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Research paper

Impact of COVID-19 disease on clinical research in pediatric and congenital cardiology

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ABSTRACT

Background: COVID-19 triggered an unprecedented crisis affecting society at every level. Research in pediatric and congenital cardiology is currently in full development and may have been disrupted. The aim of the study was to determine the impact of COVID-19 on pediatric and congenital cardiology clinical research and to analyze decision-making and adaptation processes, from a panel of ongoing academic and industry-sponsored research at the time of the pandemic.
Methods: This observational study was carried out in April 2020, from a CHD clinical research network involving five tertiary care pediatric and congenital cardiology centers. Investigators and clinical research assistants from each participating research center completed an online survey questionnaire, and each principal investigator underwent a 1-h web-based videoconference interview.
Results: A total of 34 study questionnaires were collected, reporting that 18 studies were totally suspended. Upon the investigator's decision, after discussion on ethical issues and with facilitating support from health authorities, 16 studies were resumed. The rate of study suspension in interventional research (53%) was similar to that in non-interventional research (56%). Logistical problems were predominantly reported in both continued and suspended trials. Research protocols were adapted, largely thanks to telemedicine, which in some cases even improved the course of the study.
Conclusion: The impact of the COVID-19 pandemic on clinical research in pediatric and congenital cardiology has been limited by a rapid adaptation of all research structures and an extensive use of telemedicine at all stages of the studies.

1. Introduction

From its first appearance in China in November 2019 to its evolution toward a worldwide pandemic from March 2020, COVID-19 disease has dramatically destabilized all areas of contemporary life [1]. While most countries have totally or partially confined their populations, healthcare systems have rapidly adapted to manage the influx of patients infected with SARS-CoV-2, and were simultaneously forced to prioritize their other usual work [2].

Apart from the aspects directly related to patient care, clinical research also had to face new challenges, in terms of follow-up of patients enrolled before the epidemic and of enrolment of new patients. Therefore, all actors involved in clinical research, i.e., regulatory health agencies, health authorities, ethics committees, clinical trial promoters, research center facilities, and clinical trial investigators had to determine, within a very short period of time, how to manage patients already enrolled in ongoing trials and to decide

Abbreviations: CHD, congenital heart disease; COVID-19, Coronavirus disease 2019; IRB, Institutional Review Board; M3C, French National CHD network; RCT, randomized control trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

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whether or not clinical studies should be modified, halted, or suspended [3].

Clinical research in pediatric and congenital cardiology has grown in importance over the past decade. Indeed, while congenital heart disease (CHD) is the predominant cause of birth defects worldwide, off-label use of drugs and devices has long been observed in patients with CHD, especially in children. Therefore, recent regulatory initiatives have modified the pediatric clinical trials landscape by significantly increasing capital investment and trial volume in pediatric cardiology [4]. As a result, advances in evidence-based medicine are progressively emerging in pediatric and congenital cardiology [5–7] and research protocols dedicated to patients with CHD are being increasingly published [8–13]. To note, for children with the most severe conditions, such as pulmonary hypertension, being enrolled in a clinical trial may represent a real promising opportunity [14–16].

Thus, it is certain that the unprecedented global health crisis caused by COVID-19 disease has significantly disrupted the course of clinical research in pediatric and congenital cardiology. However, much less is known about the extent of this disruption as well as any mitigation strategies to overcome it.

This study aimed to determine the impact of COVID-19 in pediatric and congenital cardiology clinical research, and to analyze decision-making and adaptation processes, from a panel of academic and industry-sponsored research ongoing at the time of the pandemic.

2. Methods

2.1. Study design

This observational prospective study was carried out in March and April 2020, from a CHD clinical research network involving five tertiary-care pediatric and congenital cardiology centers in France: Montpellier University Hospital, Bordeaux University Hospital, Marseille-La Timone University Hospital, Toulouse University Hospital, and Marie-Lannelongue Cardiac Surgical Centre. We identified the principal investigators (PIs) in each research center, as declared to the national health authorities (https://www.ansm.sante.fr), and the ongoing studies registered on an international clinical trial registry, as defined by the World Health Organization [17]. All cardiovascular trials enrolling children with any cardiovascular condition, as well as adult patients with CHD, and currently recruiting patients in March 2020 were eligible for the study. For each study, the PI and the clinical research assistant (CRA) were asked to complete an online questionnaire, and then they underwent a web-based videoconference interview.

