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COVID-19 and the Emerging Regulatory Guidance for Ongoing Clinical Trials in the European Union

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The coronavirus disease 2019 (COVID-19) pandemic and the accompanying control measures have significantly affected clinical trial (CT) conduct, and sponsors have needed to make rapid changes to their CT operations. As a result, regulatory guidance was pivotal during the initial phases of the pandemic. This study aimed to evaluate the regulatory readiness and guidance related to COVID-19 in the European Union (EU). The European Medicines Agency (EMA) and national competent authorities' (NCAs') websites were searched in September and October 2020 for guidances on the management of CTs during the pandemic published from January 2020 onward. "Regulatory readiness" was defined as the number of days from the first European COVID-19 case (January 24, 2020) to the first published guidance by the respective NCA. "Regulatory guidance" was evaluated by coding the guidances for the following predefined operational trial activities important for ongoing CTs: obtaining informed consent, participant information, clinic visits, home health visits, telemedicine visits, self-monitoring, investigational medicinal product (IMP) supply, IMP adherence monitoring, CT monitoring, documentation management, regulatory management, and safety management. Twenty-four of the 27 EU NCAs published country-specific guidance. The time from the first European COVID-19 case to the first published EMA guidance was 56 days and ranged from 47 to 66 days for the first national guidances. Guidance was provided most frequently for regulatory management (24/24), safety management (23/24), documentation management (22/24), and CT monitoring (22/24). The regulatory guidance provided during the pandemic, ensuring participant safety and data integrity, may now be the starting point to innovate future CT conduct.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The coronavirus disease 2019 (COVID-19) pandemic has impacted the clinical trial landscape. A swift response from regulators, including the provision of regulatory guidance for ongoing clinical trials, was needed during the pandemic to ensure participant safety and robustness of the data generated.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ What was the regulatory response in the European Union to the COVID-19 pandemic regarding ongoing clinical trials?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ European regulatory authorities published guidance 47–66 days after the first European COVID-19 case to ensure participant safety and valuable data generation in ongoing clinical trials. To ensure overall trial continuity, Europe-wide guidance and flexibility on various important trial activities that differed from normal on-site practice were employed. Harmonization of heterogeneous guidance could further improve clinical trial conduct in the European Union.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The regulatory guidance observed during the pandemic has the potential to transform clinical trial conduct post–COVID-19, through revisiting regulatory requirements and investigation of the quality of remotely generated data.

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In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China.[1] As of February 2021, there have been more than 106 million cases of the novel coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2.[2] The pandemic and accompanying control measures have significantly impacted global clinical trial (CT) conduct. Restricted healthcare-center visits, limitations on healthcare staff availability, and restricted travel initially led to interrupted,[3] delayed, and canceled CTs.[4–6] In addition, ongoing CTs have experienced incomplete data collection,[4] limited or geographically fragmented enrollment,[4,7] and COVID-19–affected end points (e.g., safety outcomes).[8] These factors, taken together, have made obtaining both safety and efficacy data from participants more difficult, thereby altering data quality[9] and obstructing or delaying the development and investigation of various therapeutic interventions.[10]

During the COVID-19 pandemic, sponsors and investigators have made rapid decisions to ensure both participant safety and data integrity. The continuance of CTs is vital for ensuring that participants continue to receive treatment, sponsors generate the evidence needed to support regulatory assessment of their products, and healthcare professionals can make evidence-based data-driven decisions.[11] The safety of trial participants and data integrity are of the utmost importance in CTs, and the COVID-19 pandemic has posed additional challenges to the maintenance of these. The Biostatistics Working Party of the European Medicines Agency (EMA) emphasizes that, despite these challenges, "data collection should preferably not stop and should continue as long as possible."[11] Regulatory guidance, including some regulatory flexibility, is needed to safeguard CT continuity and to allow divergence from normal clinical research practice while maintaining regulatory standards. Regulatory guidance on trial continuation during the COVID-19 crisis was needed promptly so that sponsors could continue to comply with (inter)national regulations for CT conduct. Overall, compliance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (ICH GCP) guideline and other (inter)national regulations is essential, regardless of the pandemic, to ensure the safety of CT participants and data acceptance by regulatory authorities.[12,13]

A number of flexibilities have been implemented during the COVID-19 pandemic to ensure trial continuation, limiting missing data while maintaining safety monitoring.[14] For many of these flexible approaches there is limited knowledge of whether they are equally conducive to the ascertainment of data quality or participant safety. Flexibilities included, for example, remote visits, mailing or emailing of consent forms, shipping drugs and devices to participants, data collection through electronic participant-reported outcomes, and remote monitoring visits via digital access to electronic health records.[15–18] Additionally, submission of paper documentation to the national competent authorities (NCAs) could be replaced by digital communication systems, thereby reducing further virus spread and administrative burden for investigative sites.[19] Required communication on amendments and safety measures could also be adapted to optimize the utilization of investigative and regulatory resources. Prompt regulatory guidance could address operational issues arising from the pandemic and contribute to CT continuity. However, the overall European regulatory response to the pandemic in the context of ongoing CTs has not been fully evaluated, nor has there been a systematic comparison of the responses at the country level. In this paper, we assess the overall European Union (EU) regulatory agencies' response to COVID-19—encompassing both regulatory readiness and regulatory guidance—in relation to ongoing CTs.

