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

Amos Jochanan de Jong¹, Yared Santa-Ana-Tellez¹, Ghislaine José Madeleine Wilhelmiem van Thiel², Mira Gerta Petra Zuidgeest², Satu Johanna Siiskonen¹, Dinesh Mistry³, Anthonius de Boer¹,⁴, and Helga Gardarsdottir¹*, On behalf of the Trials@Home Consortium†

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.

¹Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; ²Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; ³Covance Clinical Services Ltd, Maidenhead, UK; ⁴Dutch Medicines Evaluation Board, Utrecht, The Netherlands. *Correspondence: Helga Gardarsdottir (h.gardarsdottir@uu.nl)
†https://trialsathome.com

Received December 24, 2020; accepted March 5, 2021. doi:10.1002/cpt.2225
In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China.\textsuperscript{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.\textsuperscript{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,\textsuperscript{3} delayed, and canceled CTs.\textsuperscript{4–6} In addition, ongoing CTs have experienced incomplete data collection,\textsuperscript{4} limited or geographically fragmented enrollment,\textsuperscript{4,7} and COVID-19–affected end points (e.g., safety outcomes).\textsuperscript{8} These factors, taken together, have made obtaining both safety and efficacy data from participants more difficult, thereby altering data quality\textsuperscript{9} and obstructing or delaying the development and investigation of various therapeutic interventions.\textsuperscript{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.\textsuperscript{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.”\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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—embracing 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://eudra.ct.ema.europa.eu/nca_contactsl.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)\textsuperscript{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\textsuperscript{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.\textsuperscript{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 | Date first registered COVID-19 case | Date first restriction on outdoor gatherings | Date first country-specific guidance published | Ongoing clinical trials January 24, 2020 | No. of deaths per 100,000 14 days before guidance | No. cases per 100,000 14 days before guidance | Refer to European Medicines Agency guidance |
|---------------|---------------------------------|------------------------------------|--------------------------------------------|---------------------------------------------|------------------------------------------|-----------------------------------------------|-----------------------------------------------|---------------------------------------------|
| 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 |
| Luxembourgh (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/NCAs | Two-letter country abbreviation² | Date first registered COVID-19 case | Date first restriction on outdoor gatherings³ | Date first countryspecific guidance⁴ | Agency guidance⁴ | No. of deaths per 100,000 14 days prior to publication of first guidance | No. of cases per 100,000 14 days prior to publication of first guidance |
|--------------|---------------------------------|-------------------------------------|------------------------------------------|-------------------------------------|----------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Spain (AEMPS) | ES                              | February 1, 2020                     | March 14, 2020                            | March 16, 2020                       | Yes            | 0.61                                                                               | 24.31                                                                               |
| Sweden (MPA) | SE                              | February 1, 2020                     | March 12, 2020                            | March 20, 2020                       | Yes            | 0.26                                                                               | 13.47                                                                               |

²Two-letter country abbreviations are available at https://www.iso.org/iso-3166-country-codes.html.
³Date first registered COVID-19 case, available from the European Centre for Disease Control COVID-19 Situation Dashboard.⁴Reference made to the EMA guidance on the management of clinical trials during the COVID-19 pandemic.⁵Date first restriction on outdoor gatherings, available from the European Centre for Disease Control.⁶Date first countryspecific guidance published before guidance 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, the cumulative number of COVID-19–related deaths and cases per 100,000 14 days prior to the publication of the first guidance, and information (yes/no) on the reference to the EMA guidance 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,⁶ 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)
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 (OGYEI)) 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,
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 infor-
mation 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, re-
leased 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 guid-
ances differed between the NCAs. For example, SÚKL (CZ) pro-
vided 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 exten-
sive guidance documents (covering the trial activities displayed in
Table 2) later, after the first EMA guidance was published.

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.

Regulatory guidance: A general description of the content
The provided guidances included proposed flexibilities to sup-
port 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 ob-
tained 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 recom-
mended modifying the frequency of the visits (EE and Portugal
(PT)) or continuing normal follow-up visits if the epidemiologi-

cal 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 |
|----------------------|----------------------------|--------------------|---------------------------|---------------------------|
|                      | 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) |
| Country (NCA)        |                           |                     |                          |                           |                           |                  |                 |                    |                        |                         |                       |                   | (25)       |
| 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 (SÚKL)      |                           |                     |                          |                           |                           |                  |                 |                    |                        |                         |                       |                   | 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; 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; FMPM, 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 EMA and national authorities issued guidance to address these challenges. For example, the EMA issued guidance on the temporary halt of trials, suspension of trials, and the suspension of trial activities (e.g., recruitment) before the availability of public guidance documents. The authors also highlighted the importance of continuous risk assessment during the pandemic. Flexibility can be introduced by regulatory authorities in various ways, including nonenforcement of specific requirements, such as the use of remote telemedicine visits, HHVs, and the transfer of IMP.

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 specific requirements, such as the use of remote telemedicine visits, HHVs, and the transfer of IMP.

**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 but necessary to overcome CT conduct disruption due to restricted hospital visits, an interrupted IMP supply chain, and limited site study staff availability. 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.

