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► To cite this version:

Claire Fougerou-Leurent, Christelle Delmas, Juliette Saillard, Marina Dumousseaux, Assia Ferrane, et al.. Ensuring quality control in a COVID-19 clinical trial during the pandemic: The experience of the Inserm C20–15 DisCoVeRy study. *Contemporary Clinical Trials*, 2023, 131, pp.107267. 10.1016/j.cct.2023.107267 . hal-04163631

HAL Id: hal-04163631

<https://hal.science/hal-04163631>

Submitted on 21 Jul 2023

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**Ensuring quality control in a COVID-19 clinical trial during the pandemic: the experience of the
Inserm C20-15 DisCoVeRy study**

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ABSTRACT

Setting

Health measures taken during the pandemic deeply modified the clinical research practices. At the same time, the demand for the results of the COVID-19 trials was urgent. Thus, the objective of this article is to share Inserm's experience in ensuring quality control in clinical trials in this challenging context.

Objectives

DisCoVeRy is a phase III randomized study that aimed at evaluating the safety and efficacy of 4 therapeutic strategies in hospitalized COVID-19 adult patients. Between March, 22nd 2020 and January, 20th 2021, 1309 patients were included. In order to guarantee the best quality of data, the Sponsor had to adapt to the current sanitary measures and to their impact on clinical research activity, notably by adapting Monitoring Plan objectives, involving the research departments of the participating hospitals and a network of clinical research assistants (CRAs).

Results

Overall, 97 CRAs were involved and performed 909 monitoring visits. The monitoring of 100% of critical data for all patients included in the analysis was achieved, and despite of the pandemic context, a conform consent was recovered for more than 99% of patients. Results of the study were published in May and September 2021.

Discussion/Conclusion

The main monitoring objective was met thanks to the mobilization of considerable personnel resources, within a very tight time frame and external hurdles. There is a need for further reflection to adapt the lessons learned from this experience to the context of routine practice and to improve the response of French academic research during a future epidemic.

Keywords: quality control; monitoring; sponsoring; clinical trials; pandemic crisis

CONTEXT

In December 2019, a new Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)-associated disease (COVID-19) emerged in Wuhan, China (1) and rapidly spread worldwide; a “pandemic” was declared by the World Health Organization (WHO) on March 11, 2020 (2). The public health emergency caused by this new pandemic immediately led to the deployment of an unprecedented research effort. Concomitantly, there was significant pressure from the scientific community, society, and the media to obtain rapid, reliable results from the COVID-19 trials.

The DisCoVeRy clinical trial (NCT04315948) is a phase III, open-label, adaptive, controlled, multicenter, randomized, Inserm-sponsored trial in hospitalized adult patients diagnosed with severe COVID-19. In its first phase, the objectives of the trial were to evaluate the clinical efficacy and safety of different investigational re-purposed therapeutics. It evaluated four therapeutic strategies with re-purposed antiviral agents (remdesivir, lopinavir/ritonavir associated or not with interferon (IFN)- β -1a and hydroxychloroquine) as compared to standard of care (SoC) alone, according to the design presented in Figure S1 (see Supplementary Materials). The primary endpoint was the clinical status on Day 15 on the 7-point ordinal scale of the WHO Master Protocol (V.3.0, 3 March 2020). Oxygen-dependent patients were recruited in European academic and non-academic hospitals, both in conventional departments and intensive care units. A sample size of 3100 patients (620 per arm) was initially targeted. The complete protocol was reported elsewhere (3).

This trial began on March 22, 2020. Since April 5, 2020, DisCoVeRy is an add-on trial of the Solidarity consortium of trials conducted by the WHO worldwide. First implemented in France, it was implemented in other European countries in 2020: Luxemburg (in April), Belgium (in July), Austria (in July), and Portugal (in October).

On May 25, 2020, the hydroxychloroquine treatment arm was terminated for futility; on June 30, 2020, the lopinavir/ritonavir and lopinavir/ritonavir plus IFN arms were terminated for futility and toxicity. Due to lack of evidence of efficacy at day 15 and a low probability of trial completion with additional

participants, inclusions in the remdesivir arm were suspended on January 20, 2021, marking the end of the first phase of the study. To this date, 1309 patients had been included in the DisCoVeRy trial, of which 1176 in France.

