# Impact of the COVID-19 pandemic on the management and conduct of ongoing clinical trials with medicinal products

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## II. ABBREVATIONS AND DEFINITIONS

| ABBREVIATION | DEFINITION |
|---|---|
| AEMPS | Spanish Agency of Medicines and Medical Devices, Agencia Española de Medicamentos y Productos Sanitarios |
| AIFA | Italian Medicine Agency, L'Agenzia Italiana del Farmaco |
| AMEK | German Association of Medical Ethic Committees/ Arbeitskreis Medizinischer Ethik-Kommissionen in der Bundesrepublik Deutschland |
| AMG | German Medicinal Products Act, Arzneimittelgesetz |
| ANSM | French Medicine Agency, L'Agence nationale de sécurité du médicament et des produits de santé |
| BASG | Bundesamt für Sicherheit im Gesundheitswesen, Federal Office for Safety in Health Care |
| BfArM | German Federal Institute for Drugs and Medical Devices, Bundesamt für Arzneimittel und Medizinprodukte |
| CA | Competent Authority |
| CAs | Competent Authorities |
| CCMO | The Dutch Central Committee on Research Involving Human Subjects, (Centrale Commissie Mensgebonden Onderzoek) |
| CEC | Leading/Central Ethics Committee |
| CElm | Spanish Ethic Committees for Investigation with Medicinal Products, (Comité de Ética de la Investigación con medicamentos) |
| CFR | Code of Federal Regulations |
| CNIL | French Data Protection Authority |
| COA | Clinical Outcome Assessment |
| COVID-19 | Corona Virus Disease 2019 |
| CSR | Clinical Study Report |

| ABBREVIATION | DEFINITION |
|---|---|
| CT | Clinical Trial |
| CTs | Clinical Trials |
| DPA | Data Protection Authority |
| DPO | Data Protection Officer |
| e.g. | exempli gratia |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Form |
| ECs | Ethics Committees |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| eTMF | Electronic Trial Master File |
| EU | European Union |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials |
| GCP | Good Clinical Practice |
| HCP | Health Care Provider |
| ICF | Patient Information/Informed Consent Form |
| ICH | International Council of Harmonization |
| IGJ | Health and Youth Care Inspectorate of the Dutch Ministry of Health, Welfare and Sports (Inspectie Gezondheidszorg en Jeugd) |
| IMP | Investigational Medicinal Product |
| IRB | Institutional Review Board |
| ISF | Investigator Site File |
| LAR | Legally Authorized REpresentative |
| LEC | Local Ethics Committee |
| MR-001 | French Data Protection methodology |
| PD | Protocol Deviation |
| PEI | Paul Ehrlich Institute, German Federal Institute for Vaccines and Biomedical Drugs |
| PHEIC | Public Health Emergency of International Concern |
| PI | Principle Investigator |
| PIs | Principle Investigators |
| QP | Qualified Person |
| REC | Registro Español de Estudios Clínicos |
| rSDV | Remote Source Data Verification |
| SDs | Source Documents |
| SubI | Sub-Investigator |
| Swissethics | Umbrella organization of the cantonal Ethics Committees in Switzerland |
| Swissmedic | Swiss Agency of Therapeutic Products, Schweizerische Heilmittelinstitut |
| TMF | Trial Master File |
| UK | United Kingdom |
| USA | United States of America |
| USM | Urgent Safety Measure |
| V | Version |
| WHO | World Health Organization |
| ZLG | Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten; Central Authority of the Länder for Health Protection with regard to Medicinal Products and Medical Devices |

# III. INTRODUCTION

## A. GENERAL INTRODUCTION ON SARS-CoV-2 AND THE COVID-19 PANDEMIC

In December 2019, an increased incidence of severe respiratory diseases with unknown cause was detected by medical institutions in Wuhan, in Central China [1,2]. The clinical conditions of infected patients resembled known viral pneumonia infections, but the severe acute respiratory syndrome (SARS), the Middle East respiratory syndrome (MERS), avian influenza, and several other common respiratory pathogens have been ruled out as causes of this outbreak. Finally, on 31 December, the Chinese authorities reported to the World Health Organization (WHO) the local outbreak of pneumonia infections with an unknown etiology [3,4]. The follow-up of contact persons revealed a putative linkage of 66% of the infected patients to the seafood and wet animal wholesale Huanan market in Wuhan [5,8]. Thus, a zoonotic pathogen was assumed to be the putative cause [3,7].

## B. IDENTIFICATION OF CORONAVIRUS SARS-COV-2 AS CAUSATIVE AGENT

Genetic analyses of samples of infected patients resulted in the identification of a novel human coronavirus, which was officially declared as the cause of the new disease by the WHO on 09 January 2020 [5,6,7]. Temporarily named 2019-nCoV, the virus received, based on its phylogenetic relationship to SARS, its official term "*severe acute respiratory syndrome coronavirus 2*", abbreviated SARS-CoV-2, by the International Committee on Taxonomy of Viruses on 11 February 2020 [8].

SARS-CoV-2 was demonstrated to belong to the phylogenetic family of beta-coronaviruses [8,7]. Members of this family are known to lead to respiratory diseases e.g. human coronaviruses cause 15-30 % of the common colds [9]. This family includes the zoonotic strains SARS-CoV (80% similarity) and MERS-CoV (50% similarity), which are known as causing agents for two former large-scale epidemics SARS and MERS (Middle East Respiratory Syndrome) in the first decade of the 2000s [7]. The genome highly resembles a strain previously isolated from bats, supporting its zoonotic origin. As of 01 December, the infection route of the Wuhan outbreak remains unclear, and recent publications indicate that first human infections might have occurred already in autumn 2019 [11].

## C. THE NOVEL INFECTION DISEASE CAUSED BY SARS-COV CORONAVIRUS: COVID-19

On 11 February 2020, the WHO renamed the novel respiratory disease officially COVID-19, the abbreviation for coronavirus disease 2019 [10]. The clinical manifestation of COVID-19 is diverse and varies significantly from symptomless progression, common cold symptoms, disturbance of the sense of smell and taste to severe pneumonia resulting in respiratory failure and other serious clinical conditions such as sepsis, septic shock, multiple organ dysfunction syndromes, and death [11,12]. The majority of patients (app. 70%) show no or mild symptoms [11].

Unlike common human coronaviruses, the COVID-19 causing strains show unique clinical features, including a higher percentage of gastrointestinal symptoms such as diarrhea [12]. A recent publication reported COVID-19 associated complications and secondary diseases like (a) damage of the central nervous systems (CNS), the kidney, and the renal system, (b) a wide range of dermatological effects, (c) cardiovascular complications, and (d) thromboembolic events [12].

COVID-19 symptoms are more severe in older adults with comorbidities. Additional risk factors, also for younger patients, are other chronic diseases including cancer, cardiovascular diseases such as high blood pressure, diabetes, and other pulmonary diseases including allergies, asthma, and COPD (chronic obstructive pulmonary disease) or other immunocompromising diseases [11].

The lethality rate is estimated to be 1-2% and appears to be lower than those determined for SARS and MERS. Based on a modeling study, Clark *et al*. estimated that 22% of humans worldwide have an increased risk for severe COVID-19 progressions due to underlying health conditions, which might result in hospitalization [13]. Based on clinical study results, the German Robert Koch Institute (RKI) estimated that 22% of the hospitalized patients died during the first wave of the pandemic. The majority of the patients currently enrolled in CTs, especially those investigating severe diseases, belong to these risk groups. Consequently, ongoing conduct of CTs requires specific precautions and measures to mitigate the risk associated with the trial participation for the subjects.

## D. HISTORY OF THE WORLDWIDE SPREAD OF COVID-19: FROM LOCAL OUTBREAK TO PANDEMIC

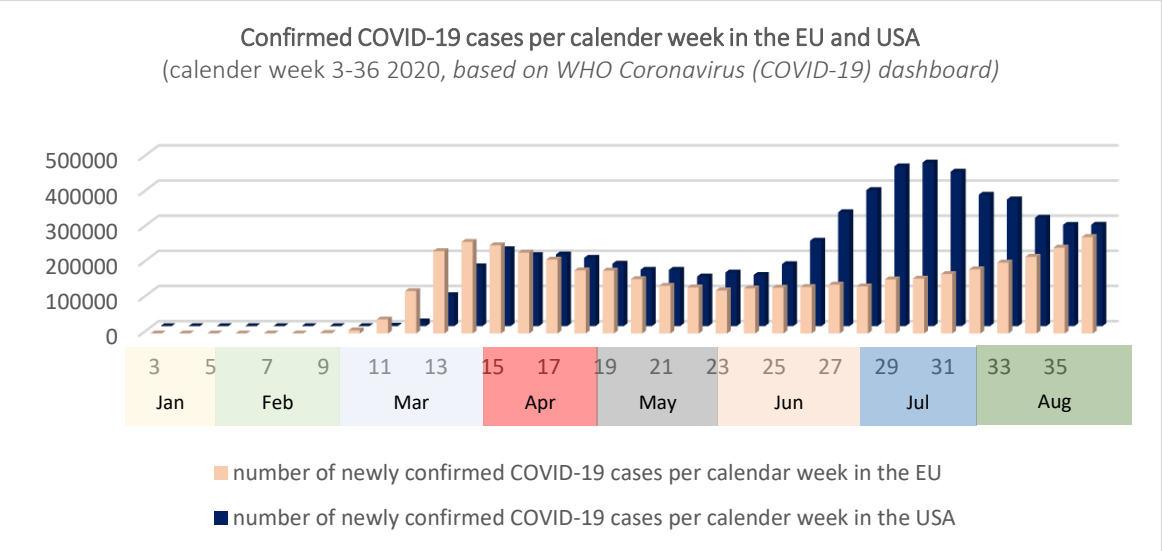
Despite tremendous global efforts, COVID-19 rapidly spread and finally emerged as a worldwide pandemic. On 13 January, Thailand confirmed the first COVID-19 case outside of China [10]. Within one month after the first report of suspicious infections, COVID-19 rapidly disseminated and resulted in 7 823 confirmed cases and 170 deaths reported by the end of January. More than 98% of those still in China, but additional cases were reported in 18 other countries, including the USA and three EU countries (France, Germany, and Finland) [14]. First cases in Europe were reported on 24 January by confirming two infected patients in France. Based on its rapid spread, the WHO classified the viral outbreak on 30 January as a Public Health Emergency of International Concern (PHEIC) [15].

As of mid-February, COVID-19 has begun to domestically spread in several countries [9]. More than 120 000 infections were reported in more than 114 countries with a 13-fold increase of new infections within 14 days. Consequently, on 11 March 2020, the WHO director announces the COVID-19 outbreak a pandemic (fig. 4.2) [16]. As of this day, only supportive therapeutic strategies were available, and thus the novel disease represented a serious public health risk worldwide [11]. The disruption of the health care systems by vast patients numbers requiring medical (intensive) care is considered the most critical threat [17]. To mitigate this, governments enforced extraordinary countermeasures mainly focusing on the isolation of infected patients, careful infection control strategies, strict

hygiene measures, and contact tracing, the reduction of interpersonal contacts by social distancing, travel restrictions, and lockdown strategies [11].

Fig. 4.1 shows the COVID-19 cases per week from January to August (week 3-36) in Europe and the USA. For the US, the spread of the virus occurred in two pandemic waves in spring (March to end of May) and summer 2020 (June to August), with the highest number of more than 400 000 weekly reported cases in July (week 29-31). Contrarily, in Europe, a relaxation of the situation between a first wave in spring (March to May) and the second wave's start in August is visible. Consequently, the strict mitigation strategies, e.g. the travel restrictions and lockdowns, were released in Europe.

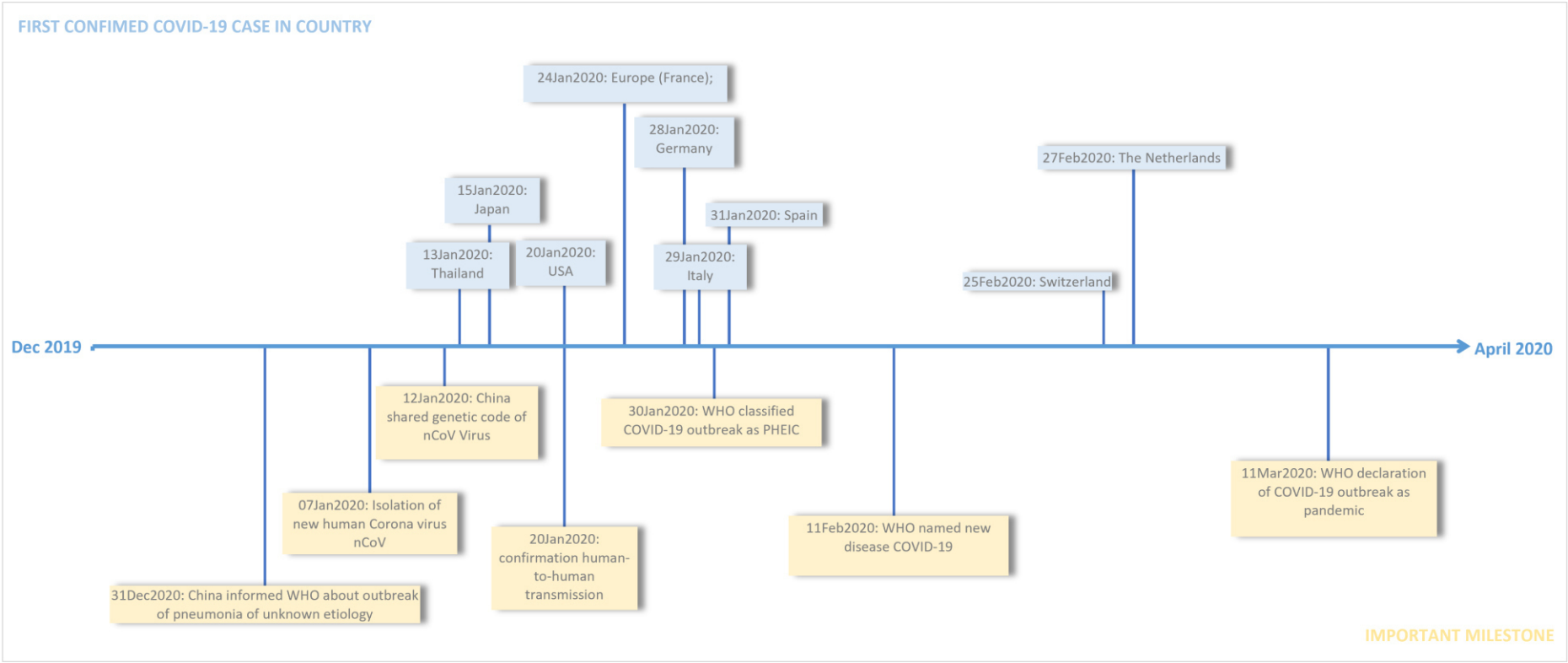
**Fig. 4.1 Number of confirmed COVID-19 cases per week in the USA and EU from January to August 2020** (based on the numbers published by the WHO Coronavirus (COVID-19) dashboard [18])




Eurostat, the EU Statistical Office, reported similar trends for Europe based on a retrospective analysis of weekly death rates from March to June. An increase of 170 000 additional deaths across the EU was reported compared to the four-year average value. These additional deaths were considered to be mainly caused by the pandemic. In line with the reported infection rates per EU country, the highest numbers were identified for Italy and Spain. The highest level with more than 35 000 death per week was reached from the end of March to the beginning of April.

First expected to not spread from human to human, person to person transmission was first confirmed on 20 January 2020 [9]. Transmission occurs by direct contact or through droplet spread by coughing and sneezing and has also been detected in patients with no or few symptoms or before the onset of COVID-19 symptoms [11]. A viral transmission via contaminated surfaces, including medical devices, has also been demonstrated, indicating an increased infection risk within health care institutions. Besides, higher transmission rates via aerosols have been described in hospitals and nursing homes [19]. Consequently, specific mitigation measures were required to be established in in the health care sector [11] . Thus, health organizations and regulatory authorities issued COVID-19

Fig. 4.2 Critical milestones of the COVID-19 pandemic from the first outbreak to the declaration of the COVID-19 pandemic in March 2020



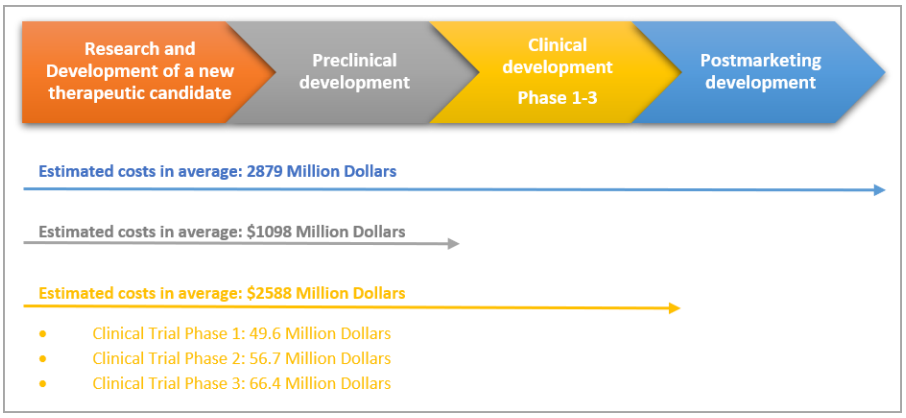
related directives and guidelines to mitigate the threat's effect to avoid burnout status of the health care institutions and protect the public's health. In this context, regulatory authorities also established guidance documents for sponsors and investigators of clinical trials to allow ongoing investigational patient care during the pandemic.

## E. THE IMPORTANCE OF CLINICAL TRIALS AND CLINICAL TRIAL DATA FOR DRUG DEVELOPMENT

The conduct of clinical trials (CTs) is a crucial milestone in the new drug development [20,21.] (fig. 4.3). The WHO defines a CT as "*any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes*" [22]. The influence on patients' health outcomes thereby comprises the identification of side effects and therapeutic effects of drug candidates [23]. Competent authorities(CA) would grant marketing authorization of new drugs if a favorable benefit over risk ratio was successfully demonstrated in phase 1-3 trials for its intended use. An ongoing reevaluation of this favorable risk-benefit profile is expected in the post-marketing authorization stage by conducting phase 4 trials, observational studies, and pharmacovigilance measures [20].

Based on the financial data shared by ten pharmaceutical companies on the development of 106 new medicinal products, a total of 2.6 billion dollars was calculated by DiMasi *et al.* for the pre-authorization cost for new drugs [21]. With an average of 1.46 billion dollars and 96.8 months, clinical development is the most cost and time-intensive stage (fig. 4.3).

Fig. 4.3 The four stages of drug development and estimated costs (based on the financial data published by DiMasi *et al*., 2016 [21])




While Hayden *et al*. calculated the annual increment of CTs to be 10-12%, the number of new drug authorizations only increased 1.76%, indicating a disconnect between the costs and the final output of drug development [24]. The authors identified patient recruitment and retention as critical milestones for the finalization of CTs. A comparison of two reports published by the Tufts Center for the Study of Drug Development in 2013 and early 2020 indicate that patient recruitment rates were significantly increased in the last years. Whereas the first report identified that nearly 50% of trials failed their intended recruitment timelines, this was significantly decreased to 23% in January 2020.

In this context, the COVID-19 pandemic is intended to represent an additional challenge for sponsors concerning study timelines and development costs.

## F. THE EUROPEAN AND AMERICAN CLINICAL TRIAL REGISTRIES: EudraCT AND ClinicalTrials.gov

As of 2004 and in compliance with art. 11 of the European CT Directive (CTD) 2001/20/EC, interventional trials on medicinal products conducted in the European Economic Area (EEA) need to be registered in the European Clinical Trial database, abbreviated as EudraCT (European Union Drug Regulating Authorities Clinical Trials) [20,25]. Upon trial registration, a written confirmation of the assigned EudraCT number is provided, which is also part of the national CT application dossiers.

The EudraCT database is maintained by the European Medicinal Agency (EMA). It consists of two separate sections: (a) the non-public section for EU authorities and (b) the public CT registry, the EU Clinical Trials Register.

Based on art. 57(2) and 41 of the EU regulation 726/2004 and 1901/2006 respectively, the CT registry was established in 2011 to allow better transparency on clinical research to the public [26,27]. Following this legislation, the publication of basic study information including the aim of the study, sponsor details, current status, involved trial sites, targeted subject population, and eligibility criteria along with further details on investigated drugs and used placebos is mandatory for pediatric CTs and phase II-IV trials in adults [26,27,28]. Predefined filters are available, allowing an advanced search in addition to a keyword search across all registered trials by e.g. country, study phase, current study status, age. Generally, a download option for search results is available but only allows downloads of short study summaries in text format for up to 20 trials.