METHODS

Data sources

We began by performing a search for published EU regulatory guidance on the management of ongoing CTs during the COVID-19 pandemic. To that end, we reviewed the websites of the EMA and the NCAs of the 27 EU member states (MSs) in September and October 2020. The websites of the NCAs (specifically, those departments responsible for CTs) are listed on the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) website and available at https://eudract.ema.europa.eu/nca_contacts.html. This article uses the International Organization for Standardization (ISO) 3166 two-letter country abbreviations (available at https://www.iso.org/iso-3166-country-codes.html) to refer to the individual MSs and their corresponding NCAs (**Table 1**).

Data search and validation

Guidance publications were included in the analysis if they discussed ongoing CT management during the COVID-19 pandemic. Data were collected using the following key search phrases: "COVID-19," "coronavirus," "ongoing clinical trials," and "extraordinary measures." We also explored the documents and news items published on the NCA websites from January 2020 onwards. Using these terms in combination with the NCAs' names in Google enriched the search. Documents and news items, other than those in English, Dutch, or Spanish, were translated using Google Translate (https://translate.google.com/). A complete list of the publicly available guidance documents and uniform resource locator references can be found in **Table S1**. Each NCA was approached via email to verify the publication date of the first guidance and to confirm that all relevant guidance documents had been identified. Twenty-three of the 27 NCAs replied to these requests.

Outcomes

We investigated regulatory readiness and regulatory guidance as a twofold outcome for the regulatory response. Regulatory readiness was defined as (i) the time in calendar days (hereafter referred to as "days") from the date of the first COVID-19 case identified in Europe (January 24, 2020)[20] to the publication date of the first guidance on the management of ongoing CTs by that NCA or the EMA and (ii) the time in days from the date of the first COVID-19 case identified in the MS[21] to the publication date of the first guidance by that NCA. Regulatory guidance—including regulatory flexibilities—was assessed using the Trials@Home "remote decentralized trial process" framework.[22] The framework divides the trial process into assorted trial phases and corresponding trial activities (**Figure S1**). We selected trial activities relevant to operational aspects of ongoing CTs. The selected activities, used as a combined outcome measure to assess regulatory guidance, were as follows: obtaining informed consent (IC), participant information and education, clinic visits, home health visits (HHVs), telemedicine visits, self-monitoring, investigational medicinal product (IMP) supply or resupply, IMP adherence monitoring, CT monitoring, documentation management, regulatory management, and safety management (**Table S2**). Regulatory guidance was assessed by scoring which NCA discussed the selected trial activities (yes/no) and describing the guidance for these specific trial activities. As an example, guidance on CT monitoring typically included

Table 1 Descriptive characteristics of the European member states and national competent authorities

Country (NCA)	Two-letter country abbreviation[a]	Date first registered COVID-19 case[b]	Date first restriction on outdoor gatherings[c]	Date first country- specific guidance published	Ongoing clinical trials January 24, 2020[d]	No. of deaths per 100,000 14 days before guidance[e]	No. cases per 100,000 14 days before guidance[e]	Refer to European Medicines Agency guidance[f]
European Union (EMA)	NA	January 24, 2020	NA	March 20, 2020	NA	NA	NA	NA
Austria (BASG)	AT	February 26, 2020	March 10, 2020	March 17, 2020	2,225	0.03	11.31	Yes
Belgium (FAMHP)	BE	February 4, 2020	March 18, 2020	March 16, 2020	3,539	0.17	15.15	Yes
Bulgaria (BDA)	BG	March 8, 2020	March 13, 2020	March 18, 2020	1,050	0.03	1.16	Yes
Croatia (MoH)	HR	February 26, 2020	March 19, 2020	March 27, 2020	257	0.05	11.75	Yes
Cyprus (MoH)	CY	March 10, 2020	March 10, 2020	Refer to EMA	5	NA	NA	Yes
Czech Republic (SÚKL)	CZ	March 2, 2020	March 12, 2020	March 13, 2020	2,352	0.00	1.09	Yes
Denmark (DMA)	DK	February 27, 2020	March 18, 2020	March 13, 2020	2,045	0.00	11.73	Yes
Estonia (SAM)	EE	February 28, 2020	March 12, 2020	March 18, 2020	508	0.00	16.91	Yes
Finland (FIMEA)	FI	January 30, 2020	March 12, 2020	March 13, 2020	1,460	0.00	2.77	Yes
France (ANSM)	FR	January 24, 2020	March 13, 2020	March 20, 2020	4,254	0.55	15.98	Yes
Germany (BfArM)	DE	January 28, 2020	March 23, 2020	March 30, 2020	5,249	0.54	64.45	Yes
Greece (EOF)	GR	February 27, 2020	March 19, 2020	March 17, 2020	1,131	0.04	3.22	Yes
Hungary (OGYÉI)	HU	March 5, 2020	March 16, 2020	March 11, 2020	2,445	0.00	0.12	Yes
Ireland (HPRA)	IE	March 1, 2020	March 12, 2020	March 13, 2020	732	0.02	1.43	Yes
Italy (AIFA)	IT	January 31, 2020	June 12, 2020	March 12, 2020	4,134	1.35	20.11	Yes
Latvia (ZVA)	LV	March 3, 2020	May 12, 2020	March 16, 2020	507	0.00	1.61	Yes
Lithuania (VVKT)	LT	February 28, 2020	March 19, 2020	March 18, 2020	602	0.00	0.86	Yes
Luxembourg (MS)	LU	March 1, 2020	March 16, 2020	None identified	7	NA	NA	No
Malta (MA)	MT	March 7, 2020	March 13, 2020	None identified	13	NA	NA	No
Netherlands (CCMO)	NL	February 28, 2020	March 12, 2020	March 13, 2020	3,845	0.03	3.55	Yes
Poland (URPL)	PL	March 4, 2020	March 10, 2020	March 19, 2020	1,868	0.01	0.75	No
Portugal (INFARMED)	PT	March 3, 2020	March 15, 2020	March 26, 2020	1,083	0.42	28.74	Yes
Romania (ANM)	RO	February 27, 2020	March 18, 2020	March 13, 2020	158	0.00	0.32	No
Slovakia (ŠÚKL)	SK	March 7, 2020	March 9, 2020	March 16, 2020	980	0.00	1.12	Yes
Slovenia (JAZMP)	SI	March 5, 2020	March 10, 2020	March 24, 2020	242	0.05	20.47	Yes