2.2. Survey

The online questionnaire used the Google Forms® tool to create the survey. The first part included general questions on the study and on the number of enrolled patients. The second part included questions on the impact of COVID-19 on the study, with a focus on the decision-making regarding study suspension, or on all the adaptations that made the continuation of the study possible. Study suspension was defined as a complete discontinuation in new patient enrollments, or the impossibility for participants enrolled prior to the outbreak to undergo the study intervention and/or follow-up, for any reason. Study pursuance was defined as any form of complete or partial continuation of the study (**Table 1**).

Then, each PI underwent a 30-min web-based videoconference interview, carried out by a pediatric cardiology research coordinator, previously trained in qualitative research studies [18].

2.3. Statistical analysis and formal aspects

All quantitative data were automatically generated and extracted from the Google Forms® survey. The characteristics of the studies selected are presented using frequencies. Qualitative data were rearranged in terms of similar topics and analyzed by two investigators.

The study was conducted in compliance with the Good Clinical Practices protocol and the tenets of the Declaration of Helsinki. It was approved by our Institutional Review Board on March 16, 2020 (IRB-MTP-2020-03-20200412) and registered on Clinicaltrials.gov (NCT04336384).

3. Results

3.1. Ongoing pediatric and congenital cardiology studies during the pandemic

All PIs (n=5) and CRAs (n=5), identified in the five clinical research centers, accepted to participate in the survey and completed a total of 34 questionnaires (i.e., one per study carried out in each center) in Bordeaux (**n**=13), Montpellier (n=9), Paris (n=6), Toulouse (n=4), and Marseille (n=2), respectively. As some studies were multicenter trials, a total of 23 different ongoing studies were identified when the pandemic was declared (**Table 2**). Academic studies (n=12; 52%) were promoted by a university hospital (n=8), or an academic society (n=4), and 48% of academic studies were interventional. Studies promoted by industry (n=11, 48%) were all drug trials (phase I, n=1; phase II, n=1; phase III, n=7), except for one medical device trial (interventional cardiac catheterization) and one noninterventional study (registry). Most studies were referenced on the clinical trial registry ClinicalTrials.gov (n=21; 91%). Overall, 288 participants were enrolled in the studies reported in this survey when the pandemic was declared. At the time this survey ended, no enrolled patient had contracted COVID-19, to the knowledge of the investigators.

Overall, out of the 34 studies reported by the survey, 18 were halted for an undetermined period (no further enrolment, pause of all study procedures for the previously enrolled patients), and 16 studies were continued with substantial modifications (**Table 3**). The rate of study suspension in interventional research (53%) was close to that in noninterventional research (56%).

3.2. Data on halted studies

3.2.1. Description of studies

Out of the 18 suspended studies, we identified five drug trials, four cardiac device studies, three randomized controlled trials (RCTs) on cardiac rehabilitation, three CHD registries, two RCTs evaluating a relaxation therapy (i.e., sophrology), and one study on cardiomyocytes derived from human-induced pluripotent stem cells (hiPSC).

3.2.2. Reasons for study halt

The PIs reported that the main reason for study suspension was, in order of frequency, logistical issues (n=12; 67%), sponsor's decision (n=3; 17%), patient safety (n=2; 11%), or health authorities' decision (n=1, 5%). Ethical issues were discussed but never mentioned as the main reason for study suspension.

In greater detail, logistical problems were predominantly reported as the main reason for study suspension in intervention studies involving cardiac devices (interventional cardiac catheterization procedures), home- and center-based cardiac rehabilitation programs, or blood sampling for experimental research (stem cells in children with cardiomyopathy). Indeed, enrolled patients could usually not travel to the site because of the lockdown; furthermore, all research centers involved in this study were also healthcare facilities in charge of patients with COVID-19 infection. For example, Marie-Lannelongue Hospital, one of the largest cardiac surgical centers in Europe

Table 1
Survey on impact of COVID-19 pandemic on pediatric and congenital cardiology research.