The U.S. National Library of Medicine maintains the ClinicalTrials.gov database at the National Institutes of Health (NIH) [29]. It is the largest "*database of privately and publicly funded clinical studies conducted around the world*" [29,20]. Contrarily to the EudraCT database, the registration is not limited to interventional drug trials. It enables the registration of other human studies, including medical device trials, observational studies, and further investigations e.g. on new therapeutic procedures, behavioral and dietary aspects. Section 801 of the FDA Amendments Act (FDAAA 801) mandates the legal requirement to register phase 2-4 trials in the ClinicalTrials.gov registry [30]. Trials conducted in the USA need to be registered within 21 days after the first enrolment. The registration of phase 1 trials and trials not conducted in the USA is not mandatory but recommended.

Contrarily to the EU register, this database allows detailed database searches across 208 countries either by using keyword search runs or applying predefined filters e.g. for study phases, sponsor names, or funder types. The results of up to 10 000 studies can be downloaded as study summaries or detailed data sheets per study in several file formats to allow an analysis outside of the database.

Both databases were used in this thesis to determine the number of clinical trials impacted by the COVID-19 pandemic worldwide, in the USA and the EEA.

## G. INTERNATIONAL GUIDELINES ON THE CONDUCT OF CLINICAL TRIALS – ICH GCP E6 GUIDELINE

To streamline the divers' requirements for the development and authorization of new drugs in various regions, harmonized sets of rules have been published since the 1990s by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) [31].

With respect to ethical and scientific standards for the authorization and conduct of CTs, pharmaceutical industry companies and the CAs of the three founding members USA, EU, and Japan established the E6 guideline on good clinical practice (GCP) in 1996 [32]. Revision 2 was amended in 2016 to cover new trial designs and modern electronic techniques [23].

By defining the responsibilities and determining the minimal criteria of CT procedures, including the patient consent process, monitoring activities, reporting, and archiving requirements, the E6 guideline ensures the protection of trial subjects and the trial data's reliability. These rules and conditions were implemented in the national laws and guidelines of the current ICH members, including the countries investigated in this thesis.

The rapid spread of COVID-19 and the containment measures taken by the national governments mainly impact the conduct of CTs under ICH GCP standards. Therefore, COVID-19 guidance documents were published by the CAs in the different regions to support sponsors, investigators, and CROs in continuing ongoing trials even under these demanding circumstances.

## H. FOCUS OF THIS THESIS

In 2020, the worldwide spread of the SARS-2-coronavirus disrupted several aspects of health care around the globe. Aiming on the protection of the public health, governments imposed precautionary measures to reduce the spread of the virus. These measures have the potential to negatively impact the safe conduct of ongoing clinical trials. This raised, practically overnight, various regulatory hurdles for sponsors, CROs and investigators. As a result, several regulatory authorities t published COVID-19 recommendations to assist involved stakeholders by setting out conditions for exceptional strategies and arrangement to ensure a safe management of ongoing trials under COVID-19 from March 2020 onwards.

In this thesis, the impact of the COVID-19 pandemic on the conduct of ongoing and new clinical trials (CT) was analyzed based on a database analysis in clinical trial registries and the comparison of the COVID-19 guidelines issued by the competent authorities (CA) during the first wave of the pandemic and the relaxation of the COVID-19 situation in the European Union in summer 2020.

Database analyses in the European EudraCT and the ClinicalTrials.gov registries were performed to identify and characterize the number of ongoing CTs worldwide, in the EU and USA. Based on a

ClincalTrials.gov dataset published by B. Carlisle, further investigations were made to analyze and characterize clinical drug trials that were stopped until September 2020 [33]. Additionally, the COVID-19 impact on the start of new trials was determined by comparing the number of new trials registered per months before and during the pandemic.

The database analysis identified Spain, Germany, France, Italy and the Netherlands as TOP5 EU countries conducting the highest numbers of ongoing CTs during the pandemic. The national COVID-19 guidelines published in these five EU countries and the other two countries of the DACH region (Austria and Switzerland) were analyzed and compared to the European and the US COVID-19 recommendations with a focus on (a) the type of COVID-19 measures recommended, (b) the different regulatory requirements for their implementation and (c) the history of changes added in the COVID-19 guideline revisions published during the first six months of the COVID-19 health care crises until October 2020.

The results of the database analysis and the comparative analysis of the regulatory requirements and the COVID-19 mitigation measures recommended by the competent authorities in the different regions and countries were analyzed and discussed for their negative and positive short- and long-term impact on the conduct of clinical trials and the clinical development of new drugs in future.

# IV. MATERIALS AND METHODS

## A. DATABASES, TRANSLATION TOOLS, AND CLINICAL TRIAL REGISTRIES USED IN THIS THESIS

Table 5.A CT registers, databases, and translation tools used in this thesis

| CATEGORY | NAME | LINK |
|---|---|---|
| CT registries | ClinicalTrials.gov | https://clinicaltrials.gov |
| | EudraCT - European Registry of CTs with Medicinal Products conducted in EU/EEA | https://eudract.ema.europa.eu/ |
| | SNCTP (Swiss National CTs Portal) | https://www.kofam.ch/de/studienportal/nach-klinischen-versuchen-suchen/ |
| CTs stopped due to COVID-19 | Data set on the studies stopped due to COVID-19 published by Benjamin Carlisle [33] | https://covid19.bgcarlisle.com/ |
| COVID-19 Databases | WHO Coronavirus Disease Dashboard | https://covid19.who.int/ |
| Literature search | PubMed | https://www.ncbi.nlm.nih.gov/pubmed/ |
| | EFGCP-AWP Covid-19 Repository: Repository of publications for Clinical Trials in relation to COVID-19 [34] | https://efgcp-events.eu/Clinical-Trials-COVID19-Repository.php |
| Translation tools | DeepL | https://www.deepl.com/translator |
| | Google translate | https://translate.google.com/?hl=de |

Database searches were conducted in the CT registries and COVID-19 dashboard listed in table 5.A. Literature searches were performed using the NCBI Pubmed engine and google. COVID-19 guidelines were downloaded from the webpages of the authorities and the „*repository of publications for Clinical Trials in relation to COVID-19*“ on the webpage of the European Forum for Good Clinical Practice (EFGCP) [34].

## B. DATABASE SEARCH: NUMBER OF COVID-19 CASES AND DEATHS

Confirmed COVID-19 cases and deaths globally and per country were identified using the WHO corona disease dashboard. Pre-defined search functions and graphs were used.

## C. DATABASE SEARCH: ONGOING CLINICAL TRIALS WORLDWIDE AND PER COUNTRY

Database searches in the ClinicalTrials.gov registry were performed to identify the number of interventional CTs ongoing worldwide and in the USA. Used search parameters are listed in table 5.B. As data cut-off date, 11 March 2020, the date the WHO classified the worldwide spread of COVID-19 as a pandemic, was chosen to identify the number of ongoing CTs affected by the first wave of the pandemic and the COVID-19 recommendations. The database search was performed on 02Jul2020. Consequently, the results included CTs that (1) started before the WHO declaration and (2) were continuously conducted during the first pandemic wave. For the identification of the number of ongoing drug trials in the EEA region, database searches in the EudraCT database were conducted (table 5.B). Separate database searches were done for each EEA country to determine the five countries with the highest numbers of ongoing CTs (TOP5 EU countries). CTs not conducted in the EEA, but linked to a European PIP, were omitted since these do not fall within the scope of responsibility of any CA/EC in the EEA region. Consequently, these are not covered by the EMA COVID-19 guideline or any country guideline issued by an EU member state.

Table 5.B Search parameters used for the database searches in the EudraCT and ClinicalTrials.gov register (ongoing trials per country, EEA, and worldwide)

| | ClinicalTrials.gov | EudraCT |
|---|---|---|
| Country | no entry for worldwide, separate searches per country: USA, Spain, Germany, France, the Netherlands, Italy, Austria, Switzerland | all EEA countries for the identification of the number of ongoing CTs, single country searched to identify the number of CTs per country |
| Condition/Disease | no entry added: all available | no filter available |
| Terms | no entry added: all available | no filter available |
| Study type | interventional studies | only interventional CTs registered |
| Age Range | all available | all available |
| Trial status | recruiting, active, not recruiting, recruiting on invitation | ongoing |
| Trial Phase | early phase 1 - 4 | phase 1-4 |
| Gender/sex | all | both |
| Funder type | all available | no filter available |
| Start date | study start before or on 11Mar2020 | study start before or on 11Mar2020 |
| Date of search | 02 Jul 2020 | 02 Jul 2020 |

The search options in this EU database are very limited and do neither allow an investigation on study details such as funder-types nor provide any possibility to download complete datasets for further evaluation outside of the database. Thus, additional investigations were made in ClinicalTrials.gov. These results were checked for the number of ongoing CTs worldwide per study phase and funder type using the pre-defined filter options and keyword searches in separate database

queries. The ClinicalTrials.gov registry lists CTs with investigational drugs, medical devices and other investigations. Pre-defined filter options to easily differentiate between drug and other trials are not available. Thus, the following keywords were added in the investigation/treatment search fields in subsequent search queries: drug, biologic, device, behavioral, diagnostic test, and diet to gain insight into the value of drug (chemical and biological) CTs present in the database.

For the identification of the TOP5 industry sponsors, pre-existing filters were chosen: (a) The results gained with the search parameters listed in table 5.B were filtered within the database by using the "by topic" result tab; (b) The results were additionally filtered for involved sponsors/collaborators by funder type "industry"; (c) The results were sorted by the value of registered CTs per sponsor to identify the TOP5 pharmaceutical industry sponsors funding the highest number of CTs worldwide.

### D. IDENTIFICATION OF CLINICAL TRIALS STOPPED DUE TO THE COVID-19 OUTBREAK

The data set published by B. Carlisle on studies stopped due to COVID-19 were used for a more detailed analysis of the pandemic impact on investigational trials with chemical and biological drugs (abbreviated as clinical drug trials below) [33]. This dataset was downloaded on 06 September (status 31Aug2020). The information of two tsv files ("Covid-19 arm per-trial data set" and "Drugs and biologics in stopped trials") were combined in one excel file and used for further analysis by using pivotal tables and diagrams. Missing information, e.g. on industry sponsor names, were manually updated based on database evaluations applying the NCTC number in ClinicalTrials.gov.

The datasets include (non-)interventional trials and studies testing drugs, devices, dietary supplements, procedures, radiations, and other investigations. The data set was filtered for investigational trials stopped due to COVID-19 testing biologic and/or chemical drug candidates. Further analyses of the results per study phases, indication class, funder type, overall study status, and timepoint of the (temporary) stop indicated by the date of the last database update were performed. Also, the overall study status of suspended trials was rechecked by performing database searches in ClinicalTrials.gov as of 06 October to investigate the number of CTs still on hold. These data were also checked for sponsor types, study phases, and the TOP5 pharmacy companies.

### E. DATABASE SEARCH: IMPACT OF COVID-19 ON NEW CLINICAL TRIALS WORLDWIDE

Additional database searches in the ClinicalTrials.gov registry were conducted to identify the number of newly registered CTs worldwide from January 2018 to August 2020 (table 5.C). The average values of new entries per month before the COVID-19 crises (Jan 2018 to Dec 2019) and during the pandemic were determined and compared (Jan to Sep 2020). For the latter, also the number of CTs investigating COVID-19 was determined by adding COVID-19 in the pre-defined indication filter. The data were analyzed by using pivotal tables and diagrams in excel.

Table 5.C Search parameters used in ClinicalTrials.gov (identification of new trials worldwide)

| Search parameters used for advanced search queries in ClinicalTrials.gov | |
|---|---|
| Country | no entry for worldwide |
| Condition/Disease | no entry added: all available, COVID-19 for separate search on COVID trials |
| Terms | no entry added: all available |
| Study type | interventional studies |
| Age Range | all available: child (birth-17), adult (18-64), older adult (65+) |
| Trial status | Recruiting, Enrolling by invitation, active/not recruiting |
| Trial Phase | early phase 1, phase 1, phase 2, phase 3, phase 4 |
| Gender/sex | all |
| Funder | all |
| Last update published | first day of month to last day of month from January 2018 to August 2020 |
| Date of search | 02 September 2020 |

### F. COMPARATIVE ANALYSIS OF THE COVID-19 GUIDELINES FOR ONGOING CLINICAL TRIALS DURING THE COVID-19 HEALTH CARE CRISES

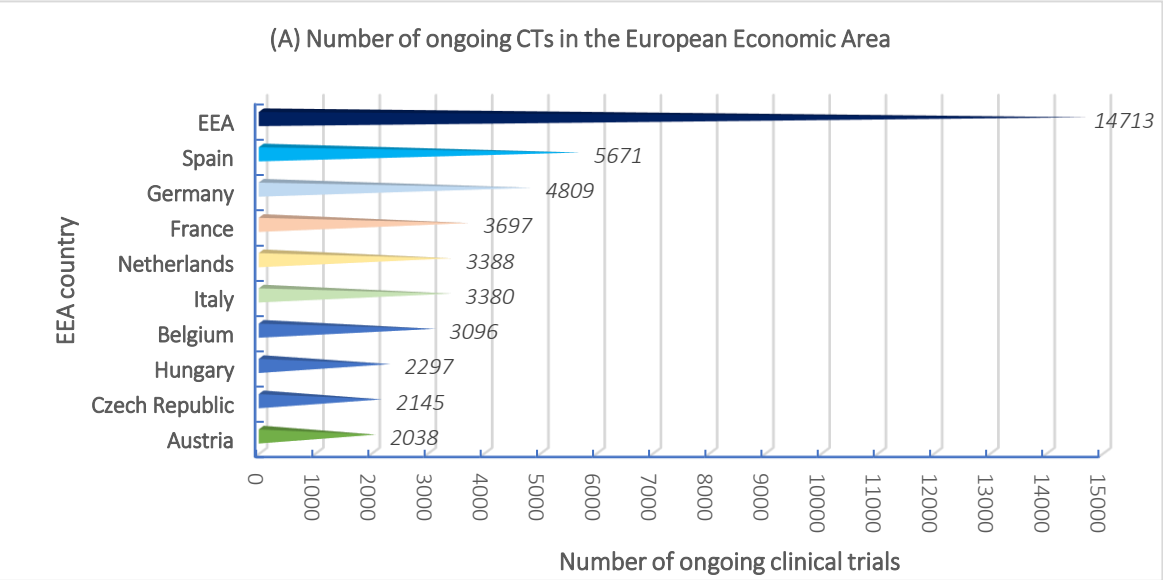
To investigate the impact of the pandemic on ongoing CTs during the COVID-19 health care crises, the guidelines published by the European Commission and the European Medicine Agency (EMA), the Swiss Agencies (Swissmedic and Swissethics) and the American Food and Drug Agency (FDA) were analyzed and compared. Additionally, the national COVID-19 recommendations issued by EU country agencies and local institutions involved in clinical research in the TOP5 EEA countries and Austria were analyzed and compared to the EMA and FDA guidelines with a focus on the (a) date of its publication, (b) type of recommended COVID-19 measures, (c) country-specific differences in the regulatory requirements for their implementation and (c) history of changes and updates published during from March to October 2020.

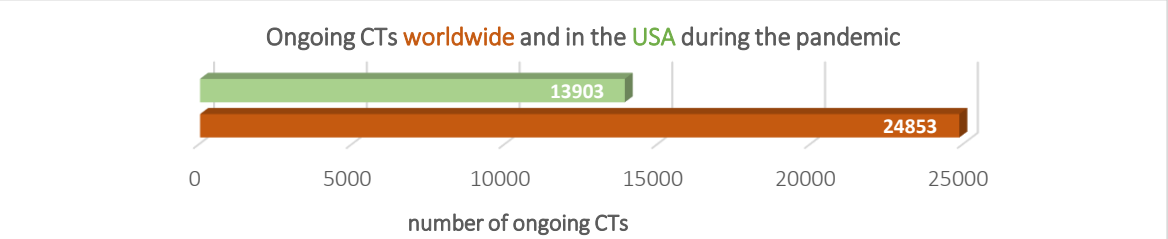
## V. RESULTS I: DATABASE ANALYSIS FOR THE NUMBER OF ONGOING CLINICAL TRIALS WORLDWIDE, IN EUROPE, THE USA AND SWITZERLAND

### A. DATABASE ANALYSIS IN THE CT REGISTRIES FOR THE IDENTIFICATION OF CTs CONDUCTED WORLDWIDE, IN EUROPE, AND THE USA DURING THE PANDEMIC

A database search in the CT registry EudraCT was conducted to analyze the number of ongoing CT impacted by COVID-19 during the first wave of the pandemic in the EEA region. A total of 14 713 ongoing phase 1-4 trials were identified (fig. 6.1 A). The majority of these are conducted in the following EU countries: Spain, Germany, France, the Netherlands, and Italy. With 2 038 CTs, Austria is ranked 9$^{th}$ among the EU countries. The database analysis in the ClinicalTrials.gov registry identified 24 853 CTs worldwide and 13 903 in the USA that were started before the declaration of the pandemic and are still ongoing in July 2020 (fig. 6.1 B).

Fig. 6.1 Numbers of CTs ongoing in the EEA (A), USA and worldwide (B) during the pandemic
14 713 phase 1-4 CTs are conducted in at least one of the EEA states. The majority are conducted in Spain Germany, France, the Netherlands, and Italy. More than 24.800 and 13 903 CTs are ongoing worldwide and in the USA, respectively.




A further analysis of the above results showed that nearly half of the worldwide ongoing trials are phase 2 trials, while app. 30% and 20% are phase 1 and 3 trials, respectively. 12% belong to phase 4 studies (table 6.A). The majority (58.5%) receives funding from non-commercial sponsors, comprising universities, research organizations, and individuals (76%) or US agencies and the National Health Institute (24%). Out of 10 740 commercially sponsored trials, 5.4% are funded by the pharmaceutical companies Merck Sharp & Dohme (MSD), Bristol Myers Squibb (BMS; 4.8%), AstraZeneca (4.2%), Novartis (3.2%) and Pfizer (3.2%).

Trials belonging to more than one category, e.g. due to cofounding or combined phase 1 and 2 trials, can't be distinguished since (a) the available pre-filtering features do not allow the entry of combined runs and (b) a download of results containing more than 10 000 trials is not possible for analysis outside of the database. Consequently, entries belonging to both categories are counted twice in the separate search runs described above and below. The sum of the result per category, therefore, is higher than 100%.

Contrarily to the EudraCT, the US database searches results include interventional CTs with medicinal devices and other studies such as behavioral, procedural, and nutritional studies. The available

filtering features do not distinguish between drug and non-drug trials. Therefore, the results presented above, include data from interventional non-drug trials too. Subsequent search runs were conducted using different search terms for drug and non-drug interventions to provide a sense of the value of the non-drug trials compared to CTs investigating new drugs. 87.9% and 14% of the above-identified ongoing trials worldwide are investing chemical and biological drugs, respectively, 4.5 % were identified as medical device trials. Consequently, most CTs registered in the ClinicalTrials.gov database can be considered drug trials (see fig. A.1 in the appendix).

Table 6.A Number of trials ongoing during COVID-19 per funder type, phase, and the TOP5 industry sponsors

| ONGOING CTs WORLDWIDE | 24853 (100%) |
|---|---|
| SPONSOR-TYPE | |
| CTs funded by industry sponsors, including cofounded trials | 10740 (43.2%) |
| CTs funded by non-industry sponsors, including cofounded trials | 14530 (58.5%) |
| *University and other organizations and individuals* | 11043 (76%) |
| *US agencies and the National Health Institute (NHI)* | 3487 (24%) |
| STUDY PHASE | |
| Phase 1 *including early phase 1 and combined phase 1/2 trials* | 7839 (32%) |
| Phase 2 *including combined phase 1/2 and phase 2/3 trials* | 11894 (48%) |
| Phase 3 *including combined phase 2/3 trials* | 5481 (22%) |
| Phase 4 | 3194 (14%) |
| TOP5 INDUSTRY SPONSORS | |
| MSD (Merck Sharp & Dohme) | 581 (4.8%) |
| BMS (Bristol Myers Squibb) | 512 (4.8%) |
| AstraZeneca | 450 (4.2%) |
| Novartis | 340 (3.2%) |
| Pfizer | 340 (3.2%) |

## B. DATABASE SEARCH FOR THE IMPACT OF COVID-19 ON STOPPED CTS

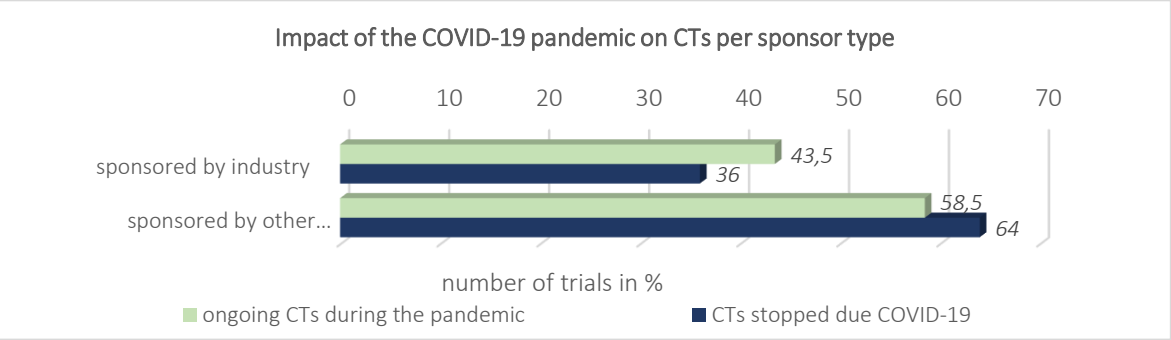
Based on daily searches in the ClinicalTrials.gov registry, B. Carlisle published a dataset of studies stopped due to COVID-19 worldwide [33,35]. The author identified 4 024 studies that were stopped from December 2019 until the end of August 2020. These include observational and interventional studies listing different interventions, e.g. drugs, biologics, devices, dietary supplements, behavioral or medical procedures. 1 670 (42%) of the stopped trials were classified as stopped due to COVID-19, with 84% of these being investigational trials [35].

