Challenges of a tertiary hospital's clinical ethics research committee in evaluating research during the COVID-19 pandemic. The CEICOV study.

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ABSTRACT:

Background: The COVID-19 pandemic led to an increase in research activity worldwide. The Vall d'Hebron University Hospital Research Ethics Committee (VH-REC) adapted its procedures to give out the opinion rapidly. We aimed to describe the characteristics of the VH-REC activity and studies evaluated during the first outbreak. **Methods:** Clinical trials (CT), post-authorization studies (PAS), and research projects (RP) on COVID-19 were included and followed-up. Variables were described through usual descriptive methods. **Results:** 157 studies were evaluated: 10 CT, 16 PAS and 131 RP, in 25 bi-weekly online meetings. Non-commercial, unicentric and national studies predominated (95%, 54% and 88%, respectively). The main objective of CT and PAS studies was to test efficacy and safety, and for RP to describe patients' outcomes. Some studies focused on specific interest groups, such as healthcare professionals or immunosuppressed patients (10% both). The median time of protocols' evaluation was 3 days. 58.6% (92) required further clarifications, mainly due to aspects of data protection, informed consent, and biological samples. The final opinion was favourable in 93% (146). Regarding follow-up, 123 studies had been initiated and 64 also finalized. Results have been published in 59% (51) of studies. **Conclusions and implications:** COVID-19 pandemic has led to greater academic and local research, especially through research projects. Electronic sources were implemented for evaluation shortening and ease follow-up. These measures should remain to streamline VH-REC processes, and trends to publish results favoured. This study could allow comparisons with other activity periods (e.g. pre or post-pandemic), or with other REC's.

What is already known?

- Literature published until now scarcely offers information on ethical research during the pandemic.
- The need for rapid results can pose a risk for rigor and ethics, thus some guidance documents were published offering strategies for Ethics Committees.

What this study adds:

- Here we provide the perspective of a Clinical Research Ethics Committee (REC) on the research performed during the first outbreak of the COVID-19 pandemic.
- Further information is needed on other periods and committees to contrast the generalizability of our results.

Clinical significance:

- The activity of our REC during the COVID-19 pandemic can provide knowledge in case of future health emergencies.
- REC members acquired an active role on protocol elaboration and ensured researchers collaboration to avoid redundancy, small studies and patient overexposure to research, while promoting more solid evidence on COVID-19.

MAIN TEXT

Introduction

The coronavirus disease 2019 (COVID-19) pandemic due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is undoubtedly responsible for one the most serious and unprecedented health crises in recent history [1].

Adjustments and adaptations to the pandemic have entailed a huge challenge for society and the health system. The need for biomedical research has been especially important to find therapeutic strategies that contain the spread of the virus and mitigate its effects. Carrying out quality clinical trials and other research projects that generate evidence and reduce uncertainty in decision-making is not only necessary, but moreover, a moral duty. Only in the World Health Organization (WHO) platform of international clinical trial registries, there are 912 records regarding COVID-19 between March, 9th and April, 26th 2020 [2-5].

Catalonia is an autonomous community located in the northeast of Spain with around 7.5 million inhabitants. It currently has 23 active Clinical Ethics Research Committees (RECs), responsible for evaluating research with medication products, and guaranteeing the safety and quality of these trials. The Vall d'Hebron University Hospital´s REC (VH-REC) was established in 1993 and is one of the largest research ethics committees in Spain. It is responsible for the ethical conditions that should govern investigations involving human beings in 35 tertiary and primary care centres. It carries out the evaluation and follow-up of more than 850 investigational studies per year. It is formed by twenty-three members with a multidisciplinary composition: seventeen health-care professionals (which include five clinical pharmacologists), two pharmacists, a lawyer, an expert in data protection, a representative of patients' interests, and a member of the technical secretariat. Ordinarily, the meetings are face-to-face and take place on a weekly basis, with an established quorum of attendance of at least half of the REC´s members plus one [6].

Investigators send the research protocols as categorized into clinical trials (CT), post-authorization studies (PAS) or research projects (RP) and other study documents electronically. After being formally validated by the technical secretariat, they are mainly evaluated by clinical pharmacologists and then submitted to subsequent deliberation with all the members of the REC in the corresponding plenary session [7].