(Continued)

Table 1 (Continued)

Country (NCA)	Two-letter country abbreviation[a]	Date first registered COVID-19 case[b]	Date first restriction on outdoor gatherings[c]	Date first country- specific guidance published	Ongoing clinical trials January 24, 2020[d]	No. of deaths per 100,000 14 days before guidance[e]	No. cases per 100,000 14 days before guidance[e]	Refer to European Medicines Agency guidance[f]
Spain (AEMPS)	ES	February 1, 2020	March 14, 2020	March 16, 2020	6,363	0.61	24.31	Yes
Sweden (MPA)	SE	February 1, 2020	March 12, 2020	March 20, 2020	2,259	0.26	13.47	Yes

AEMPS, Spanish Agency of Medicines and Medical Devices; AIFA, Italian Medicines Agency; ANM, National Agency for Medicines and Medical Devices of Romania; ANSM, French National Agency for Medicines and Health Products Safety; BASG, Austrian Federal Office for Safety in Health Care; BDA, Bulgarian Drug Agency; BfArM, Federal Institute for Drugs and Medical Devices; CCMO, Central Committee on Research Involving Human Subjects; DMA, Danish Medicines Agency; EMA, European Medicines Agency; EOF, National Organization for Medicines; FAMHP, Federal Agency for Medicines and Health Products; FIMEA, Finnish Medicines Agency; HPRA, Health Products Regulatory Authority; IFARMED, National Authority of Medicines and Health Products; JAZMP, Agency for Medicinal Products and Medical Devices; MA, Medicines Authority; MoH, Ministry of Health; MPA, Swedish Medical Products Agency; MS, Pharmacy and Medication Department; NA, not applicable; NCA, national competent authority; No., number; OGYÉI, National Institute of Pharmacy and Nutrition; SAM, State Agency of Medicines; SÚKL, State Institute for Drug Control; URPL, Office for Registration of Medicinal Products, Medical Devices and Biocidal Products; VVKT, State Medicines Control Agency; ZVA, State Agency of Medicines of the Republic of Latvia.

[a]Two-letter country abbreviations are available at https://www.iso.org/iso-3166-country-codes.html. [b]Date first registered COVID-19 case, available from the European Centre for Disease Control COVID-19 country overviews.[21] [c]The date of the first restriction on outdoor gatherings of 5, 50, 100, 500, or 1,000 participants, available from the European Centre for Disease Control.[23] [d]Ongoing interventional clinical trials on medicines, retrieved from https://www.clinicaltrialsregister.eu (see methods for search string). [e]The cumulative number of deaths/cases per 100,000 14 days prior to the publication of the first guidance, available from the European Centre for Disease Control COVID-19 Situation Dashboard.[24] [f]Reference made to the EMA guidance on the management of clinical trials during the COVID-19 pandemic.[25]

a recommendation to enhance centralized monitoring, but remote verification of source data was only permitted if the CT focused on COVID-19 or was a pivotal CT for a serious or life-threatening disease.

Member state characteristics

To contextualize the regulatory readiness, descriptive characteristics were presented for each MS including the number of ongoing interventional trials on medicines as of January 24, 2020 (date of first confirmed COVID-19 case in the European Union) retrieved from https://www.clinicaltrialsregister.eu (EudraCT database) on November 16, 2020. All trial phases were included, and trials were considered ongoing as of January 24, 2020, when the trial status was "ongoing" and the trial start date was before January 24, 2020, with the addition of trials that were "completed" or "suspended by NCA" or "temporarily halted" or "prematurely ended" between January 25 and November 16, 2020, with a start date before January 24, 2020. If the trial start date was not indicated in EudraCT, it was assumed to have been before January 24, 2020. Descriptive characteristics included the date of the first national restriction on outdoor gatherings of more than 5, 50, 100, 500, or 1,000 individuals,[23] the cumulative number of COVID-19–related deaths and cases per 100,000 14 days prior to the publication of the first guidance,[24] and information (yes/no) on the reference to the EMA guidance[25] in the NCAs' guidelines or on their websites.

Data analysis

Descriptive statistics were used to report on regulatory readiness. Regulatory readiness was presented as the difference in days between the date of the first registered European or national COVID-19 case and the publication date of the NCA's first guidance document. Guidance documents and website items were independently coded for the selected Trials@Home trial activities by two authors (A.J.d.J. and Y.S.-A.T.) using NVivo 12 Pro, QSR International, Burlington, MA. The coded trial activities from the Trials@Home framework, the definitions, and the example codes can be found in **Table S2**. The two authors who coded the documents compared and resolved the disagreements (A.J.d.J. and Y.S.-A.T.). The coded segments were presented as the total number of NCAs that mentioned that specific trial activity, relative to the total number of NCAs that provided country-specific guidance. The content of the guidance on the trial activities was analyzed by extracting the corresponding coded segments and describing the recurring topics, similarities, and differences.