The data published by Carlisle were further analyzed to assess the effect of the pandemic on the investigational clinical development of not yet approved biologic or chemical drugs [35]. 683 of the stopped studies were proven to be CTs investigating chemical drugs or biologics and are named COVID-19 stopped drug trials below. These represent (a) 20% of all trials stopped, (b) 48.6% of the investigational studies stopped due to COVID-19, and (c) 2.7% of the trials classified as ongoing during the pandemic (table A.2 in the appendix).

64% of the COVID-19 stopped trials are funded by non-industry sponsors, and 36% are sponsored by industry (fig. 6.2). This results in a 1:1.8 ratio of industry-sponsored to non-commercially

sponsored trials. Comparing these data with the ratio obtained for ongoing CTs (1:1.3) indicated a higher amount of non-commercially funded trials to be stopped due to COVID-19.

**Fig. 6.2 CTs investigating new drugs ongoing and stopped due to COVID-19 per funder type**
Out of 683 trials stopped due to COVID-19, 64% are funded by non-industry sponsors and 36% are sponsored by industry, while 43.5% of the ongoing trials receive funding by industry.




The clinical drug development of 68 industry sponsors is affected by stopping 246 trials due to the pandemic from March to September. The TOP5 impacted companies fund more than half of the identified stopped trials and include: Boehringer Ingelheim, Eli Lilly and Company, UCB Pharma, Novartis Pharmaceuticals, and GSK with 16 up to 45 trials stopped per company (fig. 6.4). Several IMPs and indication fields are affected, demonstrating a broader impact of COVID-19 on the development of different drug candidates (table 6.B).

**Table. 6.B Pandemic effect on the drug development of the TOP5 COVID-19 impacted industry-sponsors**

| TOP5 pharma companies | COVID-19 stopped drug trials | in % | effected substances | effected indications |
|---|---|---|---|---|
| Boehringer Ingelheim | 45 | 18.3 | 38 | 22 |
| Eli Lilly and Company | 32 | 13.0 | 32 | 25 |
| UCB Pharma | 21 | 8.5 | 7 | 16 |
| Novartis Pharmaceuticals | 19 | 7.7 | 12 | 17 |
| GSK | 16 | 6.5 | 12 | 11 |
| Sum | 133 | 54.0 | 54.0 | 54.0 |

The majority of the COVID-19 stopped trials belong either to the phase 2 (38.9%) or phase 1 (36.4%) category (table 06.C). The same trend is visible for ongoing CTs (table 6.A and C). In contrast, 38.9% and 16.8% of the stopped trials are phase 2 and 3 trials, whereas 48% and 22% of the ongoing trials belong to these categories indicating a higher impact of the pandemic on the termination/suspension of phase 1 trials. Phase 4 trials seem to be less affected since both datasets show similar values.

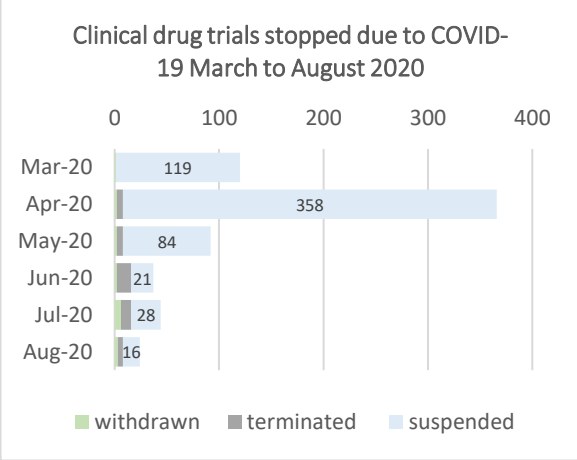
**TABLE 6.C Comparison of the values identified for ongoing and stopped interventional drug trials during the pandemic per study phase**

| Study phase | Clinical drug trials stopped due to COVID-19 | Investigational trials ongoing during the pandemic |
|---|---|---|
| Phase 1 | 36.4% | 32% |
| Phase 2 | 38.9% | 48% |
| Phase 3 | 16.8% | 22% |
| Phase 4 | 13.8% | 14% |

The overwhelming majority of the COVID-19 stopped trials were suspended (91.7%), whereas only 6 % were prematurely terminated, and 2.3% withdrawn (fig. 6.3). An analysis of the timing of the study stop showed that the greater value was stopped in March (18%), April (54%), and May (16%). While most of the suspended trials were stopped in April, the largest number of terminated and withdrawn trials were identified in June and July.

Fig. 6.3 Number of drug trials stopped due to COVID-19 from March to August 2020
The majority were (temporarily) suspended (91.7 %) with the highest number of trial suspensions in April.

| Stopped | Suspended | Withdrawn | Terminated |
|---|---|---|---|
| 638(100%) | 626 (91.7%) | 16 (2.3%) | 41 (6%) |
| **March** | | | |
| 120 (18%) | 119 (19%) | 1 (6%) | 0 (0%) |
| **April** | | | |
| 366 (54%) | 358 (57%) | 2 (13%) | 6 (15%) |
| **May** | | | |
| 92 (13%) | 84 (13% | 2 (13%) | 6 (15%) |
| **June** | | | |
| 37 (5%) | 21 (3%) | 2 (13%) | 14 (34%) |
| **July** | | | |
| 44 (6%) | 28 (4%) | 6 (38%) | 10 (24%) |
| **August** | | | |
| 24 (4%) | 16 (3%) | 3 (19%) | 5 (12%) |




Because a later restart of suspended trials is expected, the overall study status of drug trials suspended through 31 August 2020 was rechecked in the ClinicalTrials.gov database on 06 October 2020 (table 6.D). 31.6% of these trials are still suspended, while 62.6% restarted in the meanwhile, with the majority returning to an active enrollment. For a smaller percentage (5.2%), the study status was changed to terminated, completed, or withdrawn. Noteworthy, 81.3% of the still suspended trials are funded by non-industry sponsors. Accordingly, a larger value of resumed CTs is funded by commercials sponsors, suggesting that trials funded by non-commercial organizations such as universities and private organizations are more severely affected by the pandemic situation.

The author B. Carlisle classified the stopped studies in the downloaded dataset into five indication categories: pain, neuro, cardiovascular, cancer, and COVID-19 [33,35]. Based on this assignment the most affected indications for investigational drug trials were analyzed. More than half of the trials did not belong to any of these categories. Among the classified trials, most investigate cancer (32.4%), while, for the other categories, less than 10% were detected. Concerning the resumption of suspended trials, the results showed that more than half of the cancer and cardiovascular studies already restarted. However, the larger number of trials belonging to the pain and neuro categories are still suspended.

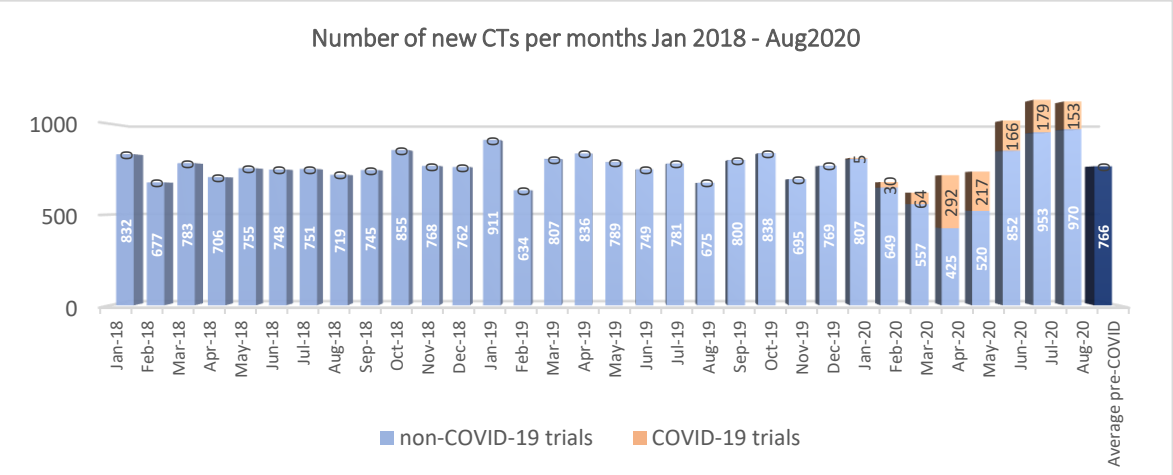
**Table 6.D CTs stopped due to COVID-19 by funder type and indication category** following the publication of Carlisle, 2020 [33,35]

| Status of drug trial | Number of CTs | in % |
|---|---|---|
| **initially suspended** | **626** | **100** |
| sponsored by industry | 217 | 34.7 |
| non-industry sponsors | 409 | 65.3 |
| **still suspended** | **198** | **31.6** |
| sponsored by industry | 36 | 18.2 |
| non-industry funders | 161 | 81.3 |
| **restarted** | **392** | **62.6** |
| sponsored by industry | 234 | 59.7 |
| non-industry sponsors | 158 | 40.3 |
| restarted recruiting | 361 | 57.7 |
| restarted not recruiting | 31 | 5.0 |
| **other study status** | **36** | **5.8** |
| terminated | 11 | 1.8 |
| completed | 20 | 3.2 |
| withdrawn | 5 | 0.8 |

| Indication category | stopped | restarted | still stopped |
|---|---|---|---|
| Pain | 45 (7.2%) | 22 (49%) | 23 (51%) |
| Neuro | 45 (7.2%) | 14 (31%) | 31 (69%) |
| Cardiovascular | 55 (8.8%) | 34 (62%) | 21 (38%) |
| Cancer | 203 (32.4%) | 150 (74%) | 53 (26%) |
| COVID-19 | 2 (0.3%) | 0 (0%) | 2 (100%) |
| No category | 379 (60.5%) | 188 (50%) | 191 (50%) |

To assess the COVID-19 impact on the initiation of new CTs, a database analysis was performed in ClinicalTrials.gov to compare the number of new trials registered from January through September 2020 with the mean value of CTs started under pre-COVID-19 conditions (Jan 2018 – Dec 2019). On average, 766 CTs were started in this pre-COVID arm with a minimum of 634 trials (Feb 2019) and a maximum of 911 trials (Jan 2019) per month (see table A.3 in the appendix and fig 6.4).

**Fig. 6.4 Impact of COVID-19 on the number of CTs started per month**
The number of non-COVID CTs started per month during and before the pandemic was compared. The analysis showed a significant decrease in new non-COVID-19 targeting trials from Mar to May 2020. The data collected for Jun to Aug instead showed an increase in new trial registrations even higher than the maximum in pre-COVID times.




From March to May 2020, a comparable number of newly started studies were demonstrated for the pre-COVID and the COVID-arm. Contrarily, with more than 1 000 studies, an increased number

of trials were started in June through August 2020, representing the highest number of new CTs since January 2018. For a further analysis, the data collected for the COVID-period were divided into two groups: new studies investigating COVID-19 and non-COVID studies (fig. 6.4). As a result, a significantly lower number of non-COVID studies were initiated in these months, with a decrease of up to 44% compared to the pre-COVID average. The highest number of COVID-trials was registered in April and May 2020. Data collected for June through August also showed an increase in new trial registrations for non-COVID trials at a level even higher than the maximum value of the pre-COVID phase (see also table A.2 in the appendix).

## VI. RESULTS II: COMPARISON OF THE COVID-19 GUIDELINES ON ONGOING CLINICAL TRIALS PUBLISHED IN EUROPE, THE USA, AND SWITZERLAND

With the increase of the pandemic spread of the new Coronavirus, more and more guidelines on the continued CT management under the COVID-19 crises were published in spring and summer 2020. These provide sponsors, CROs, and investigators suggestions on recommended mitigation measures allowing a safe conduct of CTs in compliance with the ICH-GCP standards even under these demanding circumstances. In this thesis, the guidelines published during the first wave of the pandemic and the relaxation of the situation in summer 2020 in the EU were analyzed and compared. The COVID-19 guidelines published by the EMA, FDA as well as the TOP5 EU countries identified in the database analyses and the DACH (Germany, Austria and Switzerland) were compared. Regular updates and revisions of the COVID-19 recommendations were monitored in the "*EFGCP-AWP Covid-19 Repository*" and on the webpages of the responsible authorities [34].

The impact of COVID-19 on the CT management is manifold and include (a) increased infection risk during on-site visits, (b) delays for safety visits and other crucial study assessments due to a limited availability of site staff and equipment, and (c) IMP shortage resulting in disrupted treatments. For this very reason, sponsors are recommended to implement extraordinary strategies to assure (a) sufficient medical care and oversight by the investigator, (b) ongoing reconfirmation of the patient's eligibility, and (c) regular conduct of crucial safety assessments and trial evaluations.

### A. THE COVID-19 GUIDELINE PUBLISHED BY THE EUROPEAN COMMISSION AND THE EUROPEAN MEDICINE AGENCY (EMA)

History and general information

A harmonized set of COVID-19 measures was jointly issued by the EMA, the European Commission, and the national HMA on 20 March on the EMA webpage [36,37,38]. During the first pandemic wave, the guideline was revised twice [39,40,41]. Besides the updates summarized in table 7.A the document structure was also improved e.g. chapter numbers (V2) and a table of content were added (V3). A summary of changes is present on the first page of the revised document.

Table 7.A Overview of the revisions of the EMA guidance on CTs' management during the COVID-19 pandemic (updated, new section added in the revised document)

| Version | 1 | 2 | 3 |
|---|---|---|---|
| **Publication date** | 20-Mar-2020 | 27-Mar-2020 | 28-Apr-2020 |
| **Aim** | Recommendation for exceptional measures for ongoing CTs and initiation of COVID trials | Updates added for changes in IC process, link to guidance on statistical consideration, advice on IMP stocks, safety reporting, conduct of audits, temporary halts | Updates added for distributor to trial participant IMP shipment, monitoring, remote SDV, communication with authorities |
| **Topics** | Introduction | Introduction | Introduction |
| | Initiating New Trials | Initiating New Trials | Initiating New Trials |
| | Changes in Ongoing Trials | Changes in Ongoing Trials | Changes to Ongoing Trials |
| | | Safety reporting | Safety reporting |
| | Risk Assessment | Risk Assessment | Risk Assessment |
| | Communication with Authorities | Communication with Authorities | Communication with Authorities |
| | Agreement and communication with sites | Agreement and communication with sites | Agreement with and communication between sponsors, trial sites, and trial participants |
| | Changes to informed consent | Changes to informed consent | Changes to informed consent |
| | Changes to the distribution of IMP | Changes to the distribution of IMP | Changes in the distribution of IMP |
| | | Changes in the distribution of in vitro diagnostic and medical devices | Changes in the distribution of in vitro diagnostic and medical devices |
| | Changes to monitoring | Changes to monitoring | Changes to monitoring |
| | | Changes to auditing | Changes to auditing |
| | Protocol deviations | Protocol deviations | Protocol deviations |
| | Reimbursement of exceptional expenses | Reimbursement of exceptional expenses | Reimbursement of exceptional expenses |
| | Initiation of COVID trials | Initiation of COVID trials | Initiation of COVID trials |

## Recommendations for site initiations and new CTs

Sponsors are instructed to mainly focus on COVID trials and CTs covering unmet medical needs. The start of new trials needs to be critically assessed. Especially, patient's eligibility and safety study assessments need to be assured. In this context, the V2 of the guideline highlighted that risk-benefit sections of new protocols also need to assess COVID-19 risks and planned mitigation measures.

## Recommendations for the continuation of ongoing CTs

Following section 2 of the E6 guideline "*foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks*"[23]. Ergo sponsors are responsible for reevaluating the trial's benefit-risk profile during the complete trial lifecycle. Therefore, a reassessment of the impact of the risk associated with (a) the COVID-19 infection, (b) the governmental protection strategies, and (c) the planned mitigation measures to ensure ongoing conduct of the trial on the overall benefit-risk profile has been highlighted as crucial aspect. Safety and data integrity are at the forefront, whereas patient safety is of higher priority [38]. While sponsors are responsible for evaluating the impact on study levels, investigators are obliged to perform site- and patient-level assessments. Concerning the rapid development of the pandemic, an ongoing reassessment is expected by the EMA. Consequently, the extent and type of the mitigation measures might need to be adapted during the course of the pandemic. This assessment should also include foreseeable limitations of the planned measures in comparison to the standard procedures. Each

measure must be justified as the most appropriate and set-up in alignment with the European General Data Protection Regulation (GDPR) and the national requirements, if applicable [57]. Measures are considered sufficient if they reduce the (a) risks for study participants or involved staff and (b) burden for trial sites. All COVID-19 actions taken need to be documented in the TMF, along with a justification and the risk-assessment. Investigator-driven assessments need to be shared with sponsors and also filed in the ISF.

A general CT suspension is not expected, but if a continuous conduct without compromising participants' safety and data validity cannot be guaranteed, the postponement, suspension, termination or cancelation of treatment, enrollment for the entire study or for single sites might be the only appropriate measure. In these cases, transfer of patients and PI responsibilities to less impacted trials sites might need to be considered.

Recommendations for the application process and communication with national authorities

Following the EU CTD, COVID measures should be submitted to the national ECs/CAs, depending on their urgency and impact, either as USM (urgent safety measures) or as substantial amendment [43, 42]. With V2, instructions on submissions of combined dossiers were added and further clarified in V3 stating that single submissions per sponsor, including an aggregated list of affected trials and changes, are accepted. Applicants are asked to highlight COVID-19 dependencies in the subject lines of relevant communications to allow a prioritization by the authority. To reduce the workload, sponsors are reminded to submit high-quality dossiers with a primary focus on COVID-19 changes and to avoid over-reporting in line with art. 11b of the CTD [25]. Thus, applicants are reminded in V3 that non-substantial amendments can be implemented without prior approval and are submitted with the next substantial applications [43]. Further clarification was added in V3 for justifiable, procedural modifications triggered by COVID-19 that do not severely affect safety or data integrity, but change the administration of the trials. These can be submitted as cumulative notifications along with an updated risk assessment, justification and list of follow-up actions. The EMA recognizes that such notifications might be delayed due to prioritization. Nevertheless, submissions should occur as soon as feasible, and a justification for the delay must be documented in the TMFs.

Recommendation for communications between sponsor and sites

All measures should be agreed upon and communicated between sponsors and investigators, especially since the risk assessment require the evaluation of potential risks on study- and site-level. Sponsors are instructed to share updated documents in tracked changes or with a summary of change for more effortless follow-up and implementation at the sites. Site-sponsor agreements must be documented in writing, e.g. by filing of relevant emails. While V1 focused on the communication from sponsors to sites, the revised guidelines also contained instructions on the

communication between principal investigators (PIs) and patients. It is the investigator's responsibility to inform participants about changes promptly. In V3, instructions for the communication of site-induced changes by PIs to sponsors are highlighted as essential to allow sponsor oversight.

Recommendations for ongoing safety reporting and reporting of COVID-19 infected participants

Introduced in V2, the guideline emphasizes sponsors to proceed with the established safety-reporting and safety data collection procedures. In case face-to-face visits are not possible, the investigators should verify alternative strategies for regular safety follow-up, including telemedicine.

Recommendation for the handling of protocol deviations (PDs)

Compliance with study protocols should be ensured to the maximum extent. Following section 5.20 of the E6 guideline, persistent site protocol deviations (PDs) require prompt actions by the sponsor including a root cause analysis and the implementation of corrective and preventive actions [23]. Under COVID-19, higher values of deviations are expected that cannot be avoided. This will be considered in future inspections if the situation was handled in the best interest of patients. Deviations still need to be operated according to the standard process. Whenever possible, modifications should be implemented to adapt the protocol to avoid further PDs.

Further clarification is provided by the CHMP Biostatics Working "*guidance on the implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing CTs*" [46]. A reference to this document has been added in V2. Systematic tracking of the number and type of deviations and their classification as COVID and non-COVID related is required. As outlined in ICH E3, deviations must be assessed and reported in the Clinical Study Report (CSR) [44]. For later marketing approvals, sponsors are asked to assess the impact of COVID-19 caused deviations on the overall study conduct and data integrity. In this context, sponsors are invited to seek scientific advice from CAs.