However, the need for rapid results during the COVID-19 pandemic can pose a risk for rigor and ethics, as erroneous information may be generated and patients who participate in clinical studies may be endangered, both physically and in their rights [4, 8-9]. It is in this area where RECs play an important role. This stressful situation has been particularly challenging for RECs worldwide, which have had to adapt to these new circumstances. Part of these adjustments have meant shifting to strictly virtual online meetings, making decisions on how to collect consent from patients, and accelerating the evaluation and approval of studies [10-12].

The WHO, the Spanish Bioethics Committee, and other international associations have published guidance documents with strategies aimed at expediting the ethical review and oversight of research related to COVID-19. In Spain, the clinical trials coordination group of the Spanish Medicines and Health

Products Agency (AEMPS, from its acronym in Spanish) agreed on initiatives that included: I) the need to prioritize COVID-19-related studies with an accelerated evaluation within a maximum of 15 days, II) virtual online meetings and III) the acceptance of a minimum of three members of the REC to fulfil the quorum requirements (being only the presence of the patient's representative mandatory) [13-16].

Literature published during the pandemic until now scarcely offers this point of view of today's ethical research. In the few studies published on this matter, it is evident that clarifications prior to study approval have been requested, especially regarding informed consent (IC) and data protection. The Ethics Committees should be aware of this situation and take into account ethical commitments that include special protection to patients in the frame of the current health situation [4, 16-19].

The main objective of the study CEICOV (from its acronym in Spanish, ***C****omité de* ***É****tica de* ***I****nvestigación: análisis de estudios* ***COVID***) is to present the process of updating work methods to include, among others, the faster evaluation of studies by VH-REC that we were required to adopt during the pandemic. We also describe the main characteristics of the studies presented during the pandemic. Furthermore, we conducted a follow-up of these studies in order to analyse which of these studies are actually underway and have presented results.

Materials & Methods

We conducted a retrospective observational study, including all CT, PAS and RP related to COVID-19 that were evaluated by the VH-REC between March 16 and June 21 2020 (both included), which corresponds to the lockdown period in Spain. In order to assess our reporting transparency, STROBE guidelines were followed (*see Supplementary file 1*).

The sample was selected from the VH-RECs´ administrative database of studies and data was extracted from clinical pharmacologists' reports and study protocols. Data review from the characteristics of the COVID-19 studies was carried out by the investigator team.

The analysed variables were, on one hand, related to the study characteristics (such as type of study, primary endpoints, sponsorship, among others), and, on the other hand, related to the patients and the disease under study (such as the age of the participants, the severity of COVID-19 and other comorbidities). Furthermore, we included information related to the RECs' activity and its evaluations timelines during the pandemic outbreak. Lastly, we describe the requirement of an IC and the follow-up of protocols.

As for the study evaluation times, according to the AEMPS established deadlines, which changes due to COVID-19 pandemic have been stated above, calendar days were counted, without excluding weekends or other official holidays [15]. Therefore, it is important to note that review timings may have been even shorter if only working days were accounted for. Concerning follow-up information retrieval, the main investigators of the initially evaluated were contacted between the 20th of January and 31st of March, 2021 (both inclusive). Contact was established through an electronic survey developed and managed using REDCap electronic data capture that included variables related to the initiation and termination of the study, publication of results and funding (*see Supplementary file 2*) [20].

All analyses were performed by descriptive statistical methods. Results were calculated as frequencies and proportions. Data analysis was carried out with the RStudio 4.0.3 version software [21].

The study was approved on the 14th of July, 2020 by the VH-REC and carried out in accordance with the Declaration of Helsinki of the World Medical Association as established in the 18th General Assembly (World Medical Association Declaration of Helsinki, Helsinki, Finland, 1964) and its modifications. The Organic Law 3/2018, of December 5, on the Protection of Personal Data and Guarantee of Digital Rights was applied. Personal data of patients was not used.