RESULTS

Regulatory readiness

Overall, 25 of the 27 NCAs of the MSs published guidance (a document or a news item) on ongoing CTs during the COVID-19 pandemic (**Table S1**). Twenty-four NCAs have provided country-specific guidance on ongoing trial management supplementary to the EMA guideline,[25] and only one NCA (Cyprus) referred solely to the EMA guideline without additional specifications (**Table 1**). For 18 of the 24 NCAs, we identified at least one guidance document in English. We were unable to identify any new guidance or reference to the EMA guideline from the NCAs of Luxembourg and Malta, which had 7 and 13 ongoing CTs, respectively, as of January 24, 2020.

On January 24, 2020, the first case of COVID-19 was confirmed in Europe (France (FR)).[20] Most European countries reported their first COVID-19 cases shortly afterward (**Table 1**). **Figure 1** presents the number of days to the publication of the first guidance, with both the date of the first European COVID-19 case (gray)

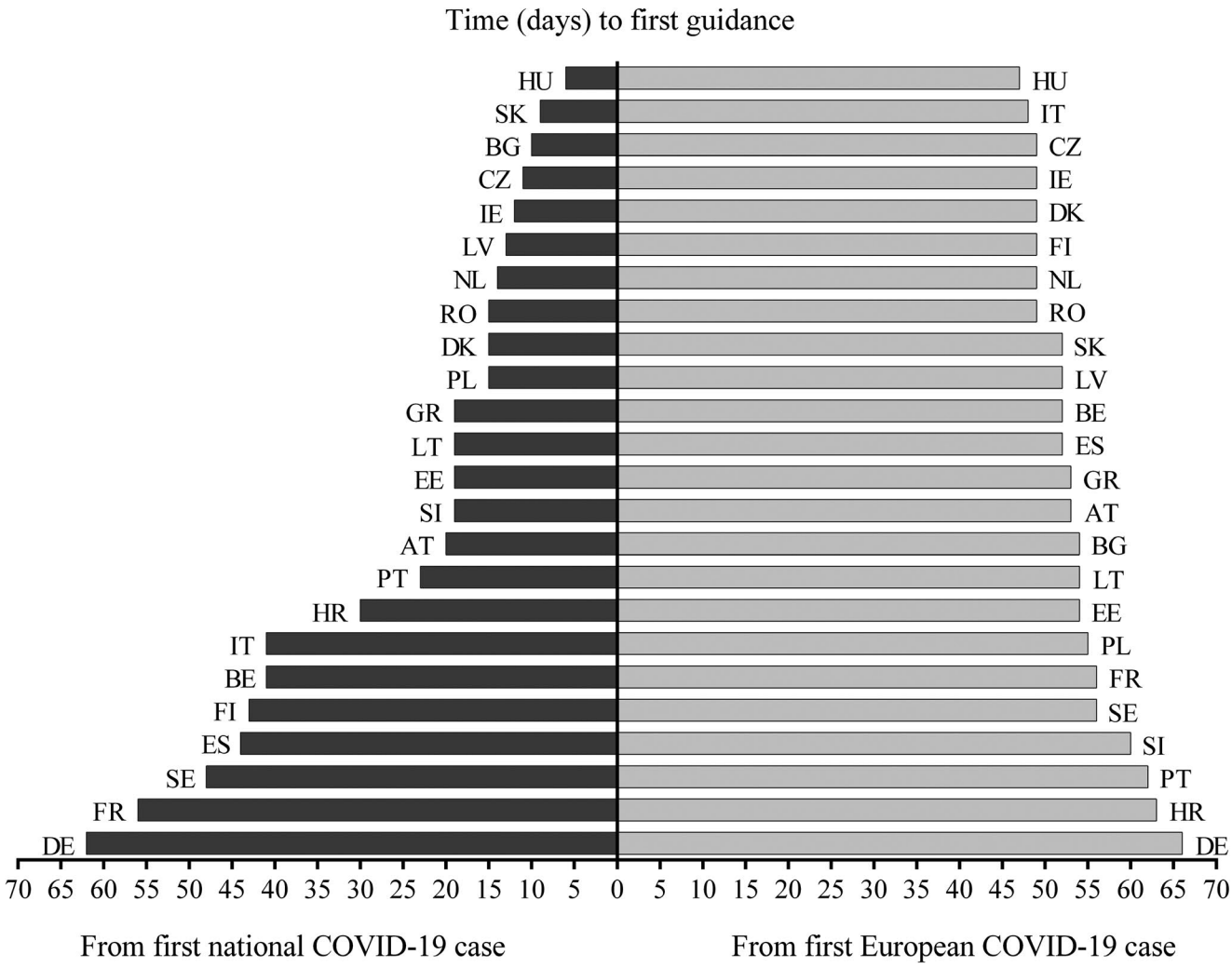

Figure 1 European regulatory readiness. The time in days between the first reported COVID-19 case in the member state (black) or the first European COVID-19 case (gray) and the first regulatory guidance on ongoing clinical trials published by the respective national competent authority. The first EMA guidance was published on March 20, 2020, 56 days after the first European COVID-19 case. Two-letter country abbreviations are available in **Table 1**. COVID-19, coronavirus disease 2019; EMA, European Medicines Agency.

and the date of the first reported COVID-19 case in the respective MS (black) as references. The median number of days between the first European-confirmed COVID-19 case and the first guidance publication was 52.5 (range 47–66). The median number of days between the first country-specific COVID-19 case and the first guidance publication was 19 (range 6–62). The Hungarian agency (National Institute of Pharmacy and Nutrition (OGYÉI)) published guidance on the management of ongoing CTs before any other MS, 47 days after the first European case and 6 days after the country's first COVID-19 case. The first EMA guidance was published 56 days after the first European case. **Figure 2** shows that NCAs in countries with a higher number of ongoing CTs did not necessarily publish guidance faster than NCAs in countries with fewer ongoing CTs. For example, the six EU countries with the highest number of ongoing CTs as of January 24, 2020 (Belgium (BE), Germany (DE), Spain (ES), FR, Italy (IT), and the Netherlands (NL)) had a median of 52 days from the first European COVID-19 case to the publication of their first guidance.