Management of the study had to take into consideration the social and regulatory context related to the pandemic. At the time recruitment started, lockdown had been decreed in France, quickly followed by the other participating countries. The first lockdown profoundly affected personal and professional practices across the country, and the sponsor had to accommodate to the multiple and evolving restrictions.

In France, temporary measures for the conduct of clinical trials were published on March 20th 2020 by the French regulatory agencies (4), and were regularly updated (last updated on August 5th 2021). As a result of these measures, sponsors were able to comply with national lockdown regulations and take into account excess workloads at research sites. This also helped to limit the risk for patients who had to visit a health care facility as part of the protocol. As for monitoring in Europe, European Medicines Agency (EMA) provided a *Guidance on the management of Clinical Trials during the COVID-19 (Coronavirus) pandemic* in late April 2020 (5), updated with recommendations on remote monitoring in February 2021, specified at the national level in France by the Commission Nationale Informatique et Libertés (CNIL) in April 2021 (6). However, even with these European guidelines, it has been necessary to adapt to each country's national regulations and each site's technical and organizational capacity.

Regulatory, legal and financial hurdles encountered within the management of the study in this unusual setting have been described elsewhere, together with proposals to overcome them (7). We present here the challenging experience of ensuring quality control of an international clinical trial in the context of a pandemic and its related constraints.

METHODS

Clinical sites identification

In France, the sponsor relied on a preexisting and operational investigator network specialized in infectious diseases, the Réseau National de Recherche Clinique en Infectiologie (RENARCI) network, to include patients from the first wave of COVID-19 hospitalizations in March 2020. The RENARCI made available to the sponsor its project manager as well as the contact details of its 84 affiliated clinical sites. After contacting the RENARCI clinical sites, a feasibility study was done to evaluate the capacity to include patients in optimal conditions.

In Europe, both pre-existing relationships between potential investigators and the European Commission supported clinical site identification in foreign countries by communicating on the DisCoVeRy Trial. National authorities also helped the sponsor identify Good Clinical Practice units able to obtain approvals quickly and set up the DisCoVeRy study in optimized conditions. Finally, the European Clinical Research Infrastructures Network (ECRIN) provided the sponsor with a clinical trial units (CTU) directory.

Site initiation visits

The site initiation visits (SIV) were performed by the sponsor's team. Due to travel constraints, and to open a large number of sites as quickly as possible, SIVs were carried out by tele- or videoconference and could involve several sites concomitantly. The SIV required the presence of at least the principal investigator (PI), the research team, and representatives of the pharmacy and virology laboratory. In the case of changes in the investigation team or the involvement of other departments of the hospital, it was the responsibility of the PI to provide training for the study.

Data quality control

DisCoVeRy is a risk D trial as defined by the sponsor using the grid described in the Optimon study (8). Considering the sanitary context at the time the study started, the monitoring objectives defined in the Monitoring Plan were as follows:

- Source data verification of 100% of the Critical data of all enrolled participants,
- Source data verification of 100% of Non-critical data of 50% of randomly selected participants in each randomization arm,
- If major deviations were raised from an investigational site, the sponsor could trigger a data monitoring of 100% of Non-critical data of 100% of enrolled participants of this investigational site.

The critical data were specified on a Key Data List: all case report form (CRF) variables to be monitored were identified on a Word version of the CRF.

Major deviations were defined in the Monitoring Plan and collected on a centralized tracking table.

The queries were programmed using SAS v9.4 (SAS Institute, Cary, NC, USA) by a data manager. The queries covered all the e-CRF data to detect missing data but also inconsistent or out-of-bounds data. A shipment was scheduled approximately every month. In addition to these queries and before each Data Safety Monitoring Board (DSMB) meeting, a methodologist sent an email to the sites summarizing the ordinal scales data missing at Baseline, Day 15, and Day 29.