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, Health Canada, US Food and Drug Administration, Japan Pharmaceuticals and Medical Devices Agency, and the Australian Therapeutic Goods Administration issued guidance on the management of ongoing CTs and the transfer of IMP. Although variation within the regulatory readiness of these authorities exists, it seems in line with the readiness of the EMA.
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 supply34,35 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 remote CT monitoring, IMP-adherence monitoring, and HHVs (Table 2) 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.

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 inspections13 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).

ACKNOWLEDGMENTS
The authors thank the participating partners of Trials@Home IMI Project Work Package 4 from the Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO) for their valuable input and review of the study proposal.
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.

© 2021 The Authors. Clinical Pharmacology & Therapeutics published by Wiley Periodicals LLC on behalf of American Society for Clinical Pharmacology and Therapeutics.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

FUNDING
The research leading to these results was conducted as part of the Trials@Home consortium. This paper only reflects the personal views of the stated authors. The Trials@Home project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement no. 851458. This Joint Undertaking receives support from the European Union’s Horizon 2020 research and innovation program and EFPIA. The Innovative Medicines Initiative website can be accessed through the following link: https://www.imi.europa.eu.

ARTICLE

1. Zhu, N. et al. A novel coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 382, 727–733 (2020).
2. European Centre for Disease Control. COVID-19 situation update worldwide <https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases> (2021). Accessed February 11, 2021.
3. Tuttle, K.R. Impact of the COVID-19 pandemic on clinical research. Nat. Rev. Nephrol. 16, 562–564 (2020).
4. Upadhaya, S. et al. Impact of COVID-19 on oncology clinical trials. Nat. Rev. Drug Discov. 19, 376–377 (2020).
5. Xue, J.Z., Smietana, K., Poda, Pawel, Webster, K., Yang, G. & Agrawal, G. Clinical trial recovery from COVID-19 disruption. Nat. Rev. Drug Discov. 19, 662–663 (2020).
6. Scheerder, B., Kamsteeg, H., Freericks, M., Vos, C. & van Woudenberg, A. Results DCRF survey bottlenecks clinical research during the corona crisis (Dutch) <https://dcrfonline.nl/resultaten-dcrf-enquete-knooppunten-klinisch-onderzoek-tijdens-coronacrisis/> (2020). Accessed September 10, 2020.
7. Strujo, E. et al. COVID-19 impact on multi-site recruitment and enrollment. Clin. Trials 17, 501–504 (2020).
8. Bagiella, E., Bhatt, D.L. & Gaudino, M. The consequences of the COVID-19 pandemic on non-COVID-19 clinical trials. J. Am. Coll. Cardiol. 76, 342–345 (2020).
9. Fleming, T.R., Labriola, D. & Wittes, J. Conducting clinical research during the COVID-19 pandemic: protecting scientific integrity. JAMA 324, 33–34 (2020).
10. Ledford, H. Coronavirus shuts down trials of drugs for multiple other diseases. Nature 580, 15–16 (2020).
11. European Medicines Agency. Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials <https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical_en-0.pdf> (2020). Accessed October 27, 2020.
12. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Guideline for Good Clinical Practice ICH E6(R2) <https://www.ich.org/page/efficacy-guidelines> (2016). Accessed December 11, 2020.
13. European Medicines Agency. Guidance on remote GCP inspections during the COVID-19 pandemic <https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-remote-gcp-inspections-during-covid-19-pandemic_en.pdf> (2020). Accessed October 9, 2020.
14. McDermott, M.M. & Newman, A.B. Preserving clinical trial integrity during the coronavirus pandemic. JAMA 323, 2135–2136 (2020).
15. Marcum, M. et al. COVID-19 pandemic and impact on cancer clinical trials: an academic medical center perspective. Cancer Med. 9, 6141–6146 (2020).
16. Li, G. et al. Digitalized adaptation of oncology trials during and after COVID-19. Cancer Cell 38, 148–149 (2020).
17. Waterhouse, D.M. et al. Early impact of COVID-19 on the conduct of oncology clinical trials and long-term opportunities for transformation: findings from an American Society of Clinical Oncology Survey. JCO Oncol. Pract. 16, 417–421 (2020).
18. Mitchell, E.J. et al. It is unprecedented: trial management during the COVID-19 pandemic and beyond. Trials 21, 784 (2020).
19. Djurisic, S. et al. Barriers to the conduct of randomised clinical trials within all disease areas. Trials 18, 360 (2017).
20. European Centre for Disease Prevention and Control. Event background COVID-19 <https://www.ecdc.europa.eu/en/novel-coronavirus/event-background-2019> (2020). Accessed September 4, 2020.