General questions	
What is your role in the study?	Clinical research associate Investigator
Which institution do you represent?	
What is the name of the study you are involved in?	
Who is the sponsor of the study?	
What kind of study is it?	Academic Industry
What type of study is it?	Interventional research Interventional research involving minor risks Noninterventional research
If there is one, please describe the intervention:	
If it is a clinical trial, which phase is it?	Phase I Phase II Phase II Phase IV
How many patients were currently enrolled in the study at the time of the outbreak announcement?	
How many enrolled patients have been infected by COVID-19?	
Did you have to interrupt the ongoing study at the time of outbreak announcement?	
Questions dedicated to studies which were not suspended	
Did you suspend new patient enrolments?	
Did you modify the process of patient or legal guardian consent? If yes, how?	
Did you continue patient follow-up? If yes, how?	
Did you organize patient visits	On site By teleconsultation Both Other (please detail)
If the study is a drug trial, how was drug dispensing organized?	On site Home delivery provided by the sponsor Other (please detail)
Have you faced any logistical problems? (Please detail)	
Have you faced any legal problems? (Please detail)	
Have you faced any ethical problems? (Please detail)	
Did other special means have to be provided to permit the study to carry on?	
Did you have to adapt or modify the research protocol? (Please detail)	
Did you report these modifications or adaptations to an institutional review board or an ethics committee and were they approved? (Please detail)	
Were you prepared for the impact of such a health crisis on your ongoing studies?	
Questions dedicated to studies that were suspended	
Were you prepared for the impact of such a health crisis on your ongoing studies?	
What was the main reason for the study suspension?	Ethical issues Logistical issues Sponsor decision Health authority decision Ethics committee decision Economic issues Legal issues Patient safety Other (please detail)
Would the continuation of the study have created logistical problems? (Please detail)	
Would the continuation of the study have created legal problems? (Please detail)	
Would the continuation of the study have created ethical problems? (Please detail)	
Please detail any other reasons leading to the study suspension	

and located near Paris, an area greatly affected by COVID-19, totally stopped the QUALIREHAB-RCT during the pandemic. Similarly, some institutions, such as cardiac rehabilitation centers, decided to totally suspend their clinical activity, meaning that RCTs involving an intervention with cardiac rehabilitation were compromised. Suspended drug trials mostly involved children or young adults with severe cardiac conditions, such as pediatric pulmonary arterial hypertension in studies testing pulmonary vasodilator therapy (selexipag, macitentan), pediatric heart failure (sacubitril–valsartan), or univentricular hearts (macitentan). Interestingly, the centers where the drug trials were totally suspended were also those where no patient had been enrolled before the pandemic. Moreover, the decision to suspend the drug trials came from the PI and not from the sponsor. As a result, for the same study, some centers allowed on-site study monitoring, while others completely suspended it (**Table 2**).

Ethical problems were not identified as the major reason for study suspension. However, it was discussed in all suspended academic studies (n=5) by the PIs who feared that CHD patients could be at risk for severe forms of COVID-19. Therefore, they expressed that patient visits at the hospital for academic research in this context may not be ethical in this population. For instance, in the SOPHROCARE-RCT, all group sessions of sophrology were cancelled, as the PIs considered it unethical to have a group of adolescents and young adult in relaxation therapy in the same room in the hospital. Nevertheless, health authorities never asked for those studies to be halted.

3.3. Data on study continuation

3.3.1. Studies' description

Nearly half of the studies (i.e., 16 out of 34 study questionnaires) were declared as nonsuspended (**Table 3**). Among them, we