Recommendations on exceptional measures for the informed consent and reconsenting process

Reconsenting of patients is challenging during the pandemic. Nevertheless, the requirement to obtain consent before the implementation of modifications remained unchanged. The EMA suggests the following strategy: obtaining oral consent via phone or video that should be confirmed in writing by a patient statement shared via email. Patients will need to reconfirm their consent by signing the updated Informed Consent Forms (ICFs) as soon as feasible. The presence of an impartial witness to confirm oral consent is only explicitly listed for the collection of initial consent from infected patients in COVID trials.

With V2, it was highlighted that ICFs need to be shared with patients via mail, email, or fax prior to the reconsent interview. All deviations from the standard must be documented in the ISF and eTMF. If not submitted as USM, EC approval for the new process is expected before its implementation.

Recommendations on exceptional measures to maintain medical oversight by investigators

In this context, the EMA provides a list of measures that can be implemented to ensure the minimal acceptable extend of medical supervision and adverse event identification and follow-up (table 7.B). This also includes the replacement of on-site visits with usually not accepted procedures such as telemedicine or the performance of study assessments like laboratory tests or imaging procedures outside of the trial site.

Table 7.B Measures recommended by the EMA guideline V1-3 to assure patient protection and data integrity

| Issue caused by COVID-19 | Recommended exceptional measure |
|---|---|
| Reduce the value of patient in-person visits | - conduct of phone and video visits<br>- postponement of non-essential visits<br>- cancelation of non-essential visits<br>*Comment: Alternative measures are limited for new participants since patient eligibility, and initial informed consent should be ensured and in line with the standard process.* |
| Change in conduct of study assessment | - transfer of patient to non-COVID-19 impacted, initiated sites (only in justified cases)<br>- transfer of patient to newly initiated site (only in exceptional cases, last option). New sites can be submitted as USM followed by substantial amendments.<br>- transfer of PI's responsibilities to Sub-Investigators for a defined time<br>- involvement of local non-trial sites for laboratory, imaging, and other diagnostic tests. Sites are not initiated for the trial but can conduct urgently needed (safety) assessment in line with their routine care. With V3 also applicable for data integrity reasons. If relevant for endpoint, this needs to be documented, explained, and assessed in CSR. Consequently, sponsors need access to reference ranges and all information to compare data collected across the study. The latter has been added with V3. |

Recommendations on exceptional measures to maintain IMP supply during the pandemic

In principle, direct study medications delivery (IMP and non-IMP) to the patient's home is recommended to ensure continuous treatment in compliance with the protocol. Whenever possible, delivery by sites is preferred and the direct transfer from sponsors to patients by contracted dedicated vendors, is limited. It is considered critical in terms of blinding and data protection and should only be exceptionally implemented based on a written contract setting all conditions and requirements. This also includes the transfer of only essentially required patient data that should be deleted as soon as feasible. It needs to be guaranteed that these will not, also not accidentally, shared with sponsors. The EMA guideline has drawn attention to the fact that the acceptance of this procedure varies between the EU countries, and national laws and recommendations must be considered.

Another strategy to avoid drug shortages is the IMP delivery between two sites. This should be set-up only if IMP supply by distributors is not possible in time and must follow the process outlined in the E6 guideline [23,45.] The appropriate set-up of the IMP delivery process is mainly related to the type of drug, its safety and stability profile, and is limited to drugs suitable for home treatment.

As clarified in V3, while it is the sponsor's responsibility to ensure that all stakeholders are appropriately trained and the transfer is correctly documented, tracked and performed in line with GMP annex 13 and the blinding procedures, the final responsibility of drug delivery to the patient

remains with the investigators (ICH E6, 4.6) [8,23,45]. Therefore, alternative IMP delivery processes should be developed in cooperation with the responsible QP, the sponsor, and the site following a written process description. PI agreement is required and adequate documentation, including vendor contracts, should be filed in the TMF, ISF and, if applicable, in the patient records. This also includes the documentation of the patient's oral or written consent on IMP home delivery and the patient's IMP receipt confirmation. The sites must train all patients on the documentation of the IMP receipt, the storage, handling and self-administration of the drug . In this context, the EMA requests the provision of written drug instructions to the patients including a list of contact details for questions or issues identified with the IMP. The return of unused medication should occur during the next face to face visit at the study site.

In terms of drug accountability sponsors/sites need to set-up specific measures to assure treatment compliance. Changes in the IMP delivery process will require updates of essential trial documents, including protocols, monitoring manuals and standard operating procedures (SOPs). These need to be shared with the national CA/EC as substantial amendment, USM or, if applicable, notification of an administrative study modification.

With V2, the handover of larger IMP amounts by investigators to patients is also considered appropriate, if this will not lead to drug shortage, especially for marketed drugs. An increase in the sponsor's IMP stock is highly recommended, also considering that delivery failures might lead to a higher number of destruction of unused medication during the pandemic. Additional clarification on IMP delivery has been added in V3 by highlighting that sponsors are responsible to provide logistical assistance and are obliged to cover the costs for this mitigation measure.

<u>Recommendations on exceptional measure related to monitoring and SDV</u>

As outlined by ICH-GCP section 5.2.2 sponsors "*should maintain oversight of any trial-related duties and functions carried out on its behalf […]*"[23]. Essential mechanisms of sponsor oversights are represented by regular monitoring of trial sites to assure regulatory compliance and quality of the data. Due to the COVID-19 emergency situation, the EMA recommends to postpone or temporarily replaced in-situ visits by remote measures. Goal is the reduction of the visit frequency based on a risk-based approach and the consequent update of monitoring plans. These should already include appropriate plans for future monitoring activities, such as an increased frequency of in-person visits after the situation is normalized. Monitoring should be limited to critical data points. The processes should be set-up in a balanced way in consultation with the PI to reduce the workload for sites while protecting patient safety and data integrity.

Adequate remote measures include (a) phone and video visits for monitoring, quality assurance, training and site selection and (b) an increase of centralized monitoring activities including central review of data in eCRFs, central laboratory software or other electronic data capture systems.

One critically discussed measure is the implementation of remote source data verification (rSDV). The recommendation provided in the EMA guideline has mainly changed from V2 to V3. In the majority of the EU states, rSDV was generally not accepted in pre-COVID times. Nevertheless, V1 already mentioned that CAs across EU started to recheck their local requirements to allow temporary solutions. While reference is still made to national laws and guidelines for country-specifics, V3 sets-up some general rules. rSDV is only acceptable under exceptional circumstances and for specific projects such as COVID trials and pivotal studies with unmet medical needs for serious or life-threatening diseases near to database locks. Three possible data sharing processes are described by the EMA guideline including (a) exchange of pseudonymized/redacted copies, (b) controlled remote access for monitors to electronic patient records and (c) in-time video-sharing of the source data (SD) by the site. A well-defined list for the set-up of rSDV systems and processes is present in annex 1 of the latest revision, with a critical view on data protection. Its implementation requires EC/RA approval as substantial amendment, if not outlined otherwise in the national guideline. The final decision on the implementation of rSDV remains with the investigators, especially with regard to the technical capabilities and the evaluation of unnecessary burden for the sites.

Recommendations for the conduct of audits

The guideline recommends the postponement of on-site audits whenever possible. Essentials audits e.g. triggered by serious non-compliance, should only be conducted with the local COVID-19 restrictions and after agreement with the investigators. Alternatively, remote audits might be chosen. This section was introduced in V2 of the EMA guidance and only slightly changed in V3 by clarifying the term non-compliance as serious deviations from protocols or national legislation.

Recommendation for the reimbursement of costs caused by the exceptional measures

If cost reimbursement is applicable in the country, exceptional patient expenses and site costs should be reimbursed, handled and documented following the local legislation in the EU states.

Comments on compliance with personal data protection rules

Especially for IMP delivery and rSDV, the EMA highlighted that COVID-19 measures need to be set-up in accordance with the GDPR and, if applicable local data protection requirements. This might require the involvement of the sponsors and site's data protection officers and, if applicable, might need a separate review by data protection authorities, based on the national requirements.

Other recommendations

V3 also introduced recommendations on the delivery of study devices and supplies which are mandatory for enrolment, safety follow-up and the evaluation of study endpoints. This might also trigger the set-up of stocks. Doing so, the risk for non-trial patients' needs also to be considered, e.g. to avoid limited availability of these supplies for routine care.

On 25 March 2020, the EMA CHMP Biostatics Working Party drafted a separate guidance on the "*points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing CTs*" for public consultation that was finally released on 29 June [46]. This guidance lists points and strategies that should be taken for the analysis and interpretation of study data collected or missed during the pandemic: (1) a systematic tracking and classification of COVID and non-COVID deviations; (2) documentation and assessment of clinical data should include the information if the data were collected pre-, during or post-pandemic; (3) COVID-19 and required measures might directly or indirectly interfere with study treatments, the recruitment and loss of patients. This will affect the data validity and interpretability. Thus, for further analysis and risk assessment of the COVID-19 impact on the final study results, especially data collected during COVID-19 should include as many details as possible, e.g. patients being exposed or infected by COVID-19; (4) The involvement of an Independent Data Monitoring Committee (IDMC) and the assessment of blinded data in interim data analyses is highly recommended. The IDMC should independently evaluate the study data to provide recommendations on the (a) stop, pause, and restart of trials, (b) adjustments of sample sizes and other biostatistical values to reduce the data bias caused by the pandemic and (c) support the assessment of this data bias on the overall study endpoints. Sponsors are encouraged to reach out to the agencies for scientific advice to ensure that these criticalities will not impact the marketing authorization later on.

On 18 May 2020, an additional COVID-19 triggered guidance on remote GCP inspections during the pandemic was published by the EMA [47.] One aspect ensuring compliance with the international GCP standard and consequently the safety and well-being of CT subjects is the regular conduct of inspections by the regulatory authorities at CT sites, sponsors and CROs. COVID-19 restrictions, including travel restrictions, social isolation, social distancing and reduced access to hospital and drug production sites also impact the frequency of such inspection and thereby enhance the risk of unidentified non-compliance issues.

This guideline recommends, again based on a case by case evaluation, the set-up of remote inspections. To reduce the burden for the sites and to be in line with local data protection requirements for sensitive patient health data, remote inspections should not occur at trial sites. Consequently, remote inspection has a limited scope on computerized sponsor and CRO systems such as CRFs and

TMFs. If possible, CROs and sponsors should provide inspectors read-only accesses to applicable systems, including audit trails, activity logs and metadata. Required documents will be shared via secured platforms or emails. Additionally, video-conferences or other electronic communication pathways are recommended to allow communications during remote inspections.

As of 26 April 2020, the European Network of Research ECs (EUREC) published a position paper on the "*Responsibility of ECs during the COVID-19 Pandemic*" emphasizing that even under the challenges caused by the pandemic the "*overarching mission of all ethics committees is the protection of the dignity, rights, safety and well-being of research participants*" [48]. Generally, remote and digital techniques are recommended to assure the continuation of the EC business operations, especially since extraordinary meetings might be required to maintain ethical standards in ongoing medical research. This guideline clearly references the EMA recommendation and no additional COVID-19 strategies for the ongoing conduct of trials are shared.

Topics not covered by the guideline

No guidance has so far been given for the restart of trials or the revocation of exceptional measures.

## B. THE NATIONAL COVID-19 GUIDELINES PUBLISHED BY THE TOP5 EU COUNTRIES AND AUSTRIA

Under the current European legal framework, the CTD, all CTs are authorized and supervised on national-level in the EU member states [25]. As highlighted in the EMA guideline, the legal requirements for the COVID-19 mitigation measures consequently might differ. Thus, additional national COVID-19 guidelines were released. Sponsors need to carefully consult these national guidelines, since, depending on the local law, these need to be taken priority over the EMA guidance. In the below section the national guidance of the TOP5 EU countries and Austria are compared.

### NATIONAL COVID-19 GUIDANCE AND RECOMMENDATIONS PUBLISHED FOR ITALY: FIRST COVID-19 GUIDELINE PUBLISHED IN THE EU

History and general information

With more than 970 COVID-19 cases and 167 death on 11 March 2020, Italy was the first EU country heavily affected by the pandemic. To mitigate the rapid spread of the virus the Italian government imposed strict emergency measures and a gradual lockdown as of 9 March [49]. With a focus on critical outbreaks in the North, the health care system in many Italian provinces were overburdened. Thus, the Italian Medical Agency (AIFA) published as the first EU country a guidance on the CT management during the COVID-19 crises on 12 March, 8 days before the V1 of the harmonized EMA recommendation was released [50]. The Italian guideline, was updated on 07 April in relation to the harmonized EMA recommendations published in the meanwhile [51,52]. Many of the updates added in V2 refer to data protection issues or provide clarification on local requirements (table 7.C). A second revision of the Italian guidance was issued on 17 September 2020.

Table 7.C History of changes of the AIFA COVID-19 guidance for ongoing CTs during the pandemic in Italy (updated and new sections in the revised version)

| Version Date | Version | History of Changes |
|---|---|---|
| 12Mar2020 | V1 | First version covering the following sections:<br>Submission of CTs and substantial amendments<br>Ethics Committees evaluations of CTs/substantial amendments<br>Management of CT activities outside investigational sites<br>Investigational medicinal product (IMP) management<br>Clinical examinations<br>Sites closing<br>CT monitoring<br>Involvement of specialized service agencies<br>Exceptional expenses reimbursement |
| 07Apr2020 | V2 | Update for EMA V1 and V2 and restructuring of the information<br>Submission of CTs and substantial amendments<br>Submission of CTs and substantial amendments of studies for the treatment of COVID19<br>Ethics Committees evaluations of CTs/substantial amendments<br>Management of CT activities outside investigational sites<br>Investigational medicinal product (IMP) management<br>Clinical examinations (tests)<br>Sites closing (transfer between sites)<br>CT monitoring<br>Alternative procedures to obtain the Informed Consent<br>Exceptional expenses reimbursement<br>Compliance with the personal data protection rules<br>General considerations |
| 17Sep2020 | V3 | Updates added for revocation of exceptional COVID-19 measures and restart of studies<br>Submission of CTs and substantial amendments<br>Submission of CTs and substantial amendments of studies for the treatment of COVID19<br>Ethics Committees evaluations of CTs/substantial amendments<br>Management of CT activities outside investigational sites<br>Investigational medicinal product (IMP) management<br>Clinical examinations (tests)<br>Sites closing (transfer between sites)<br>CT monitoring<br>Alternative procedures to obtain the Informed Consent<br>Exceptional expenses reimbursement<br>Compliance with the personal data protection rules<br>General considerations |

While V1 and 2 were published in English, V3 was only issued in Italian (status 13Oct2020). A summary of changes is not available, but all three versions are accessible as PDF [53].

Recommendations for the continuation of ongoing CTs

Following the EMA on the recommendations for the continuation CTs, country-specifics refer to the legal requirement to notify trials suspension or termination. In such cases, a submission for evaluation as substantial amendment for immediate implementation to all Italian ECs is expected at the time of study or enrollment suspension. This is also applicable for not yet initiated trial sites and the restart of the study activities. A submission to the Italian CA AIFA is not required.

Recommendations for the application process and the communication with national authorities

Initial CT and amendment applications are conducted via the OSSC (Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali) online platform followed by mail delivery of (a) a CD ROM

and (b) the originals of cover letters, application forms and fee payment confirmation [54]. During COVID-19, the AIFA releases temporary changes to the administrative management of applications, including (a) replacement of wet-ink signature by digitally signed cover letters; (b) postponement of the paper and CD-ROM submission, but which nevertheless are expected to be obtained as soon as feasible; (c) email submissions to the CA AIFA are not accepted for Non-COVID trials. However, V3 clarifies that answers to authority requests can be shared via email if followed by subsequent delivery of the paper documentation; (d) if online applications are prevented, full paper submissions to the AIFA are acceptable in combination with an email submission to the ECs.

Administrative instructions of the submission process added in V2 include a reference to an AIFA notice on the acquisition of stamp duties for online application to CA published by the Italian Agency on 26 March [55]. It is recommended to apply the stamp duties on the cover letter by virtual payment. Alternatively, paper stamp marks are accepted by inserting the serial number on scans.

All (urgently) required modifications impacting the trial execution and management are expected to be notified as substantial COVID-19 amendment (for immediate implementation) to all involved ECs [25,40]. This is also applicable for exceptional measures listed in the country guideline. The aim is to provide ECs an accurate trail of the deviations. Consequently, supporting documentation, including the risk assessments and justification, should also be submitted. To highlight these as COVID-19 related, section D2.2.3 of the online application form should be clicked as "*other*" and specified as COVID-19 emergency amendment. Consequently, this will not be submitted for approval.

Recommendation for communications between sponsor and sites

In addition to the overlapping recommendations given by the EMA and the Italian guideline on this topic, V2 of the Italian guidance emphasizes that the final trial responsibility of remains with the sponsor (ICH 5.2.1) [23]. Consequently, CROs are only allowed to implement exceptional measures in cooperation with the sponsor. A fact that has not been highlighted in the EMA guidelines V1-3.

Recommendations on exceptional measures for the informed consent and reconsenting process

Whereas the first version of the recommendation did not contain guidance on (re)consenting, clarification on this topic was added in V2. Generally following the harmonized EMA recommendations, the national guidance does not differentiate between consent and reconsent, indicating that alternative procedures will be accepted for both. In difference to the EMA guidance, oral consent should be given in presence of a witness. Alternatively, the provision of electronic signature is also accepted. For isolated patients, the use of cameras and photographs through transparent barriers is recommended to document the patient's consent. The latter procedures are not listed in the actual EMA guideline, but are recommended by the FDA. Contrarily to the EMA, the exchange of hard-copies via mail is not accepted since these are considered a putative infection source.

Recommendations on exceptional measures to maintain medical oversight by investigators

Generally, the same mitigation measures assuring medical oversight are recommended by the EMA and AIFA guidelines. Country-specific information is provided for the involvement of non-trial staff. Shared responsibilities should be documented in a delegation log or clarified in a contract. In V2, it has been emphasized that sponsors need to ensure that the study insurance also covers the exceptional measures. Interestingly, the latter aspect is not present in the EMA guideline.

In case of temporary site closures, patients should be transferred to other trial site. Contrarily to the EMA, the AIFA only accepts a transfer to another already activated site under the sponsor's supervision. In these cases, an updated contracts might be needed based on a case by case decision.

Whereas the first version suggests the performance of hematological clinical tests in external laboratories near to the patients' location only, following the EMA guidance, this was extended to other clinical and medical tests such as radiological assessments in V2. Here, the involvement of certified public health units should be prioritized. The involvement of private health institutions should be avoided and is only possible as last option.

A notification as urgent substantial amendment to the local Italian EC of impacted sites is expected if patient on-site visits are replaced by home care activities or assessments and tests are planned to be conducted outside of the initiated trials site.

Recommendations on exceptional measures to maintain IMP supply during the pandemic

Based on the fact that patients might not be able to visit the site for a longer period, limitations in IMP supply might become critical. To mitigate this risk, the AIFA recommended already in V1 the handover of an increased number of IMP to satisfy ongoing treatment for a more extended period than usual. V2 clarified that it is the investigator's responsibility to evaluate an acceptable period between two in-person visits and to assure that the IMP will not expire during this period. This measure was not present in V1 of the EMA guideline but was introduced with V2.

Following the EMA guideline, IMP delivery to the patients home is also recommended in Italy. This includes the delivery by the trials sites as well as, in exceptional cases, the direct IMP delivery from a sponsor-delegated vendor or warehouse to the patients. Contrary to the recommendations given by the EMA (a) IMP can be handed over to recipients nominated by the patient in a delegation letter; (b) IMP delivery is not limited to self-administered therapies and can be used in case home treatment is set-up either by the study team or by third vendors; and (c) a written or oral patient consent is not highlighted in the Italian guideline.

The above recommendations mainly differ from the ordinary process in Italy, which requires delivery from sponsors to pharmacies of approved sites (art. 7) [56]. Consequently, changes in IMP supply must be set-up in agreement with the PIs and under the supervision of the hospital pharmacy

directors. A notification as an urgent substantial amendment to the local Italian EC of impacted sites is expected for any change related to the IMP delivery process.

For all exceptional measures described above, adequate tracking is required to ensure control and traceability of the IMP delivery to the maximum extent possible. Contrarily to the EMA guidance, the documentation of IMP supply should be kept at the site, even by involving a vendor and direct transport from the warehouse to the patient. The latter represents a waiver to GMP Annex 13, which requires the filing by the stakeholder responsible for the delivery [45].

As highlighted in V2, derogating from the standard process, unused or expired IMP can be stored in restricted areas in the hospital pharmacies and will be returned by the pharmacy after the end of the pandemic for destruction. Tasks related to drug accountability usually handled by CRAs can exceptionally be done by sites including pharmacists. Usually, expired drugs are considered as waste that needs to be registered and stored in specific waste containers, which would usually need to be destructed or returned to the sponsor the latest quarterly by specified vendors.