Regulatory guidance: Development and identification of guidance on specific trial activities

Several guidances on the management of CTs during the COVID-19 pandemic were developed based on, or included, queries received from sponsor companies (Austria (AT), BE, Czech Republic (CZ), FR, IT, NL, and Sweden (SE)), regularly in conjunction with (national) authorities (e.g., ethics committees (ECs) and ministries of health) (EMA, BE, DE, ES, and FR). The emergency measures described in the guidelines were considered valid until there is "consensus that the period of the COVID-19 outbreak in the European Union / European Economic Area has passed" (EMA). Some NCAs (CZ and Denmark (DK)) have applied predefined expiration dates to the emergency measures, and these have been extended several times as the pandemic continued.

Table 2 presents an aggregated overview of CT activities for which guidance has been provided as a regulatory response to COVID-19. Of the 24 NCAs that have published country-specific guidance, all have provided guidance on regulatory management,

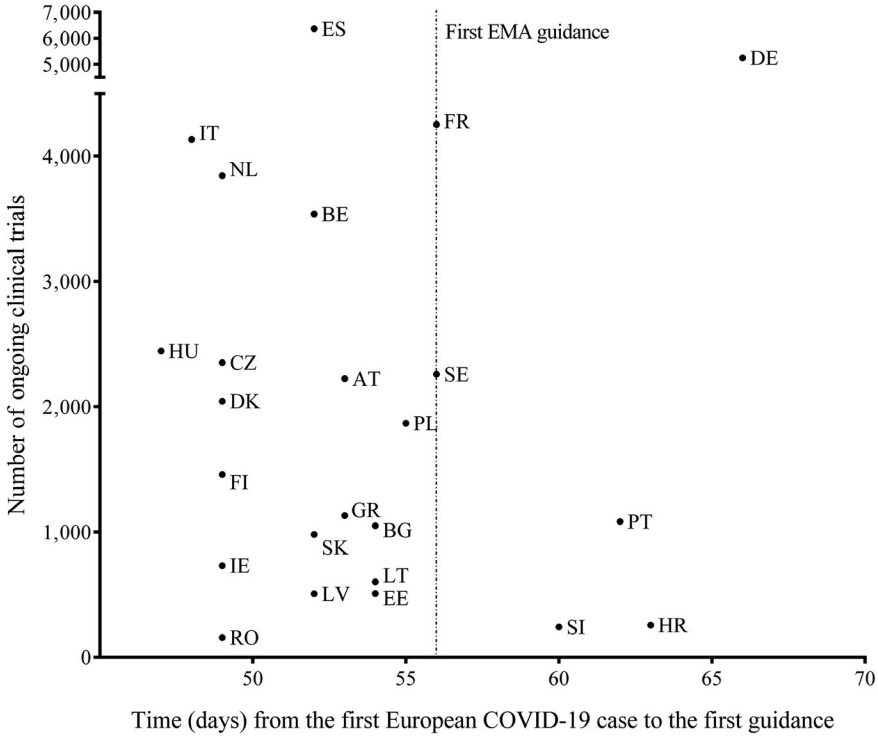

Figure 2 Regulatory readiness defined as days from the first European COVID-19 case to the first country-specific guidance is plotted against the number of ongoing interventional clinical trials on medicines on January 24, 2020, which is the date of the first reported European COVID-19 case. The dotted line represents the number of days from the first European COVID-19 case until the first guidance was published by the EMA on March 20, 2020. The number of ongoing clinical trials and two-letter country abbreviations are available in **Table 1**. COVID-19, coronavirus disease 2019; EMA, European Medicines Agency.

and 23 have provided guidance on safety management. Many have also provided guidance for documentation management, CT monitoring, IMP supply or resupply, and solutions to trial visits such as telemedicine visits and HHVs. The EMA guideline and country-specific guidelines from the State Institute for Drug Control (SÚKL) (CZ) and the Italian Medicines Agency (AIFA) (IT) included guidance on all selected trial activities except self-monitoring of CT participants.

Eighteen NCAs published national guidance before the release of the EMA guidance (**Figure 2**). For 13 of these, updated information or a new guidance document was identified after the first EMA guidance was issued (AT, BE, CZ, DK, Estonia (EE), ES, Greece (GR), Hungary (HU), Ireland (IE), IT, NL, Romania (RO), and Slovakia (SK)). The updated guidance documents, released after the first EMA guidance, typically covered more trial activities than the initial guidance including guidance for CT monitoring and remote source data verification (rSDV), obtaining IC, and IMP supply. Of note, the level of detail of the initial guidances differed between the NCAs. For example, SÚKL (CZ) provided guidance on all trial activities as indicated in **Table 2** except for "participant information and education" before the first EMA guidance was issued, and elaborated on the published guidance later. On the other hand, the Federal Agency for Medicines and Health Products (FAHMP) (BE) initially published a news item on IMP supply and documentation management, and issued extensive guidance documents (covering the trial activities displayed in **Table 2**) later, after the first EMA guidance was published.