Monitoring and coordination team

A working group was convened early on to define priority objectives concerning the situation, the needs identified, and the forces at work. This working group proposed an adapted organization, wrote the Monitoring Plan, and set up the monitoring tools. Thanks to the mobilization of all ANRS|MIE Clinical Research Department units, it was possible to set up a team of monitoring project managers, in charge of being the privileged points of contact for the sites and of supervising the monitoring clinical research assistants (CRAs). Eventually, 16 different project managers were involved in the study for the coordination of the monitoring between April 2020 and November 2021, supervised by a Monitoring Coordinator. At the time the study started, access to trial sites for non-essential staff was restricted and recruitment of staff was suspended. The sponsor had to implement a CRAs network and adapt country by country and site by site, the monitoring modalities.

RESULTS

Sites initiation and inclusions

Clinical sites identification

Between March and August 2020, 97 French clinical sites contacted the sponsor to participate in the DisCoVeRy trial. Forty-eight of them completed the feasibility questionnaire. Thirty-five (36%) sites were finally selected to participate in the study at the initiation (see Table 1). Thereafter, 8 more sites solicited the sponsor and were selected to participate.

	Solicitations		Feasability questionnaire completed		Selected	
	97		48		35	
Non university hospital	46	47,4%	14	29,2%	5	10,4%
University hospital	41	42,3%	31	64,6%	29	60,4%
Clinic/ Private institution	8	8,2%	1	2,1%	0	0,0%
Military Hospitals	2	2,1%	2	4,2%	1	2,1%

Table 1 : Clinical site profile during the initial feasibility study in France.

In Europe, the Sponsor received 46 solicitations from sites in 16 different countries outside France following the publication of the study on Clinicaltrials.gov and EudraCT. Feasibility questionnaires were sent to 35 sites and 12 (34%) were selected to participate in the study.

Site initiation visits and inclusions

Site initiation began on March 22nd 2020. Forty-three sites were initiated in France until November 2020 and 11 sites in Europe between April and December 2020. Both infectious diseases and intensive care departments were initiated for the DisCoVeRy Trial. In France, green light (authorization for inclusion) was sent by the sponsor in average 3 days after the SIV and the site included their first patient in average 2 days after the green light (see Figure 1).

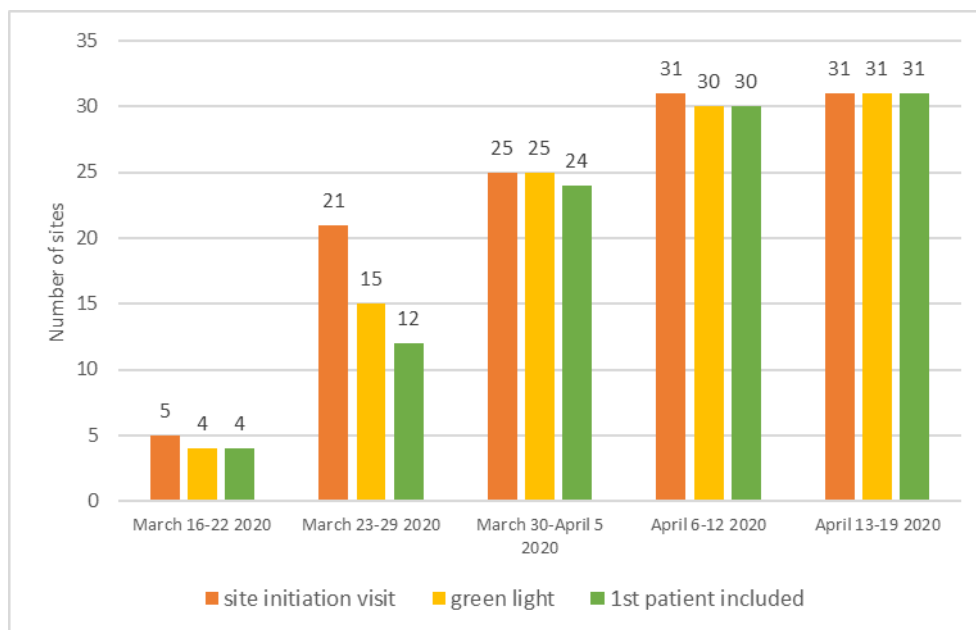


Figure 1: Site initiation visit, green light, and active site in France, within the first 5 weeks of the study.