Results

In the study period, a total of 255 studies were evaluated by the VH-REC (30 CT, 21 PAS, and 204 RP) being 157 (61%) of them COVID-19 related. The main characteristics of the overall evaluated protocols are specified in Table 1. Regarding the scope, studies included tended to be unicentric (54%), national (88%), with a non-commercial sponsorship (95%) and with a descriptive design (85%). The main in-hospital services involved were Infectious Disease, Intensive Medicine and Pneumology, which carried out 19 CT, 14 PAS, and 11 RP. Preliminary estimations of the sample size to be included in the studies were a mean of 173 patients (ranging from 40 – 466), 264 (100 – 700) and 1,241 (10 - 13,000) in CTs, PAS and RP, respectively.

The main objectives were focused on describing prevalence or incidence of outcomes related to COVID-19 (37%); for all CT the main objective was to assess efficacy and safety of both treatments or diagnose procedures, mainly using medical records for data collection. Talking about their associated main variables, these objectives were assessed through four types of primary endpoints: clinical outcomes, which dominated (e.g. epilepsy in patient COVID-19 patients); laboratory results (e.g. seroprevalence studies); health status questionnaire; and imaging tests (e.g. role of thoracic ultrasound in patient COVID-19 patients). Three PAS and 31 RP had endpoints based on blood samples or imaging and only RP used questionnaires to collect data. The most commonly used source of information was medical records, especially in descriptive studies. Most of the information collected was by the use of questionnaires and interviews, and predominantly about mental health of healthcare professionals.

Due to the strict requirements and pronity to interventionism of clinical trials, they are not likely to include the paediatric population, as shown in Table 1. On the other side, there were 9 RP that were likely to include patients younger than 18 years. It is worth saying that 6% of RP (not overlapping with the 5 of population under 18 years defined previously) and PAS paid attention to pregnant women and their neonates, so some data about paediatric patients could be indirectly collected from these. Only 3 RPs focused on elders over 65 years: one of them on elders' femoral fracture, another on frailty and medium term prognosis, and the last one on nursing homes setting.

The most frequent specific populations involved healthcare professionals and immunosuppressed patients with onco-hematological diseases. Moreover, 16 RP (12%) studied COVID-19 patients exposed to a surgical procedure, including either emergent or elective surgery. Only 3 RP (0.02%) specifically studied care-givers of patients with COVID-19 disease, focusing on the psychological impact of the

pandemic in the relatives of COVID-19 hospitalized patients, transplant patients or the paediatric population.

Concerning drug type, it seems relevant that 70% of CT evaluated commercialized medicines and 30% evaluated non commercialized medicines, such as immunosuppressants and vasodilators. Most frequent commercialized drugs evaluated were antimalarials (6) and agents acting on the renin-angiotensin system (2). RPs did not involve medicines but some involved surgery procedures (2; 1.5%) and blood products or medical devices (10; 7.6%). A high proportion of PAS were uncontrolled (81%); this ought to be justified because a lot of studies focused on how diverse items affected COVID-19 patients, without comparative aiming. Some examples include psychobiosocial effects of the pandemic or retrospective data collection for drug repurposing, but as there were neither standardized guidelines on COVID-19 disease management nor proof of effective treatments, it was not always possible to establish a control group.

We also assessed whether the evaluated COVID studies by the VH-REC used biological samples and if they were stored or not. In Spain, biobanks store biological samples for open use in biomedical research, and its transfer must be authorized by a REC. Instead, collections include samples of a private collection; a single project collection; or line of research collections for a certain topic [22]. In the CEICOV study, 32.5% (51) of studies requested biological samples, of which 37.3% (19) were preserved, mainly as collections (68.4% stored in collections vs. 26.3% in biobanks). Stratified by study type, 90%, 29.8% and 18.8% of CT, RP and PAS respectively, collected biological samples. The leading objective for biological samples was efficacy assessment (25.5%, 13), and they were collected mostly in studies involving severe COVID-19 population.

VH-REC timelines for evaluations

During the study period, the VH-REC held twenty-five meetings, all of them via videoconference (15 ordinary and 9 extraordinary, of which two were emergent), with an average of eighteen attendees, even a minimum quorum attendance of at least 3 members was established according to AEMPS recommendations. In contrast with the pre-pandemic situation, the meetings were biweekly [15-17]. The average time of issuance from initial submission to final decision was 8 days, with an interquartile range (IQR) of 3-14 days. This was mainly at the expense of the time of response of the investigators, which were issued in an average of 5 days (IQR 3.8 - 7.3). Timing for evaluation of RP was the greatest. Review times are detailed in Table 2.