Table 2
Ongoing studies at the moment of the outbreak*

Study name	Acronym	Clinical trial registration number	Number of centers involved in the study & participating in the survey	Sponsor	Type of study	Intervention study	Design	Intervention	Phase	Number of patients enrolled in the study*	Patient age range	Study population	Number of study suspensions (S) or continuations (C)
Clinical Study Assessing the Efficacy and Safety of Macitentan in Fontan-palliated Subjects	RUBATO	NCT03153137	2	Actelion - Janssen &Janssen	Industry	Yes (drug)	Randomized, parallel assignment, double-blind, multicenter	Drug Study	III	1	> 12 years	CHD (Fontan)	C: 1 S: 1
An Upcoming Clinical Study to Measure the Safety and Impact of a Drug Called Macitentan in Teenage and Adult Fontan Patients.	RUBATO-OL	NCT03775421	1	Actelion - Janssen &Janssen	Industry	Yes (drug)	Prospective, Single arm, multicenter	Drug Study	III	5	> 12 years	CHD (Fontan)	C: 1
A Study to Assess Whether Macitentan Delays Disease Progression in Children With Pulmonary Arterial Hypertension (PAH)	TOMORROW	NCT02932410	3	Actelion - Janssen &Janssen	Industry	Yes (drug)	Randomized, parallel assignment, multicenter	Drug Study	III	1	2–17 years	Pulmonary arterial hypertension	C: 1 S: 2
Edoxaban for Prevention of Blood Vessels Being Blocked by Clots (Thrombotic Events) in Children at Risk Because of Cardiac Disease	ENNOBLE-ATE - U313	NCT03395639	2	DAIISHI-SANKYO	Industry	Yes (drug)	Randomized, parallel assignment, multicenter	Drug Study	III	2	0–17 years	Prevention of venous	
thromboembolism	C: 1												
Open-Label, Single-Dose Non-Randomized Study to Evaluate Pharmacokinetics and Pharmacodynamics of Edoxaban in Paediatric Patients	HOKUSAI DU176b-A-U157	NCT02303431	1	DAIISHI-SANKYO	Industry	Yes (drug)	Single arm	Drug Study	I	0	0–18 years	Confirmed veinous	
thromboembolism	C: 1												
Hokusai Study in Paediatric Patients With Confirmed Venous Thromboembolism (VTE)	HOKUSAI DU176b-A-U312	NCT02798471	1	DAIISHI-SANKYO	Industry	Yes (drug)	Randomized, multicenter	Drug Study	III	1	1–17 years	Confirmed veinous	
thromboembolism	C: 1												
Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of LCZ696 Followed by a 52-week Study of LCZ696 Compared With Enalapril in Paediatric Patients With Heart Failure	PANORAMA	NCT02678312	2	Novartis	Industry	Yes (drug)	Randomized, parallel assignment, double masking	Drug Study	III	3	1 month to 17 years	Pediatric heart failure	C: 1
Rehabilitation of Adolescents and Young Adults With Congenital Heart Diseases	QUALIREHAB	NCT03690518	5	Montpellier University Hospital	Academic	Yes (rehabilitation program)	Randomized, parallel assignment, multicenter	Cardiac Rehabilitation	III	35	13–25 years	CHD	C: 3 S: 2
Transition From Adolescents to Adulthood for Patients With Congenital Heart Diseases	TRANSITION	NCT03005626	1	Montpellier University Hospital	Academic	Yes (patient education program)	Randomized, parallel assignment	Therapeutic Education	III	0	13–25 years	CHD	C: 1
French Observatory of Congenital Ventricular Septal Defect With Pulmonary Overload	FRANCISCO	NCT03363932	2	French Society of Cardiology	Academic	No (registry)	Registry	NA	NA	13	> 1 years	CHD (VSD)	C: 1
French Observatory for Heart Failure in Adults with Congenital Heart Disease	Fresh ACHD	NA	1	French Society of Cardiology	Academic	No (registry)	Registry	NA	II	43	NA	Adult with CHD	C: 1
A Study of Selexipag as Add-On Treatment to Standard of Care in Children With Pulmonary Arterial Hypertension	SALTO	NCT04175600	1	Actelion -			Janssen&Janssen	Industry	Yes	(drug)	Randomized, parallel assignment, double masking	Drug Study	III
0	2–17 years	Pulmonary arterial hypertension	S: 1										
A Clinical Study of to Confirm the Doses of Selexipag in Children With Pulmonary Arterial Hypertension	SELEXIPAG	NCT03492177	1	Actelion -			Janssen&Janssen	Industry	Yes	(drug)	Nonrandomized, prospective, multicenter	Drug Study	II
0	2–18 years	Pulmonary arterial hypertension	S: 1										
Comparison of Amplatzer Amulet and Watchman Device in Patients Undergoing Left Atrial Appendage Closure. (SWISS-APERO)	SWISS-APERO	NCT03399851	1	Bern University	Academic	Yes (device)	Randomized, parallel assignment	Medical Device	NA	0	> 18 years	Prevention veinous	
thromboembolism	S: 1												
Assessment of the WATCHMAN™ Device in Patients Unsuitable for Oral Anticoagulation	ASAP-TOO	NCT02928497	1	BOSTON Scientific	Industry	Yes (device)	Randomized, parallel assignment	Medical Device	NA	0	> 18 years	Prevention veinous	
thromboembolism	S: 1												
Post-approval Study of Percutaneous Left Atrial Appendage Closure (FLAAC-2)	FLAAC2	NCT03434015	1	French Society of Cardiology	Academic	Yes (device)	Prospective	Medical Device	IV	25	> 18 years	Prevention veinous	
thromboembolism	S: 1												
4DFlow Magnetic Resonance Imaging in Patients With Pulmonary Hypertension Associated With Congenital Heart Disease	IRM 4D Flow HTAP CC	NCT03928002	1	Marie-Lannelongue Cardiac Surgical Centre	Academic	Yes (medical imaging)	Non randomized, parallel assignment	Medical Device (IRM 4D)	NA	23	> 7 years	CHD	S: 1
ToyCar: a tool to reduce the anxiety of children with congenital heart disease during a catheterization procedure	Toy Car	NA	1	Marie-Lannelongue Cardiac Surgical Centre	Academic	NA	NA	NA	NA	44	NA	CHD	S: 1
Can the ventilatory response to CO2 at rest predict ventilatory efficiency and tolerance to exercise in patients with a single ventricle?	REVENVU	NCT03818373	1	Montpellier University Hospital	Academic	Yes (functional tests)	Cross-sectional	Stress Test	NA	15	> 8 years	CHD	S: 1
Observatory of Pulmonary Arterial Hypertension of Congenital Heart Disease	ITINERAIR	NCT02260362	1	French Society of Cardiology	Academic	No	Registry	NA	NA	45	> 1 month	CHD	S: 1
Modelling and Pharmacological Targeting of Genetic Cardiomyopathy in Children Via Cardiomyocytes Derived From Induced Pluripotent Stem Cells (DMDstem)	DMStem	NCT03696628	1	Montpellier University Hospital	Academic	Yes (blood sample)	Case-control	Blood Sampling	NA	2	0–17 years	CHD	S: 1
Sophrology and Congenital Heart Disease	SOPHROCARE	NCT03999320	2	Montpellier University Hospital	Academic	Yes (relaxation therapy)	Randomized, parallel assignment	Supportive Care	III	10	13– 25 years	CHD	S: 1
Non-Interventional Study on Pulmonary Valve Replacement by Transcatheter Pulmonary Valve Melody™	MELODY	NCT02023775	1	MEDTRONIC	Industry	No	Nonrandomized, prospective, longitudinal cohort study	NA	NA	1	NA	CHD	S: 1