21. European Centre for Disease Prevention and Control. COVID-19 country overviews <https://covid19-country-overviews.ecdc.europa.eu/> (2020). Accessed September 3, 2020.
22. Trials@Home. D2.3 — Technology scan. Work package 2 (TECH) <https://trialsathome.com/wp-content/uploads/2020/10/D2.3-Scanning-results_Master.pdf> (2020). Accessed November 30, 2020.
23. European Centre for Disease Prevention and Control. Data on country response measures to COVID-19 <https://www.ecdc.europa.eu/en/publications-data/download-data-response-measures-covid-19> (2020). Accessed October 29, 2020.
24. European Centre for Disease Prevention and Control. COVID-19 Situation Dashboard <https://qap.ecdc.europa.eu/public/extractions/COVID-19/COVID-19.html#Global-overview-tab> (2020). Accessed January 29, 2021.
25. European Medicines Agency. Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic <https://ec.europa.eu/health/sites/health/files/files/eudradex/vol-10/guidanceclinicaltrials_covid_19_en.pdf> (2021). Accessed February 11, 2021.
26. European Commission. Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1) <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52020CO330(01)> (2010). Accessed November 30, 2020.
27. Asaad, M., Habibullah, N.K. & Butler, C.E. The impact of COVID-19 on clinical trials. Ann. Surg. 272, e222–e223 (2020).
28. Medicines and Healthcare Products Regulatory Agency. Guidance: managing clinical trials during Coronavirus (COVID-19) <https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-s-covid-19> (2020). Accessed January 29, 2021.
29. Health Canada. Management of clinical trials during the COVID-19 pandemic: Notice to clinical trial sponsors <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/management-clinical-trials-during-covid-19-pandemic.html> (2020). Accessed January 29, 2021.
30. US Food and Drug Administration. Clinical Trial Conduct During the COVID-19 Pandemic <https://www.fda.gov/drugs/coronavirus-s-covid-19-drugs/clinical-trial-conduct-during-covid-19-pandemic> (2020). Accessed January 29, 2021.
31. Pharmaceuticals and Medical Devices Agency, O and A Related to clinical trials of pharmaceutical products under the influence of the new coronavirus (Japanese) <https://www.pmda.go.jp/review-services/trials/0020.html> (2020). Accessed January 29, 2021.
32. Therapeutic Goods Administration. COVID-19: Guidance on clinical trials for institutions, HRECs, researchers and sponsors <https://www1.health.gov.au/internet/main/publishing.nsf/Content/CliniCal-Trials> (2020). Accessed January 29, 2021.
33. Fernandez Lynch, H., Dickert, N.W., Zettler, P.J., Joffe, S. & Largent, E.A. Regulatory flexibility for COVID-19 research. J. Law Biosci. 7, Isaa057 (2020).
34. French Republic. French Public Health Code Article R5124-3-1 (French) <https://www.legifrance.gouv.fr/codes/id/LEGIA RTI000033857013/2017-01-12/> (2017). Accessed November 2, 2020.
35. European Medicines Agency. Q&A: Good clinical practice (GCP) Q10 <https://www.ema.europa.eu/en/human-regulatory/resea rch-development/compliance/good-clinical-practice/gq-good-clini cal-practice-gcp>. Accessed November 28, 2020.
36. Federal Institute for Drugs and Medical Devices. Electronic submission of clinical trial applications <https://www.bfarm.de/EN/Drugs/licensing/clinicalTrials/news/ElectronicSubmission. html> (2013). Accessed October 27, 2020.
37. European Medicines Agency. Reflection paper on risk based quality management in clinical trials <https://www.ema.europa. eu/en/documents/scientific-guideline/reflection-paper-risk-based -quality-management-clinical-trials_en.pdf> (2013). Accessed November 28, 2020.
38. German Medical Association. Notes and explanations on Section 7 (4) - remote treatment (Professional Code for Physicians in Germany, MBO-Ä) (German) <https://www.bunde saerztekammer.de/fileadmin/user_upload/downloads/pdf-Ordner/Recht/2015-12-11_Hinweise_und_Erlaeuterungen_zur_Fernbehandlung.pdf> (2015). Accessed November 23, 2020.
39. French Republic. Decree No 2010-1229 relating to telemedicine (French) <https://www.legifrance.gouv.fr/jorf/id/ JORFTEXT000022932449/> (2010). Accessed November 23, 2020.
40. Stewart, J. et al. COVID-19: A Catalyst to Accelerate Global Regulatory Transformation. Clin. Pharmacol. Ther. (2020). https://doi.org/10.1002/cpt.2046.
41. Gaba, P. & Bhatt, D.L. The COVID-19 pandemic: a catalyst to improve clinical trials. Nat. Rev. Cardiol. 17, 673–675 (2020).
42. Tan, A.C., Ashley, D.M. & Khasraw, M. Adapting to a pandemic - conducting oncology trials during the SARS-CoV-2 pandemic. Clin. Cancer Res. 26, 3100–3103 (2020).
43. European Parliament and the Council. Regulation (EU) No 536/2014 <https://ec.europa.eu/health/sites/health/files/files/ eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf> (2014). Accessed November 30, 2020.
44. Lumpkin, M.M. & Lim, J.C.W. Pandemic best regulatory practices: an urgent need in the COVID-19 pandemic. Clin. Pharmacol. Ther. 108, 703–705 (2020).
45. European Medicines Agency. Accelerated assessment <https://www.ema.europa.eu/en/human-regulatory/marketing-authorisat ion/accelerated-assessment>. Accessed November 2, 2020.