Considerations during protocol review

Out of all the studies, in the initial evaluation, they mainly required further clarifications (92; 58.6%). Onwards, except for three studies, all clarifications were solved and studies were favourable. Thus, there were 146 favourable VH-REC opinions, 3 unfavourable and in the remaining 8 cases, investigators did not answer clarifications and therefore the committee´s opinion was undetermined. The evaluation flux by study type is illustrated in Figure 1.

The main reasons for clarifications concerned the IC form, information on the use and preservation of biological samples, and administrative issues. In most cases, there was more than one issue to clarify.

Other reasons included methodology (calculation of study sample, design or analysis), grammar/writing, economy report, insurance policies, data protection, as well as selection criteria.

Informed consent form

Keeping close to the IC process, 54 sponsors (37% of total sample) requested exemption from collecting it (45;34% RP and 9;56% PAS). All CTs required IC in writing form or even orally with later writing ratification according to European Medicines Agency (EMA) and AEMPS' recommendations on the management of CT during the COVID-19 pandemic [15-17].

The 39% of studies which got the IC exemption had a retrospective design (19 RP and 3 PAS) and concerned codified data. A 23% had a prospective design and another 23% were ambispective, for which collecting data prospectively was a public health reason. However, in 3 prospective and 2 ambispective studies, oral consent was obtained regarding any follow-up of patients that required any intervention. Furthermore, in 5 of 6 cross-sectional studies whose objective was response through a survey, it was considered that implicit consent was granted by the subject. Related to observational studies with biological samples, in 11 RP the sponsor requested consent exemption because they used anonymized data, and in 8 cases due to global public health interest.

Follow-up of evaluated studies

From the whole study sample, between January and March 2021, we achieved an answer on follow-up from 138 (88%). At the time of this study 89% (thus, 123) had initiated the study, and 64 also finalized. Among those who had not initiated the study (15;11%), the main causes were they had not received final approval from the VH-REC or had not recruited sufficient patients or samples (see Figure 2). In contrast, among studies that had not yet been finalized, the main reason was they were still in the recruiting phase (34;58%). In 6 studies two or more reasons for no finalization were identified. It should be noted that 5 studies were not able to go ahead due to lack of funding, and that 36 studies had still not published their results. Results from studies during follow-up were obtained in 87 (63%) cases, of which 48% were final results and the rest intermediate. Of all these results, 51 (59%) had already been published at the time of the survey; 43 (84%) in a medical journal, 15 (29%) in a congress and 4 (8%) in a symposium. To note, in 8 studies, results were published in two or more areas.

Discussion

To respond efficiently to this health emergency, it was necessary to adapt existing ethical review procedures and seek alternatives to reduce practical obstacles to conduct research as much as possible [10, 13-16]. Increase in research led VH-REC to adapt and enhance its procedures, providing effective and quality evaluation of 157 studies in a short period of time and prioritizing COVID-19 related ones.

As can be seen in the AEMPS standard operating procedures, the usual maximum time allowed for the full evaluation of a protocol was 76 days, which contrasts with our median time of evaluation (3 days) and issuance of the committee's decision (8 days), similar to the study of Agrawal et al [11]. It should be taken into account that timelines were calculated by calendar days so shorter evaluation lag could

happen if we consider periods by working days. Flexibility was necessary in the requirements for the initial submission of documents (for example, lack of complementary documents or signatures on documents). As stated by other authors, in order to facilitate this adaptation, guidelines should be prepared to assist with the coordination and conduct of meetings [12-13,18,24]. The switch to strictly virtual meetings was achieved as well as adherence to the evaluation timelines, despite increasing the frequency was necessary [11,25]. The minimum quorum required by was reduced [6]; nevertheless, virtuality allowed our quorum to increase.