Regulatory guidance: A general description of the content

The provided guidances included proposed flexibilities to support the continuation of CTs during the pandemic. Sixteen NCAs have provided guidance on obtaining IC as this could be hampered by the imposed COVID-19 restrictions and the risk of spreading the virus when traveling to the trial site or using paper IC forms. Guidance has been provided on substantial changes to which participants should consent and how the IC should be obtained if on-site was not possible or not advised. Namely, clinic visits should only take place if strictly necessary, such as for IMP administration by a nurse or physician (EMA, Bulgaria (BG), DK, ES, Croatia (HR), HU, IT, RO, and SK). Other NCAs recommended modifying the frequency of the visits (EE and Portugal (PT)) or continuing normal follow-up visits if the epidemiological situation allowed (CZ). If strictly necessary, site-based clinic visits could also continue by transferring participants to new or existing sites (EMA, BG, CZ, DK, EE, ES, FR, HR, HU, IE, IT, Lithuania (LT), Latvia (LV), and PT). To maintain trial integrity and to ensure participant safety, regulatory bodies have provided guidance on alternative visit methods such as telemedicine visits (EMA, BE, BG, CZ, DE, DK, EE, ES, FR, HR, HU, IE, LV, NL, PT, RO, and SK) and HHVs (EMA, BE, CZ, DK, EE, HR, IE, IT, LT, and LV). Only the OGYÉI (HU) did not permit HHVs, as this could put an additional burden on the site study staff and increase SARS-CoV-2 infections. Self-monitoring as a solution for continued participant monitoring and data collection was only discussed in the Estonian NCA's guidance. The guidance

Table 2 Guidance published by the EMA and national competent authorities for different trial activities

Clinical trial phase	Recruitment and enrollment	Patient engagement	Intervention and follow-up						Operation and coordination				
Country (NCA)	Obtaining informed (re-)consent	Participant information and education	Clinic visits	Home health visits	Telemedicine visits	Self-monitoring	IMP (re-) supply	IMP adherence monitoring	Clinical trial monitoring	Documentation management	Regulatory management	Safety management	Total (12)
European Union (EMA)	■	■	■	■	■		■	■	■	■	■	■	11
Austria (BASG)		■					■		■	■	■	■	6
Belgium (FAMHP)	■	■		■	■		■		■	■	■	■	9
Bulgaria (BDA)			■		■		■		■	■	■	■	7
Croatia (MoH)	■		■	■	■		■		■	■	■	■	9
Czech Republic (SÚKL)	■	■	■	■	■		■	■	■	■	■	■	11
Denmark (DMA)	■	■	■	■	■		■		■	■	■	■	10
Estonia (SAM)	■		■	■	■	■	■		■	■	■	■	10
Finland (FIMEA)							■		■	■	■		4
France (ANSM)			■		■		■		■	■	■	■	7
Germany (BfArM)	■				■				■	■	■	■	6
Greece (EOF)	■	■					■		■	■	■	■	7
Hungary (OGYÉI)	■	■	■	■	■		■		■	■	■	■	10
Ireland (HPRA)	■		■	■	■		■		■	■	■	■	9
Italy (AIFA)	■	■	■	■	■		■	■	■	■	■	■	11
Latvia (ZVA)			■	■	■		■		■	■	■	■	8
Lithuania (VVKT)	■	■	■	■			■		■	■	■	■	9
Netherlands (CCMO)	■	■			■		■		■	■	■	■	8
Poland (URLP)										■	■	■	3
Portugal (INFARMED)	■	■	■		■		■		■	■	■	■	9
Romania (ANM)		■			■		■		■		■	■	6
Slovakia (ŠÚKL)	■	■	■		■		■	■	■	■	■	■	10
Slovenia (JAZMP)											■	■	2
Spain (AEMPS)	■	■	■		■		■		■	■	■	■	9
Sweden (MPA)							■		■	■	■	■	5
Total (25)	16	14	15	11	18	1	22	4	23	23	25	24	

The trial activities were aggregated from all the guidances that were identified.
Gray, guidance identified; white, no guidance identified.
AEMPS, Spanish Agency of Medicines and Medical Devices; AIFA, Italian Medicines Agency; ANM, National Agency for Medicines and Medical Devices of Romania; ANSM, French National Agency for Medicines and Health Products Safety; BASG, Austrian Federal Office for Safety in Health Care; BDA, Bulgarian Drug Agency; BfArM, Federal Institute for Drugs and Medical Devices; CCMO, Central Committee on Research Involving Human Subjects; DMA, Danish Medicines Agency; EMA, European Medicines Agency; EOF, National Organization for Medicines; FAMHP, Federal Agency for Medicines and Health Products; FIMEA, Finnish Medicines Agency; HPRA, Health Products Regulatory Authority; IFARMED, National Authority of Medicines and Health Products; IMP, investigational medicinal product; JAZMP, Agency for Medicinal Products and Medical Devices; MA, Medicines Authority; MoH, Ministry of Health; MPA, Swedish Medical Products Agency; MS, Pharmacy and Medication Department; NA, not applicable; NCA, national competent authority; No., number; OGYÉI, National Institute of Pharmacy and Nutrition; SAM, State Agency of Medicines; SÚKL, State Institute for Drug Control; URPL, Office for Registration of Medicinal Products, Medical Devices and Biocidal Products; VVKT, State Medicines Control Agency; ZVA, State Agency of Medicines of the Republic of Latvia.

described measurements that the site study staff would normally perform but which could temporarily be done by the participants themselves such as temperature and blood pressure.