* Declared at the time of the pandemic (March 2020). C: n, number of continued studies; S: n, number of suspended studies; CHD: congenital heart disease; NA: not attributed; VSD: ventricular septal defect.

Table 3
Survey main results.

				Number of study questionnaires	Study continuation	Study suspension
General survey data	Type of sponsor	Academic studies		18 (53%)	7 (21%)	11 (32%)
		Industry studies		16 (47%)	9 (26%)	7 (21%)
	Type of study	Interventional studies		29 (85%)	13 (38%)	16 (47%)
			Drug trials	14 (41%)	9 (26%)	5 (15%)
			Rehabilitation trials	6 (18%)	3 (9%)	3 (9%)
			Medical device trials	4 (12%)	0 (0%)	4 (12%)
			Other interventions[a]	5 (15%)	1 (3%)	4 (12%)
		Noninterventional studies		5 (15%)	3 (12%)	2 (6%)
	Total			34 (100%)	16 (47%)	18 (53%)
Main problems reported by research centers	Logistical issues			26 (76%)	10 (29%)	16 (47%)
	Legal issues[b]			5 (15%)	0 (0%)	5 (15%)
	Ethical issues			0 (0%)	0 (0%)	0 (0%)

Values are *N* and (%).
[a] Sophrology, therapeutic education, blood sampling, mini-cars.
[b] It includes all restrictions or procedures from any local (university, hospital), regional (ARS, regional health agency), national (ANSM, *Agence Nationale pour la Sécurité du Médicament et des Produits de Santé*), or European (EMA, European Medical Agency) health authorities.

identified, in order of frequency, nine drug trials, three rehabilitation trials, and three noninterventional studies, which were national CHD registries, and one RCT on patient therapeutic education.

3.3.2. Issues encountered and solutions adopted

In many cases, some studies have been continued, but new patient enrolments were stopped during the pandemic period (*n*=10; 62%), mainly because all physicians had suspended routine clinical outpatient follow-up to focus on cardiac and COVID-19-related emergencies. Nevertheless, all patients enrolled before the pandemic were able to undergo the follow-up as defined by the study protocol (*n*=15; 94%), at the cost of a protocol adaptation involving telemedicine (*n*=6), consultation in a hospital "COVID-19-free" area (*n*=4), or both (*n*=2).