From a general scope, it has been seen that descriptive studies increased during the pandemic period and also single centre small studies, which is consistent with our results [26]. During the pandemic, Spain was considered as one of the 5 countries where more clinical trials have been authorized, but only a minority of these, included a sufficient population sample to make the results able to change the usual clinical practice [28]. Moreover, as indicated by González-Duarte et al 2020, in the context of the COVID-19 pandemic, patients may be exposed to various investigations [19]; in this concern, another role that the committee and clinical pharmacologists acquired was linking various heads of department and promoters to unify similar projects in order to avoid cherry picking, scientific redundancy, overexposure of patients to research studies and duplication of efforts, while keeping an eye on aspects of organization, ethics and relevance [3-4, 29-30]. Creative options have been performed to palliate all these to enhance collaboration and efforts' unification [10,31].

The pressure to find an effective treatment for a highly contagious disease with fatal potential, increased the number of repurposing studies, what has many advantages from an economic and temporal point of view because they can reduce drug development timeline [2,28,32-33]. However, the implication of using already commercialized medicines can lead to drawing rapid conclusions and sometimes overestimated extrapolations when there is still not enough evidence about their effectiveness in a new disease [2]. An example of this was the advertising and premature implementation of antimalarials as COVID-19 disease therapeutic option [4,34-35]. It has also been seen a tendency to non-commercial promotion, aligned with the information provided by the Spanish Registry of Clinical Studies (REec) (95% from our sample vs. 76% reported by REec) [28,32].

In the studies reviewed, the most widely used instrument for access to information were electronic medical records, with a quantitative approach predominantly [29,36]. However, interviews and online surveys have also become an important tool for COVID-19 research. Qualitative research complement epidemiological data by providing information on people's experiences of disease and care and response to the pandemic, despite this technique is less frequently used compared to other research designs and the virus did not allow face-to-face strategies [37]. There is some discrepancy on practical issues when dealing with this type of research, as ethical review is not specifically designed to evaluate qualitative studies [38]. In CEICOV, we found a large number of studies that analyzed the emotional disorders of health workers associated with COVID-19 patients. This interest has also been shared by other countries [39]. Therefore, it is noted that mental health of medical personnel must be considered an urgent public health problem.

In 2016, the WHO published a guidance to ensure the scientific validity of and participants' rights and safety in studies conducted during outbreaks, in the frame of the Ebola crisis, which evaluation times were longer than ours (median of 18 days) [40]. In this context, the *Médicins Sans Frontières* ethics review board, took a mean time of 12.4 days to first issuance. Zhang et al 2019 examined all COVID-19

related applications to the Henan Provincial People's Hospital CREC consistently with the WHO document. They evaluated 41 studies increasing their meetings to 4 each 35 days, and took an average of 2.13 days for the first evaluation, compared with 3 days in our study [41]. Shortening evaluation timeline is not easy because it depends on several factors, which include complexity, level of development and technical rigor of the study, number of observations, response times of the researchers, duration of the sessions, etc [6,13,22].

During this period, over half of the total studies required further clarifications, which matches with Henan Provincial People's Hospital casuistry, who had a first-time study approval rate of 14.6 % (lower than 33.4% during a usual non-epidemic period) [41]. The main reason for clarifications concerned the IC form and biological samples, which obtention process is briefly described in some settings [30]. Also, there were some cases where REC's clinical pharmacologists assessed investigators in the making and/or correction of the study protocols, possibly reflecting the hasty preparations of these protocols and related documents due to the pandemic situation and the urgent need for data. So, the clinical pharmacologists acquired a formative role on protocol elaboration maintaining, at the same time, review standards.

Regarding the consent process, studies with a retrospective design account for the group that more frequently requested grant exemption. The main reasons to grant consent exemption included descriptive and/or retrospective study design, and/or the use of coded data. In the case of emergency situations, article 7 of Royal Decree 1090/2015 applies [15]. Moreover, regulatory agencies permitted to collect consent orally instead of written form to avoid the patient having to go to the sites to sign the consent. This process should be documented in the patient's medical record and ratifying it later in writing [16]. When describing our data, it should be kept in mind that it only reflects the evaluation pre-approval status of the studies described [2,9,13-14,17,19,42-43].