In the other countries, as they joined between the first and second waves of the pandemic, the site authorization to start the inclusions was given in average 22 days (between 2 days and 3 months) after the SIV and the first patient was included in average 27 days (between 10 days and 2 months) after the green light.

Patients recruitment

Overall, 1309 patients were included between March 22nd 2020 and January 20th 2021, in 48 active sites in 5 countries, including 39 in France (*see Figure 2*).

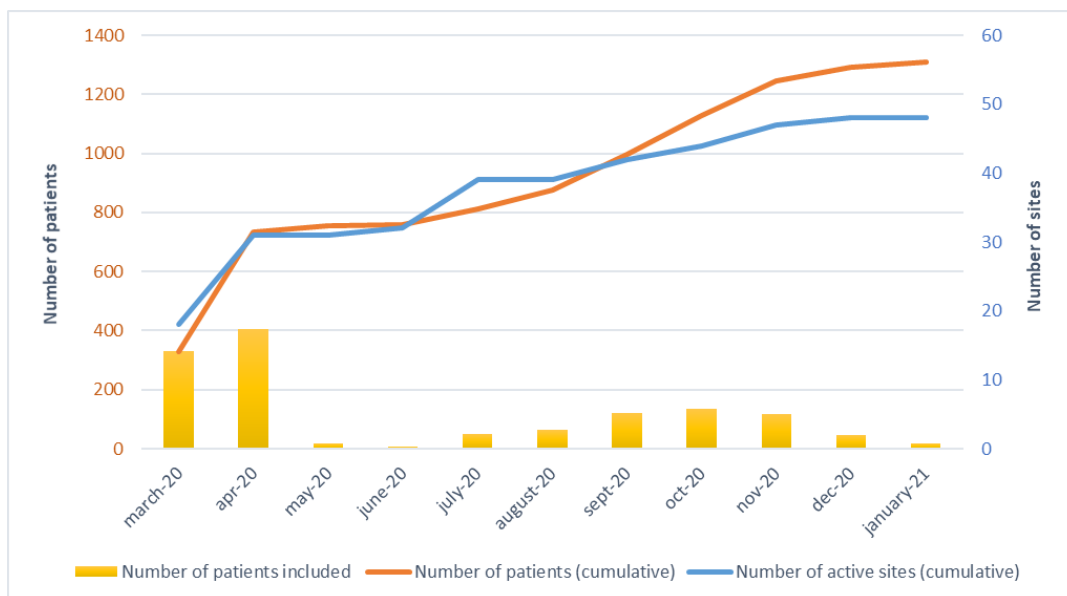


Figure 2: Timeline of site activation and inclusions

Patients were followed up to 90 days after randomization and the last visit of the last patient occurred on April 26th 2021.

Monitoring

Monitoring organization

In France, as a result of the temporary measures for the conduct of clinical trials published by the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), many trials were temporarily suspended and monitoring visits were postponed. The CRAs dependent on the Research Departments of the institutions have thus experienced a drop in activity that was not compensated by the implementation of COVID studies.

This situation allowed us to set up an initial organization based on these available and operational personnel, by delegating to the Clinical Research and Innovation Delegations (DRIs) of the participating sites the monitoring of the data of patients included on their sites. As most of these staff had secure electronic access to the patient medical files, the monitoring could be carried out without having to physically go on site, thus guaranteeing the security of the CRAs. Therefore, by June 2020, monitoring was delegated to the DRIs for more than 60% of the recruiting sites (*see Figure 3*). With the end of the

lockdown, then the lifting of travel restrictions, and the resumption of the usual activities, the availability of the CRAs initially identified became more limited, and we had to call on a network of freelance CRAs to support or replace these teams in more than half of the recruiting sites by the end of the study. Finally, Inserm was able to recruit an internal CRA as of September 2020, making it possible to take charge of 8 sites where monitoring had not yet been initiated. Eventually, the Sponsor had to set up 21 contracts of delegation of tasks with the DRIs and one public contract with the freelance CRAs network.