Despite the fact some studies could continue, significant logistical problems were reported (*n*=10; 63%), and most PIs and CRAs declared having drafted new organizational set-ups or processes to enable study continuation. Thus, many centers reported significant issues in organizing follow-up visits involving blood sampling, as in all drug trials from the survey (edoxaban, sacubitril-valsartan, macitentan, selexipag). Therefore, with the sponsor's authorization, blood samples were sent to a local laboratory for analysis instead of to the central laboratory. For enrolled participants with the most severe cardiac conditions, such as in children with pulmonary arterial hypertension (macitentan, selexipag), a nurse was sent to the patient's home to take the blood sample and the tube was sent to the local laboratory.

Another main issue in drug trials was about treatment delivery. All sponsors but one had the treatment delivered directly to the patient's home.

In the study continuation group, the main adaptation during the protocol relied on telemedicine, which was considered by most PIs and CRAs as the major reason why study suspension did not occur. In many drug trials, most visits required by the research protocol were organized through teleconsultation, using medical websites approved by health authorities (Qare™, Doctolib™, Teleo™), or non-medical videoconference software (Teams™, WhatsApp™, StarLeaf™, Whereby™, Zoom™). CRAs indicated they had to reach enrolled participants or their parents/legal guardians by telephone more frequently than usual, in order to organize drug delivery, blood samples, and teleconsultations with PIs. In the QUALIREHAB trial, an RCT evaluating the impact of a 12-week center- and home-based cardiac rehabilitation program in children and young adults with CHD, 54 participants were enrolled in the study when the outbreak was declared, of whom 26 were randomized in the intervention group. The coordinating center of the QUALI-REHAB trial managed to transform the center-based sessions into a full "web-workshop" including all sections of the program: medical follow-up with the PI using teleconsultation, patient education with a specialist nurse using teleconsultation, and interval training bicycle exercise sessions supervised by a physical education teacher, using a videoconference software. As a result, all patients enrolled in the intervention group (i.e., cardiac rehabilitation) from all participating centers in France were able to follow the intervention.

Interestingly, no patient or parent/legal guardian expressed the wish to withdraw from any clinical trial. Moreover, CRAs reported that patients were reassured to have regular contact with the research center, which in all cases was also their referral tertiary care center.

Interestingly, no ethical or legal issues with health authorities were reported in the study continuation group. Some investigators stated they had informed their IRB that they needed to modify the initial protocol (use of telemedicine) or to have a patient come to the hospital for study follow-up, despite containment instructions. Fortunately, the response of the health authorities was described as prompt and facilitating. Furthermore, when the investigator was also the referring doctor, all patients enrolled in a nonsuspended trial were satisfied with having a medical follow-up during the COVID-19 outbreak, whether as part of research or not.

4. Discussion

All research centers that participated in this study had to both face a health crisis of unprecedented magnitude, as all of them were also major tertiary care regional hospitals, and at the same time make quick decisions regarding clinical trials taking place at the time of the outbreak.

Surprisingly, this study showed that the impact of the COVID-19 disease outbreak on pediatric and congenital cardiology research, in this network of major French research centers, was not as dramatic as anticipated. Indeed, nearly half of the studies were not suspended, and most decisions were made by the PIs and not by sponsors or health authorities, as may have been expected.

With regard to the management of clinical trials during the COVID-19 pandemic, health authorities were able to rely on the proposals from the European Commission [19]. Therefore, national drug agencies facilitated every change in the study protocols, and protocol amendments directly related to the COVID-19 pandemic did not require any notification to health authorities, new patient consent, or ethics committee approval [20]. For instance, European health authorities stipulated that, the "failure to complete a protocol visit should not be considered as a reason for study discontinuation and should not be considered as a major deviation that must be notified

to the national drug agency" [20]. Moreover, the European Commission provided various solutions for managing on-going clinical trials, such as changing physical visits to teleconsultation, postponement or complete cancellation of visits, transfer of trial participants to investigational sites away from risks zones, or carrying out examinations related to the study (blood sampling, imaging, or other diagnostic test) at a local laboratory, in accordance with local restrictions on social distancing [19]. According to health authority regulations on clinical research, the responsibility for decisions concerning the patient rests entirely with the PI, who should systematically be a physician. Few PIs had probably anticipated to fully assess the scope of this responsibility during the COVID-19 pandemic. Our study suggests that the decisions of the PIs were probably influenced by the local prevalence of COVID-19 and the usual activities of the centers. Moreover, recently open studies without any enrolled patient prior to the pandemic were more likely to be suspended. This is well illustrated in the QUALIREHAB-RCT [11,21], which was very active in terms of patient enrolment prior to the outbreak: The study was suspended in the largest institutions in charge of both COVID-19 and invasive cardiac procedures, but was continued in regional medical CHD centers.