When focusing on the follow-up of those protocols evaluated in the first pandemic outbreak, we got a high response from investigators (88%), despite their workload, in contrast with previous publications [44]. As a result of this follow-up, not a meaningless proportion did not finalize at our time-cut, because lack of funding or cancellation, which illustrates the scarce resources for research in some settings [27]. A longer follow-up would be needed to assess the current situation of those studies still recruiting. From all studies finalized, almost all had results published in some area even positive or negative results raised, without fear of reprimand, oppositely from other studies [44]. This highlights the importance and benefit of transparency and ethics in the scientific community [4,45]. We would need further information on other periods and/or RECs to assess if our results are concordant with routine practice or represent a significant change.

The main strengths of this study are the contribution of information that has been scarcely or not described, both in articles and scientific events, and especially follow-up of studies execution. To our knowledge, the characteristics of both the studies and the activity of a REC itself have not previously been described in such a broad way. Moreover, the fact that it has been carried out by members of a committee gives a perspective and impressions that are not always available to health professionals (nor overall population) outside the committee.

This in turn constitutes a limitation, in the sense that during the pandemic, the activity of the VH-REC has increased significantly and it was very difficult to conduct the project presented here, and also continue

with the daily tasks of the VH-REC. With more staff and time, perhaps more data could have been collected, or in a more optimal way.

There has been a lot of information for which we have not found comparator studies, which makes it difficult to generalize our results, given that each REC in each hospital in our setting has its own peculiarities in its process flow and evaluation methodology. There is also little information on ethical activity in previous pandemics like Ebola or flu due to underreporting, so we should try to provide such results publicly for future pandemics [40, 46].

It should also be noted that, as this is the first time we have had the opportunity to carry out a project like this, we do not have information from the period prior to the state of alarm due to the COVID-19 pandemic, despite which we have been able to appreciate certain contrasts (although sometimes somewhat subjective) with the previous period, taking advantage of the participation of VH-REC members in CEICOV.

Based on the above arguments, we believe that it would be of great relevance the execution of studies of this type at a multicentre level, in order to have a more global vision, and to try to standardise the collection of this information in other time periods outside the pandemic in order to assess the changes that could be made to optimise study evaluation and follow-up.

Conclusions

Here we provide the perspective of Clinical Research Ethics Committees on the research performed during the first outbreak of the COVID-19 pandemic. The additional evaluation burdens related to COVID-19 has permitted us to take consciousness on the need to spread our functions and grant quality to the great amount of information being published. These functions are relevant because the general population (either linked to healthcare or not) sometimes may not be aware of what happens behind scientific investigation. Since there is missing information from previous pandemics, we feel the need to report publicly our evidence to assure visibility for future profit in the case of new health emergencies.

As it can be perceived across our report, REC members have to deal with and are affected by different research settings, exceptional situations, innovative strategies (either concerning drug development or technological or data), legality and law, while they look after human rights and ensure research quality.

In consequence, flexibility, broad-mindedness and knowledge should be some of the leading abilities of their members, and especially, of clinical pharmacologists, who usually act as evaluation experts.

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Table 1. Baseline characteristics of COVID-19 protocols evaluated by the VH-REC during the outbreak of the first pandemic wave.

			CT	PAS	RP	TOTAL
			(N=10)	(N=16)	(N=131)	(N=157)
STUDY CHARACTERISTICS - N (%)						
COMMERCIAL PROMOTER	Yes		6 (60)	-	2 (1)	8 (5)
	No		4 (40)	16 (100)	129 (98)	149 (95)
SETTING AND PARTICIPATING CENTERS	Unicentric National		5 (50)	12 (75)	68 (52)	85 (54)
	Multicentric National		4 (40)	4 (25)	45 (34)	53 (34)
	Multicentric International		1 (10)	-	18 (14)	19 (12)
DESIGN	Descriptive		-	16 (100)	118 (90)	134 (85)
	Experimental		10 (100)	-	9 (7)	19 (12)
	Qualitative		-	-	4 (3)	4 (3)
CONTROL ARM	Controlled	Active treatment	7 (70)	3 (19)	NA	10 (6)
		Placebo	3 (30)	-		3 (11)
	Not controlled		-	13 (81)		13 (8)
DRUG TYPE	Commercialized		7 (70)	15 (94)	-	22 (85)
	Not commercialized		3 (10)	-	-	3 (11)
	None		-	1 (6)	-	1 (4)
PROTOCOL CHARACTERISTICS - N (%)						
MAIN OBJECTIVE	Description of prevalence or incidence of outcomes		-	3 (19)	55 (42)	58 (37)
	Diagnostic utility and tools		-	2 (13)	17 (13)	19 (12)
	Efficacy and safety of treatments or measures		10 (100)	5 (31)	13 (10)	28 (18)
	Impact of the pandemic in different areas		-	-	17 (13)	17 (11)
	Pharmacokinetics and metabolomics		-	1 (6)	1 (1)	2 (1)