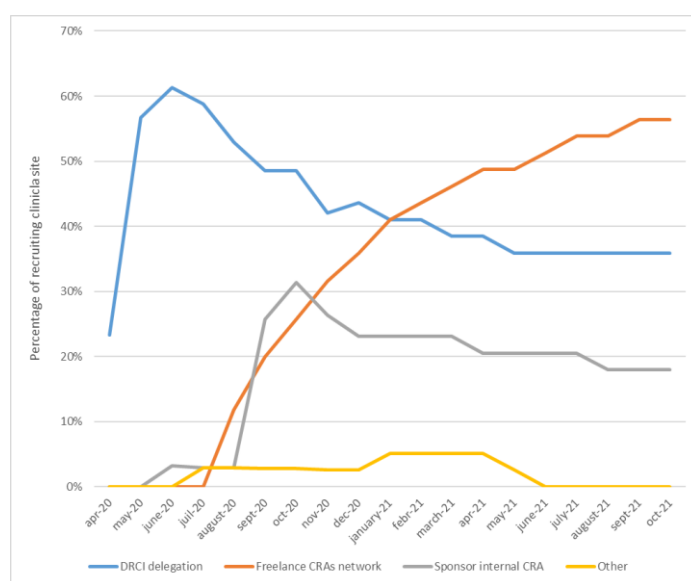


Figure 3: Monitoring delegation in France, in percentage of recruiting sites

Monitoring modalities

Globally, on-site, remote, and off-site monitoring were done, constantly adapting to the pandemic situation and site capacities. Remote monitoring consisted in Source Data verification (SDV) against data available in the patients' electronic hospital files. In centers where the monitoring was delegated to the DRI, remote access for local monitors to the patient's electronic files helped enable data monitoring with minimized site input. However, when monitoring was delegated to external staff, it raised technical and confidentiality considerations. In most cases, hospitals had to draft *ad hoc* procedures to allow access to patients' electronic files by external staff. In one case, the hospital had to send the appropriate computer equipment to the CRA to allow access. In all cases, it took several weeks to set up these

procedures.

Whereas remote monitoring allowed a rapid SDV of most clinical and biological data with no site input, it could not be considered as comprehensive as an on-site monitoring. Indeed, the latter remained relevant as it was instrumental for the verification of several critical aspects such as informed consent (as most of patients' electronic files did not incorporate a copy of the patient's consent), a comprehensive SDV (as there are still many non-computerized source documents), and investigational medical product handling on site (in pharmacies and in the wards). Moreover, on-site monitoring allows face to face discussions between CRA and site staff to clarify comprehension of study protocol and SOP.

Details of the evolution of the Monitoring Plan are presented in the supplemental materials. In Luxembourg, Belgium, and Austria, local CTUs were identified to carry out the monitoring of the sites in their respective countries. In Portugal, the monitoring was done by a Clinical Research Organization (CRO) identified by ECRIN. In Luxembourg, when the study started, only remote monitoring visits were possible, enabled as CRAs had access to the patient medical records.

In some sites in Belgium and Portugal, remote monitoring by phone were performed while waiting for sites to be accessible again. In Austria, during several lockdowns, neither on-site nor remote monitoring visits could be planned and were thus postponed until allowed.

In general, these resulted in some delays in the monitoring.

Quality control

Investigation and data collection involved 1177 investigators and 601 clinical study technicians. Globally, centralized data management was performed throughout the study by the data-management team. Overall, 9 waves of requests were transmitted to the sites with a scheduled shipment every month and then every 15 days from the 5th wave with an average percentage of response of 53%. On the whole, 97 (including 91 in France) CRAs were trained in the Monitoring Plan. The first Monitoring Plan version is dated April 17th 2020, before the first monitoring visits (*for a timeline of the study, see Figure S2 in Supplemental Material*),.

The first monitoring visit took place on April 24th 2020 and the last on October 15th 2021. Overall, 909 monitoring visits were conducted by CRAs (corresponding to a mean 43 visits per months, *see Figure*

4) in all investigational sites, either remote or on-site, resulting in 576 monitoring reports.