Recommendations on exceptional measure related to monitoring and SDV

Generally following the EMA recommendation, the reduction of on-site visits and its replacement by alternative remote strategies, including centralized monitoring, is recommended by the AIFA. Already V1 of the national guidance generally allowed the conduct of rSDV but should not result in a higher workload for the sites. Sponsors/CRO are obliged to provide the site's data protection officers detailed description of the process in a SOP for their evaluation and approval. Especially for the transfer of SDs and sensitive personal data via video recordings or electronic share drives, the AIFA suggests the involvement of the Italian Data Protection Authority. Implementing the EMA guideline updates, this section was updated in V2 to clarify robust follow-up strategies to compensate postponed monitoring activities when the situation is normalized. In V3, it has been highlighted that alternative monitoring measures adopted must be described in the monitoring report and the CSR. Referencing to the EMA guideline, rSDV is generally possible as outlined in the EMA recommendation V3, with the exception of the exchange of redacted copies, since rSDV should not put additional burden to the trial sites.

Recommendation for the reimbursement of costs caused by the exceptional measures

Following the standard process, only reimbursement of reasonable travel expenses related to public transport is accepted. There are general exceptions for specific CT conditions, such as the reimbursement of loss of earnings for healthy volunteers in phase 1 trials. Higher amounts of reimbursements might be approved by ECs for studies investigating rare diseases that can only be conducted in specialized hospitals. As a consequence, longer travel times and higher out-of-pocket expenses are expected here. In line with this, reimbursement of costs caused by the emergency situation is

exceptionally possible. Clarification on the reimbursement process was added in V2. Reimbursement directly by the sponsor is possible based on the provision of sufficient documentation, but reimbursement via the hospital administration is preferred. This will require receipts containing either the protocol code or the EudraCT number. Guidance on the requirement of an EC approvals or agreement by data protection officers is not provided. Nevertheless, it has been highlighted that all applicable regulations should be followed to ensure blinding and data protection regulations.

This section has been updated in V3 to provide more clarification on the reimbursement of study assessments outside of the study site. Prepayment for medical assessments required for the CT in alternative institutions might be burdensome for patients. This may impact the frequency of regular follow-up visits and, consequently, may risk patient safety and data integrity. Thus, sponsors are asked to identify and set-up a framework of suitable facilities that allow patient follow-up tests without having the patient to anticipate the costs, but instead, the sponsor to cover the exceptional costs directly with these non-trial health care institutions. Selected facilities should have the capacity to perform as many assessments outlined in the protocol as possible to assure that patients will not need to visit several centers. If this strategy is impossible, an alternative strategy is given by the involvement of third-party vendors for patient reimbursement. In all cases, traceability of the examinations performed outside the site must be maintained by the investigator.

Comments on compliance with personal data protection rules

With V2, a separate section on compliance with data protection rules has been implemented. For all COVID-19 measure, the data controller will be responsible for ensuring compliance with the European GDPR by obtaining advice and support by the responsible data protection officers of the site and, if applicable, the national data protection authority should be contacted for advice before the implementation of critical procedures e.g. remote reconsent, IMP delivery [57].

Recommendations for the restart of CTs and the revocation of exceptional measures

With the release of the V3, recommendations were added for the revocation of exceptional measures. The AIFA reminds sponsors and investigators that these measures are exceptional and only applicable during an emergency. Consequently, ongoing risk-benefit evaluations of measures already implemented are required and should consider the most current COVID-19 situation at each site. With the relaxing situation, generalized measures might no longer feasible and less stringent measures need to be released on site-level. A notification should be sent to the responsible authorities in case of a trial's resume under the pre-COVID-19 approved protocol. In case the protocol needs to be updated for the restart, a substantial amendment approval is required.

Other recommendations

The AIFA guideline includes a section with extraordinary strategies that apply to Italian EC, including the switch from face-to-face meetings to videoconferencing during this emergency situation.

Topics not covered in the Italian guideline

No national recommendation is given on the conduct of audits, safety reporting, including specific requirements for COVID-19 infection reporting of participants and the tracking of PD. If applicable, the EU recommendation should be taken into consideration for these topics.

### NATIONAL COVID-19 GUIDANCE AND RECOMMENDATIONS PUBLISHED FOR SPAIN

History and general information

With around 600 confirmed cases and 55 deaths at the time of the WHO's declaration of the pandemic, Spain was one of the highly affected EU countries. The Spanish Agency of Medicines and Medical Devices (AEMPS) therefore published its guidance on the conduct of CTs during the COVID emergency on 18 March (issue date 16 March), two days before the release of the EMA guideline [58]. Following the revisions of the EMA recommendation, the Spanish guidance was updated twice on 06 April and 05 May. The recommendation is published in English on the webpage allowing also the download as pdf (Table 7.D) [59]. As of 29 June, the national recommendations were added to section 60/61 of the Spanish FAQ on CTs [61]. In line with this, the Spanish COVID-19 guideline was revised on 01 July, but is only available in Spanish (status: 14Nov2020). A summary of changes is present on the first page. An overview of the revisions of the national guidance is not available.

Table 7.D History of changes of the AEMPS COVID-19 guidance for ongoing CTs during the pandemic in Spain (updated and new sections in the revised version)

| Version Date | Publication date | History of Changes |
|---|---|---|
| 16Mar2020 | 18Mar2020 | First version covering the following section:<br>Scheduled face-to-face visits of patients in a CT<br>Enrollment of new patients<br>Access to the CT treatment<br>Monitoring visits<br>Transfer of patients from one center to another<br>CTs aimed at investigating new drugs against coronavirus |
| 06Apr2020 | 06Apr2020 | Updates for COVID-19 studies, reference to the updated EMA guidelines and clarification that national guidance only highlights country-specifics for Spain<br>Scheduled face-to-face visits of patients in a CT<br>Enrollment of new patients<br>Access to the CT treatment<br>Monitoring visits<br>Transfer of patients from one center to another<br>CTs aimed at investigating new drugs against coronavirus<br>Prospective follow-up observational studies with coronavirus-related drugs |
| 05May2020 | 05May2020 | Updates: restructuring, updated reference to the updated EMA guideline 28Apr2020, clarification on the application process in Spain, mitigation measure related to ICFs, drug distribution, rSDV, communication with AEMPS CEIm |

| Version Date | Publication date | History of Changes |
|---|---|---|
| | | Scheduled face-to-face visits of patients in a CT<br>Enrollment of new patients<br>Access to the CT treatment<br>Informed Consent for COVID trials and reconsenting in Non-COVID trials<br>Monitoring visits (rSDV)<br>Transfer of patients from one center to another<br>Notification to CEIm and AEMPS |
| 01Jul2020 | 01Jul2020 | Updates: reference to national FAQ update (28Jun2020) since COVID-19 guidance was included in this document<br>Scheduled face-to-face visits of patients in a CT<br>Enrollment of new patients<br>Access to the CT treatment<br>Informed Consent for COVID trials and reconsenting in Non-COVID trials<br>Monitoring visits (rSDV)<br>Transfer of patients from one center to another<br>Notification to CEIm and AEMPS |

Recommendations for the continuation of ongoing CTs

Due to an increased risk of COVID-19 infections, special attention is drawn in the Spanish guidance on the treatment of immunosuppressive indications. If sponsors decide to suspend study recruitment or treatment, a notification to CA and EC is required within 15 days after the trial interruption and must include information on the provision of alternative treatments for enrolled patients [60,61].

Recommendations for the application process and communication with national authorities

During the first wave, the deadlines for CT application reviews by Spanish authorities were suspended from 14 March to 01 June. Silent approval dates falling in this period are consequently delayed, and new dates should be recalculated according to the following rule: (a) calculation of the number of days from 14 March (inclusive) to the initially scheduled authorization date, and (b) addition of this number to 1 June [61]. Contrary to the CTD and EMA recommendations, the legal requirement to submit an USM within 15 days of implementation is temporarily suspended during the COVID-19 crisis in Spain if the USM is related to (a) transfer of patients between two sites, (b) performance of laboratory test at local non-trial site laboratories and (c) dispatch of study drugs to the patient's home. In comparison, ECs and CA must still be notified within 15 days in case of trial suspensions. Another regulatory deviation of the Spanish Guideline to the EMA is the submission of a COVID-19 summary report instead of individual submissions for the implementation of mitigation measures recommended in the guideline. The report is expected to summarize all exceptional measures adopted per study, the corresponding risk-benefit assessment, and justifications. It is expected to be submitted as trial progress report via the ECM online system the latest four months after the official end of the first wave COVID-19 emergency crises in Spain on 21 October 2020. A template for this report is accessible in the appendix of the CT FAQ [61].

Recommendation for the handling of protocol deviations (PD)

COVID-19 PDs should be documented but will not be reported to CA/EC. Rescheduling of patient visits will only be considered serious PDs if the postponement will put the patients' safety at risk.

Recommendations on exceptional measures for the informed consent and reconsenting process

In general, the Spanish agency and ECs follow the EMA guidance and accept verbal patient consent given during phone or video calls followed by a ratification of the consent in writing. In contrast to the EMA recommendations, scans or pictures of the patient signed ICF sent via email or mobile phones (only accessible by the study team) would be accepted as written confirmation of the re-consent. Spanish authorities do not request a subsequent collection of a wet-ink signed ICF.

Recommendations on exceptional measures to maintain medical oversight by investigators

Following the EMA guideline, postponing on-site patient visits or their replacement by telemedicine should be considered. To maintain medical oversight in case of site closures, transfer of patients between two trial sites is possible. In addition to the EMA recommendations, the following country-specifics are listed. The Spanish Agency expects a transfer agreement to be signed by both sites. This agreement should assure that the new site has access to CFR and electronic patient records. If paper records are used, the new site should be provided with a copy. The current site should provide a summary of the most important medical data for sufficient safety follow-up by the new site. The transfer must be documented in the ISF at both sites. Submission as USM or an upfront EC/CA approval for patient transfers is not expected, and the authorities will be informed later on in the COVID-19 summary report. In line with the Spanish CT legal framework, a new site requires EC approval before they are allowed to conduct any trial-related activity, this requirements still remains.

Recommendations on exceptional measures to maintain IMP supply during the pandemic

Generally following the EMA V2 guideline, IMP delivery to the patient by the site institution or the handover of a higher amount of IMP are recommended mitigation measures. Following the standard procedure, IMP delivery should be handled by the pharmacy. Direct delivery of study medication by the sponsor to the patient involving authorized distributors can exceptionally set-up in line with section 4 of the Spanish order establishing conditions for the dispensing and administration of medicines within the scope of the national health system, in the face of the COVID-19 crisis [62]. IMP can also be handed over to the subject's caregiver. Contrarily to the EMA and the other EU guidelines, the AEMP highlights that alternative treatment options need to be provided by the sponsor in case of drug shortage resulting in temporary study halts. The change in IMP delivery will be included in the comprehensive COVID-19 report.

Recommendations on exceptional measures related to monitoring and SDV

Following the EMA, rescheduling of in-situ visits and the prioritization of centralized and remote monitoring strategies are recommended. The Spanish authorities advise sponsors to update monitoring plans for a well-defined time of four months. If possible, SDV should be postponed until access to medical records in person is possible. rSDV is generally acceptable following the set-up instructions and limitation to specific study types set by the EMA. In contrast to other EU countries, first in human phase 1 studies might also be considered applicable for rSDV in Spain.

In V3, further instructions on rSDV were added following a publication of the Spanish data protection authority [63]. Contrarily to V1, which only requested the documentation of rSDV activities in eTMFs, the update of 01 July mandates sponsors to inform the AEMPS by submitting an ad hoc report or an USM about the rSDV implementation as soon as the trial sites approved the process. Remarkably, patient consent for rSDV is not required since the Spanish agencies states "*this activity is legally regulated as a necessary activity in the trial*" [58]. This non-requirement has been confirmed by the Spanish Data Protection Agency. The implementation of other remote monitoring activities does not require EC/CA approval and will instead be included in the COVID-19 summary report.

Topics not covered in the Spanish guidelines

The Spanish authorities give no national recommendation on the restart of CTs, the revocation of exceptional measures, reimbursement of costs and the conduct of audits. Also, a separate section on personal data protection was not issued, but the involvement of the local data protection officers for critical access and transfer of patient health and personal has been highlighted in the described section above e.g. for remote monitoring.

### NATIONAL COVID-19 GUIDANCE AND RECOMMENDATIONS PUBLISHED FOR GERMANY

History and general information

The German COVID-19 guideline was published jointly by both German CAs (the Federal Institute for Drugs and Medical Devices (BfArM) and the Paul-Ehrlich Institute (PEI)), after consultation with the Association of Medical ECs (AMEK) and the federal authorities on 26 March [64,65,66]. The most recent version is available as PDF in English and German on the webpages of both CAs. As explicitly emphasized, this is considered as supplemental recommendation to the EMA opinion, focusing only on the German specifics. Thus, in contrast to other country COVID-19 guidelines, no repetitions of information already contained in the EMA guideline have been issued. Administrative instructions relating to the communication between sponsors and authorities and changes in application processes are directly published on the BfArM webpage [67]. The German guideline was updated five times from March to May 2020, either due to administrative changes or updates of the EMA

guidance. A history of the changes can be found on the BfArM webpage and a summary is also shown in the table below (table 7.E) .

In particular, V3 of the EMA guidance triggered an extensive update of the German supplemental recommendation. Several aspects previously described in the local document were included in the EMA guideline and thus no longer considered Germany-specific and consequently deleted. While V1-2.2 contained instruction on remote monitoring, rSDV and IMP delivery, the latest version V3a only refers to the Germany specifics for rSDV.

Table 7.E History of the changes of the supplementary COVID-19 recommendation guideline published by the German CAs

| Version Date | Version Number | History of changes |
|---|---|---|
| 26Mar2020 | 1.0 | Publication of Germany specific recommendation as addendum to the EMA guideline. |
| 30Mar2020 | 2.0 | Updated link added for the updated EMA COVID-19 guideline V2 (27Mar2020) |
| 30Mar2020 | 2.1 | Update for CA fee reduction of costs; link added for the English translation |
| 28Apr2020 | 2.2 | Updated link to EMA COVID-19 guideline V3 (27Apr2020) |
| 19May2020 | 3.0 | Update of the guideline: information added for rSDV, deletion on information on remote monitoring in general and IMP delivery |
| 27May2020 | 3.0a | administrative changes of the wording |

In April, the AMEK issued their COVID-19 considerations on the webpage (only in German). These mainly represent the same recommendation issued by the EMA and the German CAs, but provide additional details for the expected set-up of the mitigation measures at the German sites. Updates were added on 01 July on the requirement of data protection consents for rSDV and IMP delivery.

Recommendations for the continuation of ongoing CTs

Contrarily to the standard procedure, recruitment halts can be submitted by email as combined notification for several CTs per sponsor and without using the "*Notification of substantial Amendment Form*". For a later restart, an EC and CA approval of a substantial amendment is required.

Recommendations for the application process and communication with national authorities

The German authorities promise preferential assessments of amendments arising from the pandemic. Applicants are asked to highlight these by adding COVID-19 in the cover letters' subject header. The German Medicinal Product Act (AMG) and the GCP-Ordinance (GCP-V) still mandate the submission of paper dossiers [68,69]. To accommodate that many employees work from home during the crises, this legal requirement has been suspended. CA applications should be submitted using the Common European Submission Portal (CESP). Applications via online systems or emails were established by several ECs. For more and most up-to-date details, the applicants are instructed to screen the EC webpages.

Recommendations for ongoing safety reporting and reporting of COVID-19 infected participants

Waivers are not accepted and the general requirements on safety reporting for trial sites and sponsors given by the national law (GCP-O §§ 12 and 13) remain unchanged [69]. In case of any change to

the approved safety reporting process, a substantial amendment or USM, including the risk assessment report and the evaluation on the overall impact on the trial data integrity, must be submitted to the responsible CA and the involved German ECs.

Recommendations on exceptional measures for the informed consent and reconsenting process

No instructions are given in the national CA guidance, consequently, the EMA recommendations are applicable. Additional instructions on the reconsenting process were issued by the AMEK. Generally following the EMA recommendation, Germany specifics are pointed out for the handover of updated ICF: The exchange of electronic files is only allowed for upfront information. Instead, hard-copies should be shared by the site, ideally prior to the reconsenting call, to allow patients to sign the form in addition to their oral consent. Signed ICFs should be sent back to the sites free of charge after the call. Electronic signatures are considered as not compliant with the German requirement for a valid and legally binding signature [70].

In a news release of 30 July 2020, the AMEK emphasized that the role-out of direct IMP delivery or rSDV *per se* does not trigger an update of the approved ICFs according to the German law [70]. This is mainly based on the fact that these changes do not affect the participants' medical care or safety. Instead, these are considered as data protection changes only. Following art. 14 GDPR, data protection consents are not tied to any particular form and can be obtained by email, writing or phone [57]. Documentation in the patient file is recommended.

Recommendations on exceptional measures to maintain medical oversight by investigators

No country-specific instructions are given in the national CA guidance. Consequently, the EMA recommendations are applicable. In addition, the AMEK issued Germany specific instructions for the involvement of external vendors, e.g. for homecare procedures. Here, the transfer of SDs to the responsible sites needs to be ensured and all activities require the investigator's supervision. Upfront patient consent is also needed. Changes need approval by EC/CA and the dossier should outline how these requirements will be met. The involvement of external staff might additionally require an update of the description of the site's qualification form to assure delegation to only qualified and trained staff. Whenever assessments are outsourced, it needs to be checked if the involved institutions need approval as trial sites. The latter does not apply if study assessments are conducted in accordance with routine care and do not require detailed knowledge of the protocol.

Recommendations on exceptional measures to maintain IMP supply during the pandemic

Following the EMA recommendation on the limitations, set-up instructions and documentation requirements, direct IMP shipment to the patient's home by the site and, in exceptional cases, by sponsor-contracted vendors are acceptable in Germany. While V1 and 2 highlighted details on, for example, the requirements for documentation, training, tracking and the responsibilities of

sponsors, vendors and sites, this section has been deleted in V3 because the details listed in the German guidance V2 are now included in the revised EMA guideline, and no further Germany specifics need to be considered.

Recommendations on an exceptional measure related to monitoring and SDV

In line with the EMA, the German guideline V1 and V2 and the AMEK recommendations suggested a reduction of planned monitoring activities to a minimum based on a risk-based approach. The German guidance classified monitoring procedures that are related to (a) data collection for a continuous risk-benefit assessment, (b) verification of enrolment in line with the inclusion and exclusion criteria, (c) recording of adverse events and serious adverse events and critical outcome parameters and (d) the dosing and dose regimens of IMPs as mandatory activities that are also required under COVID-19 restrictions.

Following the limitations set-up by the EMA guidance, remote monitoring is explicitly highlighted as a possible alternative [64]. This includes rSDV, although usually not acceptable in Germany. For the implementation of rSDV, EC and CA approvals must be granted based on a substantial amendment. The route of remote access, the measure planned to protect the patients' personal data and the SD that will be accessed, needs to be described in applicable study manuals, the study protocol, or a protocol attachment letter. A study-specific risk assessment is also required. Based on the chosen technologies, additional statements of involved parties confirming that the process is set-up in accordance with the applicable data protection requirements must be added in the application dossier. The list of the required information is much more detailed compared to the information shared by the EMA. It is recommended to add rSDV activities in the site's data protection register of processing activities with applicable start and end dates. The procedure should be set-up in cooperation with the sites' data protection officers since independent reviews might be required by local data protection authorities. Table 7.F lists three different set-ups for remote access by the monitor on the SD at the site and the relevant information that needs to be shared within the amendment. The national recommendations given on rSDV changed mainly during the course of the pandemic. Contrarily to the above, V1 of the German recommendation only allowed access to SDs via live-streaming. Exchange of redacted copies was regarded as not acceptable. The same information was shared by the AMEK and was not updated as of 15 November 2020. The section on general remote monitoring was deleted in V3 because the details are now covered by the EMA guideline as well.