Owing to limited on-site visits, other IMP-distribution solutions were permitted to ensure that participants received treatment. Different methods of supplying IMP included dispensing more IMP at the trial site (EMA, CZ, DK, EE, ES, HU, IT, and SK), shipment to a local pharmacy (AT, DK, NL, and RO), direct-to-participant (DtP) shipment from the site (EMA, AT, BE, CZ, DK, EE, ES, Finland (FI), FR, GR, HR, HU, IE, IT, LT, LV, NL, PT, RO, SE, and SK), and DtP shipment from the trial sponsor via a courier (EMA, AT, DK, EE, ES, LT, LV, RO, and SK). DtP shipment from the trial sponsor via a courier was not permitted in several MSs, with ethical and practical questions regarding personal data protection given as the main concern (BE, CZ, FI, FR, GR, HR, HU, IT, IE, NL, and SE).

Quality-control processes such as CT monitoring have remained essential during the pandemic, ensuring participant safety and data integrity. However, restrictive hospital measures limited on-site visits. In general, the EU NCAs indicated that sponsors should postpone or replace on-site monitoring visits with remote visits (e.g., through telephone contact) and extensive centralized monitoring (EMA, AT, BG, CZ, DK, ES, FI, FR, GR, HU, IE, IT, LT, LV, PT, RO, SK, and SE). Performing rSDV was typically not allowed in Europe. However, rSDV could be applied specifically for COVID-19 CTs and pivotal CTs for serious or life-threatening diseases with no satisfactory treatment options in the final stage before database lock in most MSs (EMA, AT, CZ, DE, DK, ES, FR, GR, IE, IT, LT, LV, NL, PT, SE, and SK). On the other hand, in Belgium, Croatia, and Estonia, rSDV was not allowed at all. The main reasons for this were the threat to participants' privacy and the additional burden that rSDV could place on the site study staff.

The NCA guidelines emphasized the importance of documenting and justifying all changes and GCP/protocol deviations due to COVID-19, as required per ICH GCP.[12] Measures, amendments, and risk assessments had to be labeled with "COVID-19" and included in the trial master file. In contrast to common trial practice, wet-ink signatures or qualified electronic signatures were not always needed on clinical trial applications and substantial amendments (SAs) (BE, DK, FR, HU, NL, and Poland). Furthermore, most NCAs have provided guidance on the electronic submission of notifications, clinical trial applications, and SAs through the Common European Submission Portal, national portals, or via email (AT, CZ, DE, DK, EE, FR, HR, HU, IE, IT, LT, NL, Poland, PT, RO, and SE). In general, SAs and safety measures needed to be communicated to the authorities without undue delay. Urgent safety measures could be implemented without prior approval, though they required notification without delay to the appropriate ECs and NCAs. However, the judgment of whether a measure was "urgent" and could be implemented without prior approval as an urgent safety measure, or whether it required approval by means of an SA, varied between countries. Typically, SAs were needed for measures that did not require immediate implementation, and the EMA guidance stressed that previous guidance on SAs remained applicable,[26] which entails that sponsors assess whether a measure is "substantial"; that is, whether it has the potential to impact participant safety and/or trial data.

The NCAs frequently reiterated and emphasized existing safety practices[12] in the guidance documents, as the monitoring and reporting of safety events should continue as per usual practice, in compliance with the applicable regulations. Additionally, all 23 countries that have discussed safety management emphasized the importance of continuous risk assessment during the pandemic. Based on this risk assessment and to ensure participant safety, several continuity measures could be implemented, such as the aforementioned remote telemedicine visits, HHVs, transfer of participants, and DtP IMP supply. Other measures discussed in the guidelines included the temporary halt of a trial, suspension of recruitment, termination of CTs with risk groups (e.g., immunosuppressant studies), and the use of local laboratories instead of central laboratories. Although the trial activities coded for were predefined, the authors did not identify other recurrent topics important for ongoing CTs in the guidance documents.

DISCUSSION

In this paper, we showed that despite the gap between the first European COVID-19 case and the date on which the first guidance was published, the NCAs published guidance 19 days (median) after the first country-specific COVID-19 case was identified. In general, the NCAs have provided guidance for various trial activities considered important for the continuation of ongoing CTs, such as regulatory management, telemedicine visits, IMP supply, and CT monitoring.

During the initial phase of the COVID-19 pandemic, the implementation of continuity measures was challenging[17] but necessary to overcome CT conduct disruption due to restricted hospital visits, an interrupted IMP supply chain, and limited site study staff availability.[27] It is assumed that NCAs and ECs provided guidance to CT sponsors prior to the availability of public guidance documents, given the extent of CT conduct in the European Union before the pandemic (**Figure 2**). Prompt availability of regulatory guidance during the initial phases of the pandemic was hugely important. The variance in regulatory readiness, as reported in this study, may partly be explained by national-level differences related to the pandemic, including the dynamics of the virus spread, pressure on the healthcare system, and country-specific response measures.[21,23]

Regulatory readiness was also required on a global scale, and various regulatory authorities issued guidance during the pandemic. The United Kingdom Medicines and Healthcare Products Regulatory Agency,[28] Health Canada,[29] US Food and Drug Administration,[30] Japan Pharmaceuticals and Medical Devices Agency,[31] and the Australian Therapeutic Goods Administration[32] issued guidance on the management of ongoing CTs 52, 63, 65, 81, and 87 days after the first national COVID-19 cases, respectively.[24] Although variation within the regulatory readiness of these authorities exists, it seems in line with the readiness of the EMA.