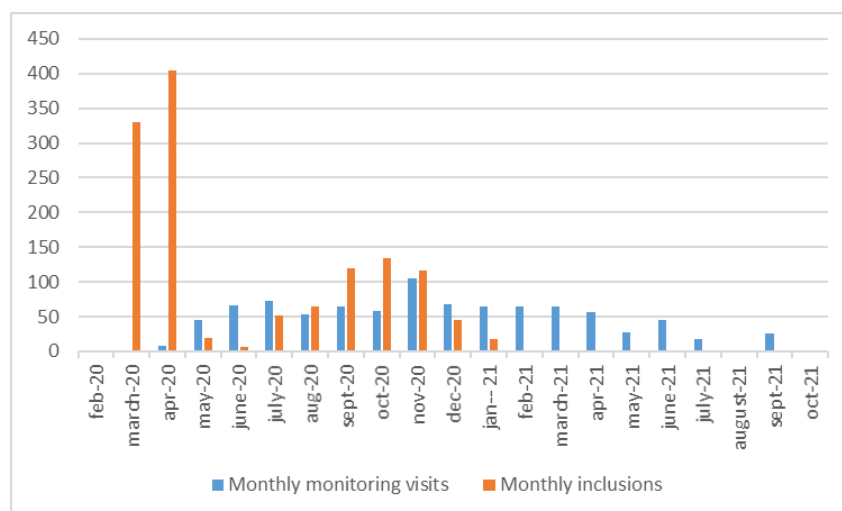


Figure 4: Number of monthly inclusions and monitoring visits

Eventually, monitoring was completed in 18 months, *i.e.* 5.5 months after the last visit of the last patient.

Data quality

Monitoring of consents

Among 1309 included and randomized patients, consent was obtained allowing for analysis of all data in 1231 (94%), of data until sedation release in 25 (2%), of data until the withdrawal of consent or PI decision in 40 (3%). Thirteen patients (1%) could not be analyzed in the absence of a conform consent. The monitoring of 100% of critical data for all patients included in the analysis was achieved, in compliance with the Monitoring Plan.

Monitoring of primary endpoint

The primary endpoint was the clinical status on Day 15 on the 7-point ordinal scale. In May 2020, an evaluation of the rate of correction of the primary endpoint during monitoring was carried out for the 4th DSMB meeting. Out of 212 patients monitored in 10 sites, 11 (5.2%) changes in the primary endpoint were observed. In all cases, the result was corrected by a single point on the scale. This evaluation reinforced the sponsor's confidence in the validity of the data provided to the DSMB and the reliability

of the decision support criteria.

Monitoring of non-critical data

Although the first objective of the Monitoring Plan was achieved (monitoring 100% of the critical data), the monitoring of non-critical data in 50% of the patients, selected by randomization, was not carried out due to a lack of resources and time. The detection of major deviations (related to critical data) in one site did not lead to exhaustive monitoring in this site, for reasons of monitoring prioritization.

Published results

Considering the importance of making the data public, the first publications were issued (9,10) without having monitored all the critical data. Monitoring of consent forms, selection criteria, and primary endpoint had been prioritized to ensure the reliability of the results on these major elements.

The results of the analyses were subsequently updated after monitoring was completed (11,12). Table 2 shows the differences between the two publications concerning the progress of the monitoring at the time of the database lock.

	« 3 arms » publication N=603		« Remdesivir » publication N=857	
Publication	Initial	Final	Initial	Final
Database lock	October 2 nd 2020	November 19 th 2021	February 22 nd 2021	November 19 th 2021
Number of patients included in the analysis	583	593	832	843
Number of declared serious adverse events	608	856	488	542
Changes in primary endpoint final value of patients included in the initial analysis (in points on the WHO ordinal scale)	10 (median 1 point; max 3 points)		19 (median 1 point; max 3 points)	

Table 2 : Characteristics of the publications related to progress of the monitoring

At the time of the first database lock (on October 10th 2020), up to 50% of the prioritized data (selection criteria and primary endpoint) of the 603 patients included in the « 3 arms » population was monitored.

At the time of the second database lock (on February 22nd 2021), up to 40% of the key data of all patients

was monitored.