Table 7.F Requirements for the rSDV set-up outlined in the German COVID-19 guidance

| Remote access type | Information required for the substantial amendment application |
|---|---|
| Direct access of the Monitor to software and databases used at site to maintain SD (e.g., electronic patient file) | Name and version of the software accessed<br>Name and version of the software used for remote access<br>Used encryptions<br>Limitation of access rights to relevant data only |

| | |
|---|---|
| | Measures taken to avoid long-term storage of data and permanent deletion of system generated temporary data<br>Written sponsor statements that access is limited to authorized monitors located in the EEA and that remote access process is described sufficiently in the ICF |
| Remote passive access of the Monitor to SD via direct live-streaming by the site | Description of the process<br>Used systems and involved parties<br>Measure taken to ensure that SDs are only accessible by authorized personnel with the EEA. This also includes the location of involved servers.<br>Written confirmation of monitors and sponsors that (a) data are not permanently stored, (b) system-generated temporary data are deleted, (c) live streaming occurs in a secured environment ,(d) process is performed in agreement with the process described in the ICF |
| Access to redacted patient SD copies | Definition of the minimum quality criteria<br>Measure to ensure completeness of the shared copies<br>Description of acceptable redaction methods<br>Description of corrective action in case of data breaches due to missing redactions<br>Description of the methods used to share the redacted copies and measure taken to avoid loss or unauthorized access<br>Description of the documentation required to allow traceability of the SD shared by the site and received by the monitor |

Comments on compliance with personal data protection rules

A separate section on data protection is not present in the supplemental guidance. Nevertheless, especially for rSDV, the protection of the study participant's rights has been highlighted as the key aspect for the benefit-risk evaluation in the German CA and AMEK recommendations [57]. Involved vendors should have appropriate certificates and experience. Generally, the guideline refers to a separate document, "*Whitepaper Technical Privacy Requirements for Messenger Services in the Hospital Sector*" for requirements that need to be considered for the set-up of remote technologies in the health care sector. Data protection-relevant topics are only cursorily reviewed by German ECs and CAs. Compliance to the GDPR must be checked with the data protection officers of involved **stakeholders and might require an evaluation by responsible data protection authorities.**

Other recommendations

The AMEK has published administrative changes applicable for CT applications to German ECs for the following topics: (a) GCP certificates: Online GCP course certificates will be accepted in the future if these courses were conducted during the COVID-19 emergency. This also includes courses that have not yet received a certification of at least one of the federal medical associations; (b) temporary absence of PIs and deputy PIs caused by sick-leaves, quarantine, or during recalls of site staff for emergency care: following the CT legislation, only long-term absence requires an EC notification along with the nomination of qualified replacements. Short-term absence should be covered by at least one fully delegated and qualified sub-investigator.

**Topics not covered in the German guidelines and recommendations**

There are no national recommendations for the restart of trials, cancellation of exceptional measures, audits, reimbursement of exceptional costs, handling of PDs and communication between sponsors and sites. For new site and CTs, only information on COVID-trials are present that are not part of this thesis. For these aspects, the EMA recommendations should be considered.

### NATIONAL COVID-19 GUIDANCE AND RECOMMENDATIONS PUBLISHED FOR FRANCE

#### History and general information

On 20 March, the French Medicines Agency (ANSM) published COVID-19 instructions on its webpage based on an FAQ in French and English [71,72]. Updates were added on 08 April and 20 May to reflect the revised EMA recommendations. With the relaxation of containment measures and the end of the first pandemic wave, a second FAQ was published in August. As of this date, two separate guidelines are available (a) recommendations for the lockdown period and (b) post lockdown recommendations [73,74]. The later emphasized sponsors to reconsider if the implemented COVID-19 measures are still appropriate and provide guidance on a step by step revocation [75].

Table 7.G History of changes of the ASNM COVID-19 guidance for ongoing CTs during the pandemic in France

| Version Date | History of Changes |
|---|---|
| 20Mar2020 | First version |
| 08Apr2020 | **Updates**: Reference to the EMA recommendation V1 and V2 added in sections safety reporting, IMP delivery; section on COVID-19 infection patient follow-up added |
| 20May2020 | **Updates:** Reference to the EMA recommendation V3 added, Restructuring of the general introduction, amendment requirement section added; reorganization of FAQ sections by topic |
| 10Aug2020 | **Renaming of previous guideline** dated 20May2020 as **recommendation for lockdown**, still applicable if locally required based on COVID-19 impact of site.<br>**Separate document released for post-lockdown** recommendation including instruction on revocation of measures and restart of suspended trials/recruitment. |

#### Recommendations for the continuation of ongoing CTs

The French guidance highlights that the suspension of CTs or recruitment and the premature discontinuation should occur in justified cases only and should be notified to the French EC and CA, in an USM notification followed by a substantial amendment application for authorization by CA and the involved EC in line with the EMA recommendation and the CTD [25]. The trial discontinuation justification needs to consider the risk associated with each patient by interrupting the treatment versus the risks and benefits related to ongoing treatment.

#### Recommendations for the application process and communication with national authorities

The ANSM invited all sponsors to contact the French Agency for questions on conducting CTs under the pandemic situation by email via questions.clinicaltrials@ansm.sante.fr.

Following the EMA, CTD and the French CT legislation, ECs and CA must be informed about any immediate change as USM, followed by a substantial amendment, within 15 days. For measures that are only implemented temporarily, an USM revocation notification is expected. Temporary CT

modifications applicable for the pandemic only should be addressed in protocol/manual addendum, while permanent modifications must be added to an amended protocol. Submissions of amendments and USMs should be sent by email following a strict naming convention to allow the ANSM to prioritize on COVID-19 application. Separate email addresses were created to differentiate USMs (vig-essaiscliniques@ansm.sante.fr) and substantial amendment requests (ams-essaicliniques@amsm.sante.fr). Guidance on submission to ECs has not been given.

Recommendations for ongoing safety reporting and reporting of COVID-19 infected participants

In accordance with the EMA guidance, the general safety reporting requirements remain unchanged with the following exceptions for DSUR submissions: (a)The legal requirement for a mandatory wet-ink signature has been suspended. Instead, scanned signatures or email confirmations by the person responsible for the DSUR validation is acceptable; (b) The annual submission deadline can be deferred for up to two months. In addition, the postponement of safety monitoring committee meetings is accepted as long as patient safety is not affected and all stakeholders, including authorities, are informed accordingly. Specific guidance is provided for infected participants by referencing to the general French instructions on COVID-19 treatment, protective measures and the use of acceptable certified diagnostic tests [76,77]. It is the investigator's responsibility, in cooperation with the sponsor, to decide on further study treatment. COVID-19 infections should be documented in patient records and reported only if infections result in SUSARs or SAEs.

**Recommendation for the handling of protocol deviations (PDs)**

The ANSM attaches particular importance to the optimal traceability of deviation. All data that cannot be collected must be documented. Missed visits will not *per se* counted as major deviation and will neither trigger patients' study discontinuation nor a notification to ANSM.

Recommendations on exceptional measures to maintain medical oversight by investigators

In agreement with the EMA, reducing on-site visits and the alternative establishment of telemedicine is recommended. The latter should be considered on a case-by-case basis to focus on safety data and primary objective endpoints. In the case of site closures, transfer of patients to initiated or new sites is recommended and requires patient consent. The French "*Direction générale de l'offre de soins*" of the Ministry of Health should be contacted for information on the COVID-19 impact on selected research sites. Patient transfers generally require prior EC approval. This requirement was temporarily waived, and EC notification is acceptable instead during the pandemic.

Recommendations on exceptional measures to maintain IMP supply during the pandemic

Following the EMA guidance, the ANSM recommends (a) the IMP supply with a sufficient amount to cover a longer period in between two on site study visits or (b) the IMP delivery by the site and in exceptional cases by the sponsor to the patient's home. A substantial amendment/USM with

subsequent substantial amendment submission is required for changes in the IMP delivery, whereas a submission for information is sufficient for the handover of a higher amount of IMP. In both cases, supportive information on planned procedures for the follow-up of adverse events and drug accountability must be included in the submission dossier. Both measures are not accepted for narcotics and are limited to self-administered drugs. IMP delivery of parental administered drugs can be considered and required submission as substantial amendment including information on the procedures planned to ensure safe IMP administration at the patient's home.

IMP delivery needs supervision by investigators and local pharmacies. Specific information on data protection requirement in this context is ruled out by a specific guidance only available in French[78]. In line with this, patients need to be informed about the changes in the usage of their personal data, especially if third party vendors are involved. In accordance with the French Data Protection Agency (CNIL), no health care data should be shared with vendors. This also includes administrative information, such as protocol numbers, since they may be used in public databases to reveal information on the patient's disease.

Contrarily to the EMA, the ANSM provides a more detailed recommendation on a two-steps approach for the patient consent in these cases: First, the site will need to inform the patient prior the IMP delivery about the delegation of tasks, the name of the contracted vendor, and the type and category of personal data shared. This should be documented in the records, including the information that the patient did not raise any concerns. Additionally, written information needs to be shared with patients via email or within the IMP delivery package. In general, IMP delivery needs to be conducted in accordance with safety instructions, ICF, and traceability requirements approved for the trial. Subsequent updates of applicable study documents are therefore very likely and will trigger substantial amendments for authorization.

Recommendations on exceptional measures related to monitoring and SDV

Following the EMA recommendation, ongoing monitoring is still emphasized but should be postponed if required by local restrictions and national COVID-19 containment measures. The sponsor is obliged to check possible monitoring visits with the investigators. Remote monitoring is, in general possible in France, but the remote exchange of patient records, including pseudonymized paper sheets, for rSDV is not allowed.

Comments on compliance with personal data protection rules

A separate guideline only available in French was issued to provide further guidance on data protection issues connected to IMP delivery. In line with French data protection requirements outlined in the reference methodology (MR-001), no health care information should be shared with vendors [79,80].

Recommendations for the restart of CTs and the revocation of exceptional measures

With the FAQ dated August 2020, recommendations for the gradual trial restart were added. The sponsor is fully responsible for the evaluation if a study can be restarted in compliance with all legal requirements. This includes (a) the sponsor's capacity to monitor and oversee the trial and, (b) the assurance that the conduct of the trial will not be affected by the site's local epidemic situation. In case the study will be continued under the same protocol conditions approved before COVID-19, a notification to EC/CA is sufficient. Temporary measures can be revoked, including a certification that the trial can be conducted in line with the initially approved set-up. If protocol changes are required for the restart, a substantial amendment of an updated protocol will be expected.

As of 10 August, the ANSM request sponsors and investigators to recheck the arrangements' adequacy, especially for IMP delivery. In exceptional cases and based on a justification shared with the authorities, the exceptional COVID-19 arrangements might be continued. In case the local COVID-19 situation worsens again, the reactivation of the mitigation measures is expected. In such cases, a notification for information to EC/CA is sufficient instead of the submission of an USM.

Topics not covered in the French guidelines and recommendations

No national recommendation is given on the communication between sponsors and sites, the informed consent and reconsenting process, the reimbursement of costs, and the conduct of audits. The EMA recommendations should be followed.

### NATIONAL COVID-19 GUIDANCE AND RECOMMENDATIONS PUBLISHED FOR THE NETHERLANDS

History and general information

Dutch country-specific recommendations were published by the Central Committee on Research Involving Human Subjects (CCMO) and the Health and Youth Care Inspectorate of the Dutch Ministry of Health, Welfare, and Sports (IGJ) [81,85]. The IGJ guideline named "*Coronavirus (COVID-19): impact on the conduct of CTs under the Medical Research Involving Human Subjects Act (WMO)*" was published on 08 April and updated four times (table 7.H) [82,83]. The CCMO published the "R*ecommendations for the conduct of clinical research at the time of restrictive measures due to the coronavirus*" in March, which underwent six updates until August (table 7.H).

Both guidelines cover overlapping topics, including alternative IMP delivery strategies, deferred ICF process, and requirements for the restart of trials. Recommendations related to remote monitoring and SDV are only covered by the IGJ. In contrast, the CCMO provides administrative information, e.g., on the application process and the legal requirements for USMs, substantial amendments, or notifications for study termination and suspension [84]. The splitting of country-specific information in two guidelines complicates the follow-up on Dutch requirements for all stakeholders. This is mainly driven by the decentralized oversight and overlapping responsibilities by the CCMO and IGJ

as national CA, depending on the trial type. Table 7.H provides an overview of the change history until September 2020. Whereas the earlier versions were generated separately, the later revisions were updated co-operatively to streamline the information.

Both guidelines are published in Dutch and English as PDFs. Further information can be found in press releases and information on the webpages of both authorities [81,85].

Table 7.H Summary of updates of the Dutch COVID-19 recommendations published by CCMO and IGJ

| | CCMO | IGJ |
|---|---|---|
| Title | Recommendations for the conduct of clinical research at the time of restrictive measures due to the coronavirus [85] | Coronavirus (COVID-19): impact on the conduct of CTs under the Medical Research Involving Human Subjects Act (WMO) |
| First version | 13Mar2020 | 08Apr2020 |
| Update 1 | 02Apr2020: Updates for deferred consent in emergency situations (general info) | Version 2: 28Apr2020: Updates added for risk associated with phase 1 trials (suspension expected) and rSDV (EMA guideline update) |
| Update 2 | 14Apr2020: Updates added based on IGJ recommendations, oral consent IMP delivery, legal requirement for restart recruitment | Version 3: 20May2020<br>Updates added for phase 1 trials (reference to CCMO requirement for a gradually restart) |
| Update 3 | 28Apr2020: Updates in line with EMA guideline on IMP distribution, monitoring, rSDV, communication with MRECs and CA | Version 4: 22Jun2020<br>Updates added for restart CTs and monitoring |
| Update 4 | 22May2020: Updates added for required notification before restart of recruitment | Version 5: 13Aug2020: Updates added for restart of CT/reference to combined separate guidance document CCMO and IJM, replacement suspension/gradually restart phase 1 CTs |
| Update 5 | 26May2020: Updates for communication with CA (information on declaration of no objection) | |
| Update 6 | 25Aug2020: Updates for the restart of CTs (link to IGJ requirement document) | |

Recommendations for site initiations and new CTs

Contrarily to the EMA recommendations, the Dutch guidelines contain detailed instructions for the start of new non-COVID phase 1 trials, which should be delayed to ensure that no participant will receive IMPs that were not tested (in the same dose) in humans before. For other trials, the EMA recommendations should be considered.

Recommendations for the continuation of ongoing CTs

In line with the above and following the amended IGJ recommendation dated 28 April ongoing non-COVID phase 1 trials should temporarily be suspended. For the continuation of phase 2-4 trials, the EMA opinion should be followed.

Recommendations for the application process and communication with national authorities

On 13 and 16 March, the CCMO issued instructions on administrative changes on the application process due to lower CCMO accessibility during the lockdown in press releases [86,87,88]. Communication should occur via email, and applications should be made electronically via EudraLink or alternative secure online means. The requirement for wet-ink signatures is suspended, and instead, scanned or digital signatures are recommended.

The majority of the national recommendations comply with the EMA guideline [89]. COVID-19 triggered modification classified as patient safety impacting should be submitted to ECs. Changes altering the overall benefit-risk-profile substantial amendments to EC and CA are required. The CCMO reminds sponsors of the requirements to report safety-related study suspensions immediately. Contrarily, premature terminations or halt caused by other reasons should be reported within 15 days [42,90]. While fast track assessment after prior consultation is limited to COVID trials in other countries, the Dutch authorities allow this also for amendments related to the pandemic [90].

Emphasized by the amended guideline dated 26 May, acknowledgments of receipt will not be provided for temporary halts or restarts. Contrary to standard procedures, the responsible CAs will also not issue a declaration of no objections for such notifications to reduce the workload for the CA [90].

Differently to the EMA, the CCMO and IGJ consider logistical changes, including the change to rSDV, not as substantial amendments, and therefore approvals are not required [85,90].

**Recommendations on exceptional measures for the informed consent and reconsenting process**

Information and instructions on deferred (re)consent processes under patient emergency situations were added to the CCMO (02Apr2020) and IGJ recommendation. In May 2020, the CCMO published a memorandum on this topic to clarify the process and the legal requirements. Following the national law (WMO, art. 6 (4)), study participation without prior written consent is generally possible in emergency situations if the EC approved the process [83]. Under these circumstances, the written consent of the participant is required as soon as possible. For most of the ongoing non-COVID trials, this deferred process is not acceptable since it is limited to the treatment of serious and life-threatening conditions that are the cause of the emergency. Consequently, reconsent processes need to be considered for applicable changes caused by COVID-19 containment measures or infections following the EMA recommendations.

**Recommendations on exceptional measures to maintain medical oversight by investigators**

The EMA recommendation on mitigation strategies ensuring a continuation of study assessments and patient follow-up should be followed. The Dutch agencies consider related changes such as the transition of in-situ patient visits to phone visits as administrative changes. Consequently, no EC/CA approval is required for the implementation of these measures [36,42].

Recommendations on exceptional measures to maintain IMP supply during the pandemic

Following the EMA guideline, IMP delivery from the site pharmacy to the patient's home is possible [85,90]. Alternatively, IMP delivery from the site's pharmacy to a public pharmacy is also recommended to maintain treatment in line with study protocols. EC/CA approval for this process is not needed. As outlined in an IGJ press release, tracking and filing of the following steps are required instead: (a) a written IMP request issued by the receiving pharmacy, (b) detailed documentation of IMP

delivery by the supplying pharmacy and (c) documentation of the IMP receipt and subsequent distribution to the patient by the receiving pharmacy [91].

Following the EMA guideline, the CCMO guideline (14 April), accepts a patient's oral agreement on the change to home delivery if documented accordingly. Ideally, the oral confirmation should be supported by a written confirmation by email [90,85]. A patient's signature is not required, also not retrospectively. Contrarily to the EMA recommendation, IMP delivery by the sponsor, the site investigator or delegated vendors is not permitted in the Netherlands [85].

Recommendations on exceptional measures related to monitoring and SDV

The authorities are generally following the rSDV limitations on specific trial types and conditions outlined by the EMA. Contrarily to this, review of redacted documents is not allowed due to (a) the process has a high risk for errors and (b) will cause extra work for the sites that was classified as an unacceptable burden. For the same reasons, aloud reading of SD information during phone calls is also not permitted. Instead, monitor's access to applicable SD by reading along the screen of trial site members is preferred. Any type of recording is strictly inadmissible. Technical requirements are described in Dutch on the Data Protection Authority webpage [92].

The IGJ guideline focuses on data protection violations and technical details that must be met to establish rSDV processes. The IGJ limitations and requirements are stricter than those published by the EMA, for example, only critical data are allowed to be shared remotely. In case other data are shared, this will be considered a severe reportable data protection breach.

Country-specific information was also shared for monitoring visits, especially for the gradual restart of on-site monitoring. Remarkably, the CCMO and IGJ confirmed that the restart of trials should not be considered as an official restart of all monitoring activities. The extend of on-site monitoring visits is finally the site's decision and should also be evaluated in view of the potential impact on the standard medical care at the site.

The CCMO classified changes of the monitoring plan as administrative changes only, and therefore approval by EC/CA is not required.

Recommendations for the restart of CTs and the revocation of exceptional measures

Whereas the CCMO recommendations published on 14 April stated that the restart of trials after a temporary suspension does not need to be approved by the Dutch committees, the revision dated 22 May clarifies instead that recruitment restart will require an EC/CA notification [84,85,85,90]. A separate CCMO guidance "*Conditions for (re)starting studies in Clinical Research Units*" was published in cooperation with the IGJ on 28 May 2020. This document focused on the gradual restart of early-phase research studies conducted in specialized Clinical Research Units (CRUs). With the relaxation of the COVID-19 containment measures and the return to standard medical care, a second guideline

was published on 25 June, allowing the restart of CTs of all other phases and trial sites. Both guidelines were finally combined by creating the IGJ guidance on the "*requirements (re)start of CTs, including CTs in CRUs*" in August [93, 94]. A cross-reference to this guidance was added in the latest revisions of the CCMO and IGJ guidance on the conduct of ongoing CTs [90].

Based on study- and site-level risk assessment reports, sponsors and investigators must carefully consider a gradual restart in summer 2020. Central oversight of the restart-decision should be granted on an institutional level, e.g. by a written approval of the hospital directors boards. Applicable documentation needs to be filled in the eTMF and the site files.

The restart in line with a previously approved protocol should be submitted to EC and CA as a notification. In case protocol updates are required for the study restart, the amended study documents require approval as a substantial amendment. For both cases, the risk analysis documentation should be added to the submission package.

**Topics not covered in the Dutch guidelines**

The CCMO and IGJ issued no country-specific guidance on the conduct of audits, sponsor/site communications, PDs, reimbursement of costs caused by the pandemic. The Dutch guidelines generally highlight in several sections that mitigation measurements need to be set-up in line with the GDPR, especially for rSDV techniques, but additional country-requirements on this topic are not given.

### NATIONAL COVID-19 GUIDANCE AND RECOMMENDATIONS PUBLISHED FOR AUSTRIA

History and general information

The Austrian CA, Bundesamt für Sicherheit im Gesundheitswesen (BASG) published their first COVID-19 recommendation on 17 March 2020 [95]. Contrarily to other countries, a separate document was not created. Instead, updates and new sections were published directly on the webpage from March to June 2020. The Austrian recommendations are available in German and English.

The status of the information shared on the homepage at different time points was compared. If applicable, single sections were updated, especially for the implementation of the revised EMA guidelines. Following V2, data integrity was added as a critical point to be considered in the Austrian guidance. The sections on IMP delivery and rSDV were updated in line with the EMA guideline V3 in April 2020. A history of changes or a summary of the fundamental changes is not present on the webpage, but for each section, the date of the latest update is visible and summarized in table 7.I.