Our analysis shows that the European regulatory authorities provided guidance and flexibility on various important trial activities to ensure overall trial continuity. Flexibility can be introduced by regulatory authorities in various ways, including nonenforcement

of regulations, waiving of regulations, and interpretive flexibility.[33] During the pandemic, NCAs temporarily permitted specific trial activities, which were not accepted before the pandemic. For example, before the pandemic, certain regulations prohibited DtP IMP supply[34,35] or required paper submission of CT documents.[36] However, other measures such as centralized monitoring, though not rSDV,[37] and telemedicine visits (as part of usual care) were already permitted in certain MSs.[38,39] As the pandemic continued, additional flexibility has been provided. For example, the recent EMA guidance on CT management during the pandemic (version 4; February 4, 2021) permits rSDV for a broad range of CTs, in addition to COVID-19 CTs and CTs for life-threatening diseases, including CTs where the absence of source data verification could pose risks to participants' safety or data integrity; CTs with vulnerable participants (e.g., children or participants incapable of giving IC); and pivotal trials.[25] The recent EMA guidance also leaves room for rSDV to be performed outside the European Union / European Economic Area provided that the data protection is equivalent to the EU standards.[25]

The guidelines on the management of CTs during the COVID-19 pandemic often lacked guidance on self-monitoring, IMP-adherence monitoring, and HHVs (**Table 2**), which could be because these measures were already permitted and performed remotely or at the participant's home before COVID-19.[35] Furthermore, we found that some NCAs provided minimal guidance on the country-specific interpretations of the EMA guideline or supplementary measures. However, this does not necessarily mean that no guidance is applicable in these MSs. For example, three NCAs (DE, Cyprus, and Slovenia) stated in their guidance that the EMA guidance had been used as the official reference, with additional interpretation only provided where this was deemed necessary (DE). Furthermore, prepandemic guidelines and regulations remain applicable. Therefore, country-level comparisons should be interpreted tentatively.

Implications of this study

Other authors have argued for applying "regulatory flexibility" beyond the current COVID-19 pandemic and against a return to previous practices, for the benefit of patients suffering from (life-threatening) diseases.[33,40–42] This study has shown that regulators have readily accepted telemedicine visits, enhanced remote CT monitoring, DtP IMP supply, and simplified interaction with the authorities via digital means during the pandemic, albeit temporarily. However, country-specific differences in the guidance provided within the European Union (mainly regarding regulatory management, DtP IMP supply from the sponsor, and rSDV; **Table S3**) could have made it difficult for sponsors to adapt to these guidances for trials conducted in multiple MSs. This would benefit from a harmonized approach. The implementation of the European Clinical Trial Regulation (No. 536/2014) will innovate and harmonize regulatory management through simplified and unified submission procedures via a digital CT platform.[43] However, the regulation does not specifically address the other "flexibilities" described in this research. Therefore, the evaluation of regulatory simplifications and innovations beyond the COVID-19 crisis should be prioritized by the NCAs and ECs,[33] to harmonize and simplify overall CT conduct across the European Union. This study's findings may serve as a starting point for revisiting existing regulatory requirements and enhanced collaboration between NCAs.

Strengths, limitations, and future perspectives

The current study contributes to an understanding of the regulatory acceptance of frequently utilized trial changes adopted during the COVID-19 pandemic. This research is the first investigation of regulatory readiness and guidance of all NCAs in the European Union. The insights gained from this study advocate collaboration between NCAs to identify best practices and promote a harmonized practice across the European Union post pandemic. However, being limited to publicly available information, this study lacks analysis of the regulatory guidance provided to individual sponsors. In addition, we demarcated our research by focusing on the management of ongoing CTs, thereby excluding other relevant processes such as remote GCP inspections[13] and the development of COVID-19 therapeutics, where greater flexibility may be required to ensure timely access to safe and high-quality COVID-19 treatments.[44] Similarly, we did not discuss exceptional regulatory tools such as expedited regulatory review methods, as these methods do not affect trial continuity and were established before the pandemic.[45] Several questions remain unanswered at present. For example, it is not yet clear how regulators will eventually assess the data generated remotely during the pandemic. Further research might evaluate the extent to which the current experience could lead to the postpandemic adoption of innovative methods by sponsors and whether sponsors, clinical trialists, and trial participants found the guidelines helpful under the circumstances and whether they would suggest any changes to them.

CONCLUSION

The present research found that, country-specific differences in guidance content notwithstanding, the EMA and most EU NCAs have published guidance on topics important for maintaining participant safety and data integrity, such as remote trial visits and DtP IMP supply. The rapid issuance of COVID-19–related regulatory guidances has potentially contributed to the continuance of many ongoing CTs during the pandemic. However, the possibility to innovate and harmonize CT practice across the European Union also through the implementation of the European Clinical Trial Regulation and opportunities engendered by the current pandemic should be seized by NCAs.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST
The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS
A.J.d.J., Y.S.-A.T., G.J.M.W.v.T., M.G.P.Z., S.J.S., D.M., A.d.B., and H.G. wrote the manuscript. A.J.d.J., Y.S.-A.T., and H.G. designed the research. A.J.d.J., Y.S.-A.T., and H.G. performed the research. A.J.d.J. and Y.S.-A.T. analyzed the data.

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