DISCUSSION

High demand for clinical trials results in the setting of a pandemic, and operational gaps in these trials may jeopardize data integrity and quality of scientific publications (13,14). Despite the start of the DisCoVeRy study before the monitoring team was put in place, the very high rate of recruitment, and the major hurdles linked to the pandemic context, all of the key data to be monitored according to the initial Monitoring Plan were monitored in only 18 months. This was made possible thanks to the huge mobilization of considerable human resources, within a very tight time frame, to the collaboration within Inserm and ANRS| MIE Clinical Research Department units, the clinical research units of the participating healthcare institutions, clinical research organizations, and the solicitation of a network of freelance CRAs.

Monitoring is essential to ensure patient safety and data integrity in clinical trials. However, a most recent work from Hsieh et al. (15) has shown that less than half of the protocol papers published in early 2020 reported the monitoring modalities of the trials. To our knowledge, very few articles have addressed the difficulties of managing a clinical trial during the COVID-19 pandemic (16,17) and none have described the monitoring management. Our work describes our experience in implementing adapted quality assurance procedures and addresses the lessons learned in this context: the safety of the participants and the quality of the data can be ensured, but this requires more resources, different approaches and some flexibility compared to usual practice.

Our results support the feasibility of monitoring of data in a crisis context for assuring regulatory aspects (consents control), safety issues (SAE declaration), and consolidating results on primary endpoint. To achieve the monitoring goals in the DisCoVeRy study phase, we put in place several innovative procedures. In France, a delegation of monitoring to investigator sites DRI allowed to overcome hurdles

related to travel of CRAs for consent and data site monitoring and could be added value to develop on a national level in routine practice. However, the difficulties during initial contracting (sometimes requiring lengthy negotiations) and the challenge in prioritizing the monitoring of DisCoVeRy when the activities of these DRIs resumed (when the confinements were lifted) make it necessary to provide a formalized framework for this type of collaboration, making it possible to anticipate these issues during the implementation of the study.

Direct access for monitors to the electronic patient's files helped enable data monitoring with minimized site input. However, it raised technical and confidentiality considerations that are still not solved for remote access to patient records. In other European countries, despite the support of ECRIN, we had to contract with each of the CTUs in the different countries, sometimes with local requirements needing specific negotiations. In addition, the rules for access to patient data have evolved differently between countries (according to local restrictions, adapted to the evolution of the pandemic), imposing the constant adaptation of monitoring at the local level.

Considerable work was done to recover patient consent forms, allowing, in the end, to analyze more than 99% of the included and randomized patients, despite the pandemic context which changed the procedures for collecting consent in a significant fashion. Indeed, in the intensive care units where visits from relatives were not allowed, the emergency procedure or an initial oral consent of a close relative had been authorized; we therefore had to manage the challenge of recovering the follow-up consents from patients sometimes still unable to consent at the end of their hospitalization. In conventional departments, consent forms were collected after a quarantine period in the patients' rooms, in order to limit the risks of contamination of the staff.

In Europe, due to different regulatory requirements, various solutions for collecting consents have been observed. Some of these solutions, such as electronic consent, could bring real improvement in study recruitment and should be considered by sponsors to be incorporated into routine use (18).

As of 2016, the FDA issued a *Guidance for Institutional Review Boards, Investigators, and Sponsors* (19), providing recommendations on the use of electronic systems and processes that may employ multiple electronic media to obtain informed consent. In a pandemic context, electronic processes may

promote timely entry of any eConsent data into a study database and allow for timely collection of the subject's informed consent data from remote locations.

Our monitoring plan has been continually adapted to the regulatory, technical and scientific constraints. In particular, the monitoring of non-critical data, planned at the initiation of the study, proved impossible to achieve given the context; therefore, all critical data were monitored for all patients included in the analyses. Several studies have assessed the value and effectiveness of alternative monitoring approaches such as targeted or risk-based monitoring (20–23) and a recent Cochrane review (24) found no evidence for inferiority of a risk-based monitoring approach compared to extensive on-site monitoring in terms of critical and major monitoring findings. However, the evaluation carried out for the DSMB showed that almost 5% of the data for the primary endpoint was modified after monitoring. Therefore, it seems crucial to us, despite the financial implications, to maintain a minimum level of quality control on critical data such as consent, selection criteria, primary endpoint, study treatment and safety, in order to guarantee the quality of data and results. It's for the sponsor an important part of the protection due to the patients.