Additional COVID-19 comments were published on 24 March on the webpage of the Forum of the Austrian ECs [96]. This document provides general comments on the conduct of trials under COVID-19, including the prioritization of applications and applicable references to national for the implementation of mitigation strategies and safety measures as modifications for ongoing CTs.

Table 7.I Update history of the national COVID-19 guidance for Austria

| Section on webpage | Date of last update | History |
|---|---|---|
| Reference to EMA guidance | 28Apr2020 | Updated with EMA guidance V2-V3 |
| COVID-19 impact on ongoing CTs | 27Mar2020 | Updated with EMA guidance V2 |
| Communication to CA | 14May2020 | Update with V2 and V 3 and national updates for clarification |
| Revocation of measures | 15Jun2020 | National updates |
| IMP Delivery | 29Apr2020 | Updated with EMA guidance V3 |
| Vendor involvement by site | 27Mar2020 | Update in line with EMA guideline V2 |
| Monitoring | 29Apr2020 | Updated with EMA guidance V2 and V3 |
| Audit during the Pandemic on site | 24Mar2020 | First recommendation published, no update added in this section |

Recommendations for site initiations and new CTs

The BASG gives no specific guidance on this topic. Interestingly, whereas the EMA guideline recommends the start of COVID trials and Non-COVID trials for trials investigating diseases with only insufficient therapies, the Forum of the Austrian ECs recommends a focus on COVID trials only. In this context, taking into account that the COVID-19 restrictions also impacted the availability and work structures of the Austrian ECs, a priority list for CT applications was published: (a) priority 1: CTs to investigate COVID-19 preventions or therapeutics and substantial AM for currently running CT caused by COVID-19; (b) priority 2: epidemiological and other studies collect data on COVID-19 and (c) priority 3: are all other applications.

Recommendations for the application process and the communication with national authorities

In line with the EMA recommendation and §37a of the national CT legislation in Austria, any change related to COVID-19 impacting CT data integrity or patient safety should be submitted as USM. Approvals will not be issued on the BASG homepage, contrary to the standard process. A downstream submission of a substantial amendment for each of these USMs is not expected, which is in contrast to other EU countries and the CTD. Instead, at the end of the pandemic, of the study or on BASG request, a combined report summarizing all COVID-19 USMs should be issued as one single substantial COVID-19 amendment. In this report, the history of the mitigation measures implementation, current status, future plans and the overall impact on data integrity should be summarized. This is not be applicable for trials that were stopped during the pandemic, and no other mitigation strategies were implemented.

USM submissions should be made via email to clinicaltrials@basg.gv.at by entering COVID-19 urgent safety notification in the subject line. Contrarily to other countries, the Austrian CA and the majority of ECs accepted electronic submissions already before the pandemic so that, in general, the application pathway did not change.

Recommendations on exceptional measures to maintain medical oversight by investigators

The BASG has not explicitly commented on this, and consequently, the EMA recommendations should be considered. The Forum of the Austrian ECs highlighted that all measures related to

homecare treatment need to be conducted by trained personnel under the PI's supervision and responsibility. Changes related to this need to be implemented in the protocol and require either approval as a substantial amendment or notification as USM.

Recommendations on exceptional measures to maintain IMP supply during the pandemic

Following the instructions on the set-up, training and documentation requirements given by the EMA guideline, IMP delivery to the patients is recommended. Hand-over of IMP to persons other than the study participants is not acceptable, and IMP dispatch via pharmacies is not foreseen.

If a site is unable to handle the on-top workload related to IMP delivery, the involvement of resources from external vendors is acceptable if set up in line with ICH GCP 4.2. (adequate resources, sec. 5 and 6) and the GCP Q&A section of the EMA [23,97]. The transfer of personal data and contact details of patients outside of the study site should be avoided whenever possible. To emphasize these requirements, clarification on the tracking responsibilities outlined in ICH-GCP (5.14: Supplying and handling investigational product, sect. 4) was added to the national guideline [23]. These tracking requirements are only applicable for delivering the IMP between sponsor and site or between two sites and are not applicable for the shipment from the site to the patient. Consequently, tracking of shipping records should only be maintained on the sites only and should generally not filed in TMF. In case filing is required to document deviations, only redacted copies should be added to the TMF.

With the release of V3 of the EMA guidance, clarification on the direct shipment from the sponsor to the patient via contracted vendors was added in this section. The same limitation given by the EMA is followed. In addition, a written confirmation of the PI is required that, even with the involvement of third vendor on-site personal, proper IMP tracking and delivery can no longer be guaranteed by the site. All delegated tasks must be tracked in a delegation log. Changes in the IMP delivery can only be implemented based on a CA/EC approval as a substantial amendment.

Recommendations on exceptional measures related to monitoring and SDV

In line with the EMA recommendations, sponsors are instructed to focus on mandatory face-to-face monitoring visits and to use alternative remote strategies and decentralized monitoring instead.

In V1 of the Austrian guidance, rSDV was considered unacceptable since sensitive patient health and personal data should only be accessible at the study site. As in Germany, this changed with the implementation of the EMA guidance V3. Even very limited, rSDV will be accepted in exceptional cases after RA and EC's approval of a substantial amendment. All temporary changes of the planned monitoring schedule and process must be documented and outlined in revised monitoring plans or an addendum according to the requirement given by section 5.18.6 (Monitoring report) ICH GCP.

Recommendations for the conduct of audits

The first COVID-19 related recommendation in Austria referred to the sponsor audit's conduct and was published on 24 March 2020. Sponsors were instructed to withdraw or re-schedule all non-mandatory audits with a special view on staff and investigators' availability during the COVID-19 emergency crises. For mandatory, e.g. for-cause audits that are urgently required to ensure participants' safety and well-being, remote procedures should be considered, including phone and video techniques. Alternatively, sponsors are instructed to focus on trial sites not or lower affected by the pandemic to maintain sponsor oversight. All conducted audits, including the changes to the standard process, should be documented in line with ICH GCP section 5.19.3 (Auditing procedures).

Recommendations for the restart of CTs and the revocation of exceptional measures

With the decrease of COVID-19 cases and the gradual reduction of the governmental COVID-19 restrictions in June, the BASG added a section on the withdrawal of measures on their webpage (15 June). Sponsors are asked to reduce the extraordinary measures gradually and to notify the Austrian authorities accordingly. Approvals will not be required. Instead, this will also be covered by the final COVID-19 summary report that will be submitted as substantial amendment serving as the formal conclusion of all COVID-19 changes and applications submitted as USM.

Topics not covered in the Austrian guidelines and recommendations

No national guidance is given on the reimbursement of additional costs, communication between sponsors and sites, safety reporting, including reporting of COVID-19 infections of study participants, handling of PDs and the consent and reconsenting process. The recommendations given by the EMA should be considered here. A separate section on the compliance with personal data protection rules has not been issued, but general compliance to GDPR has been highlighted for the transfer and review of critical personal and health data in the sections above.

## C. THE COVID-19 GUIDANCE PUBLISHED FOR SWITZERLAND

History and general information

The first COVID-19 guidance for CTs in Switzerland was published on 18 March by the Swissethics as a newsletter [98]. This document informs sponsors and investigators to ensure that CTs are conducted per the general COVID-19 ordinance issued by the government on 16 March and in accordance with the ICH standards and outlined by the Ordinance on CTs in Human Research (ClinO) [99]. The latter is particularly highlighted for the legal requirements on the implementation of COVID-19 study modifications. The first guidance was replaced by a joint guidance issued by the Swissethics and Swissmedic (CA) on 25 March (V1.1) [100]. Resembling a two paged bullet point list, this document contained first recommendation on possible COVID mitigation strategies. Revision 2.0 was released one day later and can be considered the first comprehensive and formulated COVID-19 guideline

for Switzerland. In this version, additional topics issued by the EMA and FDA recommendations were added, including the ongoing performance of risk assessments also with a view on study data integrity. The guideline was again revised in April and June (table 7.J). With each revision, details on mitigation measures and clarification on the communication with the Swiss authorities were added. A summary of history is not available, but starting with V2.0, each update contained an overview of changes to the previous version. The latest version of the joint guideline can be accessed as PDF on both authorities' homepages in English [101].

Recommendations for site initiations and new CTs

In general, the Swiss authorities follow the EMA and only expect COVID trials and trials investigating new therapies for life-threatening diseases to be initiated under the pandemic after carefully consideration based on a risk-benefit assessment on study and site level in line with ICH GCP [23].

Recommendations for the continuation of ongoing CTs

Accordingly to the EMA recommendation, ongoing treatment and recruitment should be carefully reconsidered for ongoing CTs, especially for aggressive therapies. The sponsors are recommended to take the most appropriate mitigation measures outlined in the national guidelines to reduce the risks. Depending on the risk profile, this might lead to a temporary stop of the trial or the enrollment. In such cases, sponsors are asked to get in contact with the EC for further advice. The temporary study holds, and discontinuations require an EC notification within 15 days (ClinO: article 38 (2))[99]. Subsequent extensions of timelines need to be notified to EC at the time the trial will resume. Contrarily to the EMA recommendation, there is no need to inform EC or CA about halts of recruitments only. Nevertheless, the documentation thereof needs to be filled in the TMF and ISF.

Recommendations for the application process and communication with national authorities

The mandatory requirement of originally signed paper submissions, including a CD-ROM with the electronic version of the documents, is deferred by the Swissmedic. Nevertheless, required paper documents must be submitted on top of the electronic submission as soon as possible. Any change impacting the study design or patient rights need approval before its implementation. EC and CA accept bulk submission for trials of the same sponsor. USMs should be notified within seven days (ClinO art. 31(1)) [99] and non-urgent actions as substantial amendments (ClinO art. 29 and 33) [99]. For some urgently required measures, delayed submissions or submissions for information instead substantial amendments for EC/CA approval are exceptionally accepted, as described below.

Recommendation for communications between sponsor and sites

A separate section on sponsor and site communication is not present. In general, the guidance generally states in line with the other COVID-19 guidelines discussed above, that (a) COVID-19 measures should be agreed upon between sponsors and investigators and (b) a clear

communication is mandatory to ensure proper sponsor oversight for ongoing risk assessment on the one hand and PI oversight for medical decisions on the other.

Recommendations for ongoing safety reporting and reporting of COVID-19 infected participants

Introduced with V2.1, the safety reporting section of the joint guidance clarifies that the national requirements remained unchanged (section 5(2), ClinO) [99]. Regular SAE and SUSAR follow-up should be guaranteed, e.g. by the implementation of remote strategies. Contrarily to the EMA, the Swiss authorities share specific information for COVID-19 infected study participants. General notification to EC and CA of every COVID-19 case is not expected but might be required if infections result in SAEs or SUSARs triggering EC/CA notification in line with the safety reporting requirements as defined by the local legislation (ClinO) and the protocol [99].

Recommendation for the handling of protocol deviations (PDs)

The same recommendations are given by the EMA and the Swiss guidance regarding a higher amount of deviations expected per site, their handling, documentation and assessment in CSRs.

Recommendations on exceptional measures for the informed consent and reconsenting process

Following the EMA guidance, initial consent is expected to rather occur during the pandemic and should be done in line with the standard requirements (section 3 ClinO) [99]. For reconsenting, especially for changes triggered by the emergency, a COVID-19 ICF addendum was issued by the Swissethics. New or revised ICFs need prior EC approval; nevertheless, delays will be accepted. Following the instructions outlined in detail above for the EMA, oral consent followed by written reconfirmation is accepted. While the EMA guidance recommends an upfront exchange of the ICF via email or mail before oral patient consent can be given, this is not listed in the Swiss guideline.

Recommendations on exceptional measures to maintain medical oversight by investigators

The same measures are listed in the Swiss and EU guidance to maintain medical oversight by the PI and to ensure the performance of critical study assessments focusing on safety and endpoints. In addition, the Swiss guideline emphasizes that, if required and after documentation of the patients' agreement, sites may decide to proceed with study assessments and treatment at the patients' home. In such cases, sponsors should be informed in time to ensure sponsor oversight for downstream reporting and assessments of the impact on safety and data integrity, e.g. for the CSRs. Further instructions or requirements e.g. for the exchange of patient records and SD between two sites in case of a patient transfer or the involvement of external medical care units are not present.

Recommendations on exceptional measures to maintain IMP supply during the pandemic

In general, IMP's delivery to participants is also possible in Switzerland but is limited to the direct delivery from the site to the patient's home. In line with the EMA, the implementation (a) is strictly

limited to the pandemic; (b) only possible for IMPs suitable for usage at home and (c) required patient consent. Concerning the urgency, oral consent, followed by written consent, is acceptable.

Changes in the IMP delivery process need to be notified to the EC/CA. An EC/RA approval is not expected. Sponsors are instructed to use the "*reporting related to a clinical trial form*" for these notifications to the Swissmedic, including a written confirmation that sites will be responsible for the home delivery. While the Swissethics accept this mitigation strategy silently, the Swissmedic is expected to provide an acknowledge the receipt.

Recommendations on exceptional measures related to monitoring and SDV

Similar recommendations are given by the EMA and the Swiss recommendations on the reduction of on-site visits and the establishment of remote techniques to compensate delayed on-site visits. Contrary to the EMA guideline and the national recommendations described above, rSDV was considered inappropriate in Switzerland during the pandemic's first wave. The Swiss authorities neither accept the exchange of patient data via remote techniques nor by sharing redacted patient files. All changes need to be addressed in revised monitoring plans and notified to EC for silent acknowledgment. Delayed submission due to the urgency will be accepted. Deviations to the standard monitoring process should be described in each report and finally assessed in the CSR.

Recommendation for the reimbursement of costs caused by the exceptional measures

Costs related to the pandemic should be reimbursed to the patient and the sites. The sites should handle patient reimbursement. Further financial compensation needs to be documented. A separate EC approval is not mandatory.

Recommendations for the restart of CTs and the revocation of exceptional measures

Introduced with V2.2 in June 2020, both authorities clarified that the resumption of CTs and the revocation of the exceptional COVID-19 measure (a) would depend on the pandemic status at each site, (b) only be possible if the PI can guarantee the safety and well-being of both the patients and the site staff, (c) and the sponsor ensures that all stakeholders have full capacity to follow-up and maintain the trial. A risk assessment and justification would be needed and filled in the TMF.

A separate notification to both authorities for silent acknowledgment is required for the restart. For the CA notification, the following form should be used: "*submission of changes to a CT and answer to conditions*." A trial resume is only possible with the latest approved protocol.

Thus, substantial amendments are likely required if changes need to be implemented before the restart. Ongoing reassessment of the risks based on current COVID-19 impact on study, country, and site-level is expected and might require returning to the COVID-19 measures.

Table 7.J Overview and history of changes of the COVID-19 guidelines published by the National CA (Swissmedic) and the EC (Swissethics) for ongoing CTs conducted in Switzerland during the COVID-19 pandemic 2020 (updated section, new section)

| TOPIC | Swissethics guidance INFORMATION ON COVID-19 | JOINT GUIDELINE Swissmedic and Swissethics | | | |
|---|---|---|---|---|---|
| | V1.0 | V1.1 | V2.0 | V2.1 | V2.2 |
| PUBLISHED ON | 18Mar2020 | 25Mar2020 | 26Mar2020 | 09Apr2020 | 15Jun2020 |
| TOPICS | CTs need to be conducted in line with COVID-19 ordinance 2<br><br>Communication EC: study termination or interruption, enrollment stop<br><br>Protocol deviations<br><br>substantial amendments | CRAs with limited or no access at all to hospitals and limited SDV possibilities<br>Reporting to ECs and Swissmedic<br>IMP and study medication logistic<br>Assessment by family doctor or other hospitals<br>Patient with symptomatic SARS-CoV-2 infection<br>Exceptional expenses of patients<br>Questions to EC and Swissmedic<br>Studies on COVID-19 therapy and vaccination<br>Inspections | CT with IMP to treat COVID-19<br>Risk assessment<br>Changes in the distribution of the study medication: direct to patient delivery<br>Monitoring<br>Conduct of study visits<br>Conversion of physical visits into phone or video visits<br>Administration of the IMPs at patient's home<br>Study-specific assessments<br>Informed consent procedure<br>Protocol deviation<br><br>Reporting of changes in study implementation due to COVID-19 to the authorities<br>Communication with Swissmedic<br>Communication with ECs | CT with IMP to treat COVID-19<br>Risk assessment<br>Changes in the distribution of the study medication: direct to patient delivery<br>Monitoring<br>Conduct of study visits<br>Conversion of physical visits into phone or video visits<br>Administration of the IMPs at patient's home<br>Study-specific assessments<br>Informed consent procedure<br>Protocol deviation<br>Safety Reporting<br>Reporting of changes in study implementation due to COVID-19 to the authorities<br>Communication with Swissmedic<br>Communication with ECs | CT with IMP to treat COVID-19<br>Risk assessment<br>Changes in the distribution of the study medication: direct to patient delivery<br>Monitoring<br>Conduct of study visits<br>Conversion of physical visits into phone or video visits<br>Administration of the IMPs at patient's home<br>Study-specific assessments<br>Informed consent procedure<br>Protocol deviation<br>Safety Reporting<br>Reporting of changes in study implementation due to COVID-19 to the authorities<br>Communication with Swissmedic<br>Communication with ECs<br>Resumption of CT activities following the COVID-19 pandemic |

Other recommendations

A specific section on inspections was added in V1.1. stating that inspections are on hold until further clarification. This section has been removed in version 2.0.

Topics not covered in the Swiss guidelines and recommendations

No guidance is given by the Swissmedic and Swissethics on the data protection rules and the conduct of audits during the pandemic.

## D. THE COVID-19 GUIDELINES PUBLISHED FOR ONGOING CLINICAL TRIALS IN THE USA

History and general information

On 18 March 2020, the FDA published the first guidance on the *Conduct of CTs of Medical Products during COVID-19 Pandemic* abbreviated as "*conduct guidance*" [102]. As seen for the EMA guidance, this guideline was issued immediately without prior public consultation. The guidance was updated 8 times from March to September 2020 (table 7.K). With the revision of 27 March, a list of Questions and Answers (QA) was added. Neither a history of the revisions nor a summary of changes has been published. The latest revision of the guidance is accessible on the FDA COVID-19 webpage as PDF [103],[104]. This webpage covers all available COVID-19 guidelines for several aspects in the field of the FDA's responsibility. The FDA coordinates the recommendations given by CDER/FDA/CBER for internal and external stakeholders to ensure consistency and appropriate regulatory flexibility [104]. In line with the EU guideline, patient safety and data integrity are the highest priorities. The general part of the document resembles a bullet point list with general points to consider. More details on specific measures can be found in the QA section.

Table 7.K History of changes of the FDA COVID-19 conduct guidance for ongoing CTs during the pandemic

| Date of update | No | Summary of changes added in the revision |
|---|---|---|
| 18Mar2020 | 1 | First version |
| 27Mar2020 | 2 | **Addition of QA section as Appendix: Q1-10** on suspension and key points to consider for study continuation, protocol deviation, missing patient data and COVID-19 protocol amendments, IMP delivery, home infusion, monitoring and consent process for isolated patients |
| 02Apr2020 | 3 | **Update of general section** on administrative information to the guideline development and references to other national COVID-19 guideline. Addition of a specific COVID-19 question email address for CTs (pandemic replaced with public health emergency). |
| 16Apr2020 | 4 | **Update of QA section: Addition of Q11-17** on consent process, remote monitoring, rSDV, IP infusion and sourcing, FDA communication, and CTD |
| 11May2020 | 5 | **Update of general section** on administrative changes<br>**Update of QA section:** update of Q3 (protocol deviation and amendments) and Q8 (homecare infusion); addition of Q18-Q20 on remote patient visits, post-marketing studies, conduct of imaging and laboratory study assessment in external institutions |
| 15May2020 | 6 | **Update of QA section:** Addition of Q21-22: COVID-19 as SAE and COVID trials |
| 03Jun2020 | 7 | **Update of general section:** administrative changes<br>**Update of QA section:** addition of index and Q23 on signature, update and rewording Q10, Q12: consent and remote assessments |
| 02Jul2020 | 8 | **Update of QA section:** addition of new Q12 on consent process |
| 21Sep2020 | 9 | **Update of QA section:** clarification added for esignatures, addition of new Q23 on safety reporting and IRB submission of safety reports |

Recommendations for site initiations and new CTs

In agreement with the EMA, the FDA emphasizes that the initiation of new trials and site must be carefully considered, particularly in the light of the evolving pandemic situation. The following issues should be considered (a) putative COVID-19 impact, (b) presumed mitigation measures, (c) potential inference to public health measures. In contrast to the EMA guidance, a limited scope of new trials e.g. on life-threatening diseases, is not recommended in the US guidance.