When focusing on the suspended trials, i.e., more than half of the studies in this survey, we observed that the main reason for this decision was real logistical issues or the fear of not being able to manage the logistical issues. Surprisingly, the rate of study suspension in interventional research was similar to that in noninterventional research, i.e., half of the overall survey sample. Therefore, the complexity of the study design, supposedly more marked in interventional research, seemed to have little impact on the decision for study suspension. Apart from the logistical issues, ethical issues are also intrinsically linked to clinical research and, in this study, seem to have been preponderant in the PIs' decisions, as identified in the qualitative analysis. Thus, many drug trials were not suspended as the intervention was considered to have a positive effect on the enrolled patient, especially in cases of life-threatening cardiac conditions. Moreover, previous studies have suggested that the end of a study involving drug withdrawal could generate patient anxiety [22,23]. More recently, the pandemic has given rise to complex ethical debates, as in questioning the usefulness of providing mechanical ventilators to extremely premature babies during the COVID-19 crisis, while adult patients with acute respiratory distress syndrome needing those ventilators could have a better outcome [24].

Finally, this study highlighted the rapid and effective rise of telemedicine in clinical research during the COVID-19 pandemic. Indeed, many interventional research trials were not suspended, largely thanks to telemedicine. Recent clinical reports have detailed the various uses of telemedicine to face the COVID-19 pandemic, such as online consultation, telemonitoring, sensors, or chatbots [25]. While a minority of physicians used telemedicine before the pandemic, the pandemic has led to an explosion in its use in order to respond to patients in primary care. In clinical research, the use of telemedicine has been scarcely reported. Van Bulk et al. have developed a "teleyoga" program to assess quality of life, mental well-being, sleep, and cognition in heart failure [26]. Similarly, this study has shown the value of connected tools in cardiac rehabilitation, especially in young patients, to deliver patient education, motivational reinforcement, and sports coaching. A rehabilitation research team recently reported that the COVID-19 crisis gave them "a total different human flavour, a different contact, mostly facilitator [...], team building was easier, reaction by patients less artificial" [27]. In the SOPHROCARE-RCT, patient enrolment increased during the pandemic, suggesting patients preferred sophrology sessions using videoconference rather than group sessions at the hospital [10]. Simultaneously, telemedicine enabled patients enrolled in clinical trials to keep their study follow-up visits and, in some protocols, to remain in the intervention group. Perspectives for the future may seem very optimistic for medical research [28]. Interestingly, in 1905 telemedicine took its first step in cardiology with Einthoven's telecardiogram [29]. The near future could bring medical follow-up and monitoring with free smart-phone application. Nevertheless, we must remain cautious, as this kind of technology may represent a threat for patient safety and data privacy. Such difficulties should eventually be overcome, and preliminary research on telemedicine prior to the epidemic will probably lead to further studies providing a higher level of evidence [30].

4.1. Study limitations

This study was based on a self-report survey web-questionnaire from a sample of the five most active research CHD centers in France (two out of four national referral centers, and three out of 21 regional referral centers), which therefore may not reflect the overall network of the national CHD centers.

Unfortunately, we did not collect the enrolled patient's point of view, in any form of quantitative or qualitative analysis. The absence of patient withdrawal of consent observed in this study may reflect some degree of patient satisfaction of continuing the study; however, interviewing patients and their family would have been of great interest.

Conclusion

The COVID-19 pandemic triggered an unprecedented crisis affecting modern society at every level. Interestingly, clinical research in this sample of pediatric and congenital cardiology studies was not as detrimentally impacted as we might have expected during the COVID-19 pandemic. Indeed, upon the PI's decision, and with facilitating support from health authorities, many studies were not suspended and research protocols were adapted, largely thanks to telemedicine, which in some cases even improved the course of the study (i.e., better retention and follow-up rates). Future studies should analyze whether these changes will be maintained once the crisis has passed.

Declaration of competing interest

None

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