ways to conduct ethical research during emergencies [51].

The fear but also the strongest argument against a LHCS in outbreaks is that unethical practices will be carried out in the name of public health or emergency response efforts, which as history has taught us is one of the traps of the quest for knowledge. All the literature regarding the ethical considerations in infectious diseases outbreaks, even if it maintains the research-practice distinction, has a few constant elements: providing ethics review as fast as possible, collaboration between national and international organizations, integrating research into broader outbreak response efforts, thus underlining the need of collaboration and dissemination of information in a time sensitive matter [51, 52].

In conclusion, from the very beginning of this pandemic, information came from the medical practice, observations made by the physicians that were acting in the best interest of the patient and not necessarily declared researchers. As the search for treatment began, finding themselves in the face of an unknown enemy, as more and more people were dying, the use of drugs in off-label indication until a specific medicine was created, was the first course of action. It became a recommendation and the response had to be observed, so the line between practice and research became blurred. We consider that the blurred line allowed a greater number of patients to receive the optimal treatment and in terms of published literature for some of the studies there could be an issue with peer review.

When it comes to new drugs, when safety has to be proven, very few studies showed the enrollment of healthy volunteers, as it would be expected. IRB or a form of research ethical oversight has to be provided to ensure respect for persons, scientific validity and social value with the reasonable risk-benefit ratio.

We do not consider that providing only symptomatic medical care until a course of treatment had been checked and double checked on a relatively small number of patients, would have brought beneficence and social value.

Conflict of interest

The authors declare that they have no conflict of interest.

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