	Prognosis improvement or worsening	-	3 (19)	25 (19)	28 (18)
	Prevention	-	2 (13)	3 (2)	5 (3)
PRIMARY ENDPOINT	Clinical outcomes	7 (70)	12 (75)	72 (55)	91 (58)
	Laboratory results	3 (30)	3 (19)	31 (24)	37 (24)
	Health status questionnaire	-	-	20 (15)	20 (13)
	Imaging tests	-	1 (6)	8 (6)	9 (6)
INSTRUMENTS USED FOR DATA COLLECTION	Medical records	10 (100)	14 (88)	102 (78)	126 (80)
	Questionnaires	-	-	26 (20)	26 (17)
	Interview	-	2 (12)	3 (2)	5 (3)
POPULATION CHARACTERISTICS - N (%)					
AGE	<18y	-	-	5 (4)	5 (3)
	≥18y:	10 (100)	16 (100)	126 (96)	152 (97)
	◦ Excluded elders	-	-	7 (6)	7 (5)
	Any age	-	-	4 (3)	4 (3)
SEVERITY OF COVID-19 DISEASE*	Ambulatory	-	2 (13)	21 (16)	23 (15)
	Hospitalized Mild Disease	3 (30)	1 (6)	9 (7)	13 (8)
	Hospitalized Severe Disease	7 (70)	2 (13)	24 (18)	33 (21)
	Every severity grade	-	8 (50)	60 (46)	68 (43)
	Not specified in the protocol	-	3 (19)	17 (13)	20 (13)
SPECIAL INTEREST GROUPS**	Health care professionals	-	2 (13)	14 (11)	16 (10)
	Pregnancy and neonates	-	1 (6)	8 (6)	9 (6)
	Immunosuppressed (includes oncology patients)	-	4 (25)	12 (9)	16 (10)

CT: Clinical trial; PAS: Post-authorization study; RP: Research project

**Severity of the COVID disease of the population included in each evaluated study was assessed consistently with the 7 point WHO scale [22].*

***Please, note that percentages in this category have been calculated over the total of studies (n=157), but there is no overlap among Special Interest Groups studies.*

Table 2. Review time for COVID-19 related protocols evaluated during the study period.

STUDY TYPE	Days from initial submission to VH-REC initial decision	Days from VH-REC initial decision to investigator´s response	Days from investigator´s response to VH-REC evaluation	Days from complete submission to final VH-REC approval
	Median (IQR)	*Median (IQR)*	*Median (IQR)*	*Median (IQR)*
CT	2 (2-5.5)	7 (5.7-7.5)	1.5 (1-2)	10.5 (10-13.7)
PAS	2 (1-3)	4.5 (3.2-11.5)	1.5 (1-2)	6 (4-8)
RP	3 (2-3.5)	5 (3-7.2)	3 (1-5)	7 (2-13.5)
TOTAL	3 (2-4.5)	5 (3.8-7.3)	2 (1-4)	8 (3-14)

CT: Clinical trial; PAS: Post-authorization study; RP: Research project; VH-REC: Vall d'Hebron University Hospital´s Research Ethics Committee.

Figures:

Figure 1. Vall d'Hebron University Hospital Research Ethics Committee opinions across protocol evaluation procedure by study type.

Figure 2. Follow-up of studies evaluated.

Footer of figure 2: *Reasons are not mutually exclusive.