In the pandemic context, given the burden on clinical sites and the difficulties met for achieving an adapted data monitoring, one can question complexity and quantity of the data requested, and the impact of collecting non-essential data on global data quality (25). As a matter of fact, data collection, processing and monitoring consume a large proportion of clinical trial resources, in personnel and therefore in costs. Minimizing data to what is considered critical could reduce burden on the clinical team for completion, monitors for data monitoring, data-managers for CRF and database development and quality control, and statisticians for analyses. Major clinical trials (26,27) have taken up this option during the pandemic and considering restricting data collection in the post-COVID era could be of benefit to clinical research in the long-term. However, considering a new disease caused by a new pathogen, as we faced with COVID-19, it is crucial to benefit from various secondary objectives and rich datasets such as virological and immunological, to allow for a better understanding of the disease and potential treatments mechanisms (28).

CONCLUSION

Crucial research processes, in particular those depending on personnel, have faced many hurdles during the pandemic. This particular context imposed a risk-based monitoring of the DisCoVeRy trial, allowing to ensure safety of participants (consent, tolerance monitoring). This monitoring has been made possible by strong support from French academic research actors. However, the technical and organizational limitations encountered should call for a national reflection to adapt the experience of this experiment to the context of usual clinical trial practice and to improve the response of French academic research during a future epidemic. The digitalization of practices and the delegation of monitoring should be priority areas for reflection in this context.

ACKNOWLEDGMENTS

We thank all study and site staff for their work and for their assistance in ensuring data quality.

We are grateful to the monitoring team (monitoring project managers and clinical research associates) for their strong implication, and to the people in charge of the structures that allowed them to free up time for the study. They are listed in a Supplementary Appendix.

AUTHOR CONTRIBUTIONS

CFL, CD, JS, MD, AF, SLM, SCC and HE were involved in the management of the monitoring of the study. NM, VT, AD, DB, AM, CB, FM and ADi were involved in the management of study data. CFL wrote the original draft of the manuscript, which was reviewed and edited by CD, JS, MD, AF, NM, VT, DB, MN, MH and HE. All authors contributed to refinement of and approved this manuscript. The corresponding author (CFL) had full access to all the data and had final responsibility for the decision to submit for publication.

FUNDING

The DisCoVeRy study received funding from European Union Commission (EU-Response, Grant 101015736), French Ministry of Health (PHRC-20-0351), DIM One Health Île-de-France (R20117HD), REACTing, Fonds Erasme-COVID-ULB; Belgian Health Care Knowledge Centre (KCE), AGMT gGmbH, FEDER "European Regional Development Fund", Portugal Ministry of Health, Portugal Agency for Clinical Research and Biomedical Innovation. Remdesivir was provided free of charge by Gilead.

DATA SHARING : The data used in this work include personal data from clinical research personnel. A pseudonymized dataset will be made available upon request to the corresponding author.

ETHICS : This study did not involve human participants. Patient and public involvement: it was not possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our study as we report retrospective data of a clinical trial sponsoring experience.

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Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

CFL, VT, ADI, VPS, NM, ADE, AM, FM, DB and FA have nothing to disclose. CB has received consulting fees from MYLAN and Da Volterra and participated on a DSMB for 4Living Biotech. MH has received funding from The Belgian Centre for Knowledge (KCE), the Fonds-Erasme-COVID-19-Université Libre de Bruxelles and an EU-Horizon 2020 grant, payment or honoraria for lectures from Pfizer, Gilead and INSM, support for attending meetings and/or travel from Pfizer and Gilead, participated on a DSMB for Gilead and is President of the Belgian Society of Infectious Diseases and Clinical Microbiology and expert for Belgian Taskforce on COVID therapeutics. The institution employing AF, CD, HE, JS, SCC, MD and SLM received support from the French government, the European Commission, the Region Ile de France, Gilead Sciences, Inc., Sanofi, Merck group and AbbVie for the DisCoVeRy study.