Recommendations for the continuation of ongoing CTs

The FDA reminds sponsors of the general ICH GCP principle that an assessment of the impact on patient safety and data integrity must be performed for each deviation and action. On this basis, the discontinuation of the study might need to be considered (Q2). Treatment should only be continued if the patient has a direct benefit. This likely applies only to a portion of participants in the same study. In this case, protocols should be revised after FDA consultation, and appropriate follow-up measures must be taken for patients who discontinued study treatment. The guideline summarizes the key issues to be considered in this assessment (a) potential new safety risks posed by COVID-19, (b) ensuring the availability of IMPs, required IT systems, equipment and supplies, and personnel at the sites, suppliers and sponsors to properly continue medical care and monitoring of patients, (c) the accessibility and continued operation of trial sites, ECs, and other committees involved in the study and (d) the feasibility of the ongoing study conduct in accordance with COVID-19 public health measures. It is anticipated that the halt of enrollment will have no impact on safety and data integrity per 21CFR 312.30(b)(2). Thus, unlike the changes noted above, the submission of amended protocols is not required (Q3).

Recommendations for the application process and communication with national authorities

The CT review process remains unchanged. Consequently, amendments can be implemented based on IRB approval and once FDA submission is made. Following 21 CFR 56.1088(a)(4) and 312.30(b)(2)(ii), urgent changes may be reported after their implementation through subsequent submission for formal IRB approval and FDA filing of amended protocols. If the implementation of study modifications is preferred upon FDA approval, this should be addressed in the application. Short-term waivers may be requested to allow applications in electronic formats other than eCTD.

FDA emphasizes sponsors to seek advice on mitigation measures that impact study endpoints. Regulatory project managers will serve as primary FDA contacts, especially for safety-relevant issues. General requests can be shared via clinicaltrialconduct-COVID19@fda.hhs.gov.

Recommendations for ongoing safety reporting and reporting of COVID-19 infected participants

Under the regulatory framework for CT safety reporting (21 CFR 312), sponsors must inform the FDA and all involved investigators of each SAE, including a classification of a causal relationship to the IMP [105]. This is considered essential to protect patients, and thus, this remains unchanged.

In contrast to the above EU guidelines, the FDA also indicated that additional safety monitoring, such as periodic COVID-19 testing, should be conducted. These do not need to be included in the protocol of non-COVID trials. The sponsors are directed to evaluate whether the IMP poses a higher COVID-19 risk by comparing infection rates, the severity of infections, and the reported SAE ratio between the treatment arm and (a) placebo arms or (b) appropriate literature data. This should be done by a data monitoring or safety committee based on unblinded safety data. Identification of a causal relationship triggers an IND safety report filing to FDA and IRB (21 CFR 312.32) [105].

Recommendation for the handling of protocol deviations (PDs)

As also recommended by the EMA, sponsors are advised to systematically document COVID-19 triggered deviations, including missing data. Lists per deviation type rather than listing each deviation could be provided to the standard documentation summarizing the description, reason, date, patient ID, and site number along with possible contingency actions. Updates of data management and statistical analysis plans are expected. This documentation should be part of the CSR and, if applicable, annual safety or progress reports to allow final investigation on the COVIC-19 impact on the study outcome. All changes occurring upon IRB approval and FDA submission are deviations.

Recommendations on exceptional measures for the informed consent and reconsenting process

Generally following the EMA guidance, the FDA highlighted that although oral consent will be accepted under these specific circumstances, standard consent processes are still preferred. The general GCP requirement to obtain patient consent before study-specific assessment remains unchanged. The standard approach in the US also includes eCONSENT procedures. Consequently, the FDA opened the previously developed eCONSENT app free of charge for investigators allowing the secure collection of electronic informed consents [104,106].

The guideline describes alternative procedures to obtain consent of COVID-19 infected participants (Q) and participants that are unable to participate in face to face visits (Q). In both cases, the handover of consent forms prior to the remote interview is required, as also described in the EU. The FDA recommends the exchange of investigator signed copies via email or facsimile. The main differences between the FDA and EMA guidance are seen here for the recommendations for the remote consent collection documentation. Contrarily to the EU guidelines, the FDA require a higher level of documentation, including a list of all meeting participants, written confirmation of the oral consent, and a statement that all questions were answered. The documentation of the patient's

consents should be supported by either (a) photographs of patient signatures, (b) recording of verbal consents, or (c) a written confirmation of a witness, (d) the signature of the study team member obtaining consent on the ICF including a justifying note that written confirmation by patients could not be collected. The reason for the use of an alternative procedure must be added to the patient files. For non-infected patients, the signed ICF can be returned at the next visit, or a scan can be shared by secure emails or webpage uploads. A return via mail is considered risky since paper documents might be contaminated. If patients are unable to print, consent can be given on a separate document referring to the study (title, protocol number).

Originals or certifies copies are required for archiving, especially of wet-ink signed documents. Whereas the EMA and Swiss guidelines allow alternative procedures for reconsenting only, the FDA accepts these procedures for any type of consent as long as the IRB approved it.

Recommendations on exceptional measures to maintain medical oversight by investigators

In general, the same recommendations are shared by the FDA and EMA to maintain medical oversight. This includes the conduct of safety and efficacy assessments at alternative locations such as (a) local laboratories, (b) imaging centers, (c) local health care providers. Whenever assessments relevant to eligibility, safety or study endpoints are done outside of the trial site prior FDA consultation is requested. In such situations, the variability of the data should be limited to the lowest extent possible. Delegated institutions require detailed experience by routinely performing the delegated tasks and should follow standardized procedures.

Remote techniques such as phone or virtual in-time visits might alternatively be conducted by trained staff in line with the data privacy requirements. Here again, the EU and FDA guidelines provide different details on the documentation requirements. One key point of the FDA guidance is the verification of the patient's identity, which should be documentation and follow specific identification validation plans developed by sponsors. Besides, investigators need to identify the patients' current location to allow medical emergency care, if required. The documentation of assessments performed remotely should be as detailed as possible and include information on assessments that could not be covered remotely. The FDA advises explicitly on the switch from on-site assessments to remote clinical outcome assessments (COAs) such as interview-based (ClinRO) or patient-reported outcomes (PRO). General considerations assuring patient protection and privacy requirements in this context are listed in answer to Q13 in the FAQ. Concerning data integrity, sponsors must pay special attention to the availability and consistency of standardized COA at different trial sites. They should provide technical support and training to reduce data bias. The most suitable COA procedure should be chosen to perform the assessment as similar as possible and in the same frequencies as on-site assessments to support the study's endpoints robustly.

Recommendations on exceptional measures to maintain IMP supply during the pandemic

In line with the EMA guidance, home care delivery of self-administered IMPs is also mentioned in the FDA guidance. Contrarily to the EMA guidance, the FDA allows the supply of IMPs requiring administration by a health care professional, but the risks associated with the stop or ongoing home care treatment should be discussed with the FDA prior to its implementation, especially for ATMPs. Home care treatment might be done via home nursing of the study site or the involvement of well-trained local health care providers (HPC) with sufficient experience in the product class. HCPs performing study-specific actions directly impacting study data are considered sub-investigators and therefore need to be listed on the FDA1572. Contrarily, task delegation should be listed in site records in case delegates conducting procedures in line with the clinical standard. Patients should provide an updated consent to allow the trial site to access the HCP records. Contrarily to the other COVID-19 guidelines, local sourcing, based on a local physician's prescription, is recommended as a mitigation measure for studies investigating already FDA approved IMPs. Reimbursement of the costs by the sponsor is acceptable, and even the labeling requirements for IMPs are not followed in this situation, the FDA will not request a waiver.

The implementation of alternative IMP delivery strategies needs IRB/IEC approval. If only implemented for several subjects, this can be documented as PD.

Recommendations on exceptional measures related to monitoring and SDV

In line with the EU guidelines, remote and central monitoring procedures should be established or extended to assure sponsor oversight to the greatest extent possible. Central and previous monitoring results, as well as the site's qualification, experience and recruitment status, should be considered in a risk-based approach for the prioritization of remote monitoring. If feasible, the frequency should be maintained with a focus on critical site documentation. Postponement of on-site visits and the implementation of remote measures might result in a higher number of delayed identification on GCP non-compliance. Thus, the FDA emphasizes the documentation of any discrepancy related to monitoring activities, which should be available upon request for sponsors and the FDA. The monitoring report and follow-up actions should cover the same details as for on-site visits.

If not implemented before, the FDA endorses the set-up of remote SDV in monitoring plans and SOPs. Depending on the site's resources and technical capabilities, exchange of the data should either realized by (a) granting monitors remote access to the site systems, (b) the establishment of remote viewing portals to share site documentation electronically or (b) the upload of certified copies of relevant SD and site documents into a sponsor controlled or cloud-based systems. In all cases, applicable data privacy and blinding procedure need to be maintained. As long as the

originals are archived per FDA regulations, certified copies do not need to be retained. Patient will need to consent to rSDV in the ICF.

**Topics not covered in the FDA guideline**

Contrarily to the EU guidelines described above, the FDA guidance does not provide any recommendation on the CT restart, the revocation of exception measures, the reimbursement of exceptional costs, the conduct of audits. In addition, a separate section on data protection is also not available, but it has been highlighted in the sections above that all measures need to be set-up in compliance with the applicable data protection requirements.

Other recommendations

In Q25, clarification on electronic signature has been provided, and a reference to 21 CFR part 11 for electronic records has been added. Whenever applicable, sponsors should FU with vendors of systems to certify part 11 compliance. If not possible alternative signatures need to be considered, including wet-ink, stylus or finger drawn signatures or witnessed. Additional FDA papers were issued to provide sponsors and investigators additional guidance:

**CT inspections (August 2020):** This temporary guidance addresses the conduct of inspections of facilities and sites involved in non-clinical, clinical and analytical studies during the pandemic [107]. In March, the FDA temporarily postponed their domestic and foreign inspection programs. This changed in July when the FDA announced a restart of the inspection operations following a risk-based strategy like in the EU. This follows the prioritization of urgent "*mission-critical*" inspections. The agency highlights that sponsors need to ensure that relevant COVID-19 information is submitted in time to identify these inspections. In this context, the FDA implemented alternative tools and approaches, including a review of available documentation from previous inspections or trusted partners such as the US custom and border control for IMP import documentation to the maximum extent. Contrarily to the EMA guidance on inspections during the pandemic, the FDA guideline does not recommend any remote inspection activities.

**Statistical considerations (June 2020):** The statistical guidance provides strategies to reduce the COVID-19 impact on the statistical power of ongoing CTs. It reminds the industry to proactively consider appropriate mitigations measures that allow a conduct and also minimize data bias, especially for primary and secondary endpoints. It has been highlighted that consultation with the FDA and the filing of updated analysis plans are expected before the database locks to balance the overall pandemic impact and ascertain sufficient data collection for a sufficient statistical analysis and interpretable findings in the study interim and end reports. In this context, the FDA expects sponsors to carefully evaluate the statistical power by the performance of sensitivity analyses.

## VII. SUMMARY AND COMPARISON OF THE RECOMMENDATION GIVEN FOR COVID-19 MITIGATION STRATEGIES FOR CLINICAL TRIALS

In general, the COVID-19 derogations issued by the agencies in Europe, the USA and Switzerland are aligned and include the following arrangements: (a) communication with authorities and, if applicable, switch from paper to electronic applications, (b) ongoing reevaluation of benefit-risk-profiles considering the risk associated with COVID-19, recommended mitigation measures and a consequent decision on further study conduct, (c) handling of high values of PDs and suspension of regulatory requirements, (d) practical solutions and recommendation on exceptional measures to maintain patient reconsent processes, to replace on-site visits by telemedicine, to ensure IMP delivery and to implement centralized and remote monitoring activities to reduce the risks and burden for participants and sites by simultaneously ensuring sponsor oversight and GCP compliance.

While the mitigation strategies recommended across the regions are generally similar, they differ in the level of details shared for the set-up and the legal requirements. This is mainly triggered by different acceptance levels of data protection aspects, local regulatory requirements, and the country's health care and clinical research standard. Remarkably, the implementation of alternative consent processes, IMP delivery and acceptance of rSDV strategies are affected as outlined below. For a summary and comparison of the measures accepted by country, please refer to table 7L-M.

***Alternative reconsenting procedures:***

Video or phone calls between investigators and patients for a joint remote review of revised ICFs followed by the patient's oral consent supplemented with an email confirmation are recommended in all investigated countries. The sites are asked to exchange ICFs either by email or mail prior to this reconsenting call. While most countries accept the exchange of hardcopies, the AIFA and FDA highlighted that exchange of paper documents is considered a source of COVID-19 infections. Thus, the electronic transfer is recommended instead. Contrarily, the German ECs mandatorily request the handover of paper ICFs for signatures during the reconsenting call for documentation purposes.

The main difference between the recommendation refers to the documentation strategies of the remotely given reconsent. While no country-specifics are shared by the Austrian, Dutch and French guidance, the country guidance for the USA, Italy and Spain recommends the presence of an impartial witness during the reconsenting conversation, who will be asked to confirm the patient consent in writing by signing the ICF (mandatory for Italy) or on a blank document (USA). Following the FDA, alternative strategies for the documentation of the remotely given consent are accepted by the Italian and Spanish authorities and include: (a) photograph of the patient signature, (b) recording of oral consents (c) exchange of scanned ICFs via electronic means including email, online systems and/or smartphones. A more strict procedure is mandatory in Germany since the ECs expecting the

Table 07.L SUMMARY TABLE A - Overview of the recommended mitigation measures given by the EU harmonized COVID-19 guideline, the Joint swiss COVID-19 guideline, and the FDA COVID-19 conduct guideline (recommended, not accepted, not specifically addressed)

| MITIGATION MEASURE | EU COVID-19 RECOMMENDATIONS | SWISS COVID-19 GUIDELINE | FDA COVID-19 CONDUCT GUIDELINE |
|---|---|---|---|
| **CONDUCT OF TRIALS** | | | |
| New trial initiation<br>New trial site initiation<br>Continuation of ongoing trial | Focus on COVID-19 and unmet medical needs<br>Based on risk and mitigation assessment including site-level assessment by investigator, to be added to protocols for new trials<br>Case by case decision on site and study level | Focus on COVID-19 and unmet medical needs<br>Based on risk evaluation | No limitation<br>Based on risk evaluation |
| Discontinuation/slowing of enrollment | Based on risk and mitigation strategy assessment including site-level assessment by investigator<br>Case by case decision on site and study level<br>Elongation of study timelines might be needed<br>USM/ sub. AM to EC/CA | Based on risk and mitigation strategy assessment<br>No notification needed | Based on risk evaluation including interference with public health measures for COVID-19 control, consultation with IRB expected, halt of treatment require safety follow-up |
| Discontinuation of treatment | | Based on risk and mitigation strategy assessment<br>Notification to EC/CA within 15 days | |
| **SAFETY REPORTING** | | | |
| Safety reporting | Remains unchanged – AE FU via telemedicine | Remains unchanged – AE FU via telemedicine | Remains unchanged |
| COVID-19 reporting within CT legislation | | Only if classified as SUSAR (CA, EC) or SAE (EC) | Additional COVID-19 safety testing expected, if data are used by sponsor, these need to be added to the protocol |
| **CONSENT PROCESS** | | | |
| ICF to be shared upfront | Mail, email, or fax | | investigator signed ICF recommended to be shared via email or facsimile |
| Remote reconsent conversation | Phone and video calls followed by email confirmation from patient | Phone and video calls | eConsent preferred, phone and video calls<br>Documentation of:<br>- List of participants<br>- Identification of participants<br>- Confirmation that patient signed ICF |
| Specific strategy for reconsent of infected patients in isolation | Only informationfor COVID trials shared | Only information for COVID trials shared | eConsent preferred, alternatively remote consent in presence of witness, oral confirmation of patient that ICF has been signed, documentation of consent via photograph or witness confirmation or recording |
| Oral reconsent | Oral reconsent by patient given during video and phone call | Oral reconsent by patient given during video and phone call | Oral confirmation that patient has signed ICF, alternatively blank document with reference to protocol title and number can be signed and dated by patient |
| eSignature | If accepted by EU member state | | In line with 21 CFR part 11 |
| eConsent | eConsent currently not acceptable in EU | eConsent currently not acceptable in Switzerland | preferred: FDA APP free of charge |

| Mitigation measure | EU COVID-19 recommendations | Swiss COVID-19 guideline | FDA COVID-19 conduct guideline |
|---|---|---|---|
| Documentation of remote reconsent | Orally given reconsent to be documented by investigator in source data/patient record | Orally given reconsent to be documented by investigator in source data/patient record; use of ICF addendum created by the Swissethics recommended | To be documented in patient record and ISF<br>Description of alternative process<br>confirmation of patient consent:<br>- recording of the conversation<br>- justification why patient signed consent cannot be obtained<br>- photograph of patient signature including informationhow this picture was shared OR<br>- written investigator and witness confirmation of oral consent OR<br>- written consent by LAR<br>- scan of signed consent shared with site via email or shared drives<br>- originally signed consent handed over to site by mail<br>- filing of originals or certified copies |
| Reconfirmation of remote reconsent | ICF signature as part of standard reconsent procedure during next on-site visit | ICF signature as part of standard reconsent procedure during next on-site visit | No additional reconfirmation needed |
| Also applicable for initial consent | Mitigation measures only for COVID trials | Mitigation measures only for COVID trials | |
| (Regulatory) requirement | USM or EC approval required for updated consent process | EC approval expected for updated ICFs, delayed submissions will be accepted | IRB/IEC approval of the consent procedure as outlined in protocol. |
| MEDICAL OVERSIGHT | | | |
| Phone and video visits/telemedicine | Replacement for on-site visits based on risk assessment | To be documented in SDs<br>Patient consent by using ICF addendum required (EC approval required)<br>Change of visit conduct to be notified to EC | Safety follow-up: Notification of USM, single cases to be documented as PD<br>Sub. AM for protocol AM for other assessments based on risk and mitigation strategy evaluation<br>Change of on-site COAs to remote COAs, e.g. interviews, patient or observer reported, based on risk assessment incl. bias for study endpoints |
| Transfer to other sites | New site as USM plus sub. AM possible<br>Transfer of all applicable data/records<br>Access to CRF | EC notification required<br>Only in exceptional cases to ensure patient safety | |
| Involvement of other healthcare institutions | For critical lab tests, imaging or diagnostic tests<br>Focus on patient safety and data integrity<br>Local analysis for safety purpose<br>Analysis for endpoint preferred by central lab, if not possible to be done locally and explained and assessed in CSR, sponsor to be provided with all required documentation including normal ranges | For critical lab tests, imaging or diagnostic tests<br>Family doctor, officially healthcare institution authorized and certified for these assessments in routine care<br>Local analysis for safety purpose<br>Analysis for endpoint preferred by central lab, if not possible to be done locally and explained and assessed in CSR | Infusion centers, local laboratory or imaging facilities<br>If safety or primary and secondary endpoints affected, consultation with FDA required<br>Data bias to be minimized: standard procedures, variation tests |

| Mitigation measure | EU COVID-19 recommendations | Swiss COVID-19 guideline | FDA COVID-19 conduct guideline |
|---|---|---|---|
| Homecare treatment | | By trained study team<br>PI decision<br>To be documented in patient record<br>Patient consent by using ICF addendum (EC approval required) | Qualified and trained HCP if experienced with drugs of same class<br>HCP to be added in site record including delegation log<br>If protocol AM needed to involve HCP: IRB sub. AM approval required |
| Homecare assessment | | | Qualified and trained HCP if experienced with requested assessment<br>If results will have impact on clinical data, HCP to be added to FDA1572 form |
| IMP DELIVERY | | | |
| Handover higher amount of IMP | | | |
| Drugs for infusions/injection | Drugs with suitable use at home by patient | Drugs with suitable use at home by patient | FDA advice highly recommended; based on risk assessment |
| Delivery by site | | Only trial site mentioned | To be added to protocol if not already present (site delivery is possible in US also under non-COVID-19) |
| Delivery by site pharmacy | | | |
| Direct delivery by sponsor/vendor/warehouse | In exceptional cases to be done by contracted vendor on behalf of sponsor, contract need to list involved sites, IMP handling instructions, data protection requirements: deletion of patient data ASAP, action required to maintain blinding | Due to data protection and blinding | |
| Delivery to other person than patient | Delivery to patient/LAR | Delivery to patient/LAR | To local health care provider for home infusions or infusion in alternative infusion centers |
| Other recommendations | Transfer between two trial sites as last option to avoid drug shortage at site<br>Increase of IMP stocks<br>Also applicable for non-IMP drugs and other urgently required devices | | Local sourcing of already FDA approved drugs for out of label usage |
| Documentation | Training materials to be provided by sponsor<br>Written information on process, dose regimen, and site contact details to be shared with patient<br>Tracking of delivery<br>AoR by patient to be shared with site<br>Documentation to be filed in ISF/TMF<br>Drug Accountability: patient returns unused drug and containers to site at next visit | Training materials to be provided by sponsor for transport, storage, and usage<br>AoR by patient to be shared with site | |
| (Regulatory) requirement | PI decision since PI remains finally responsible for drug accountability<br>Involvement of QP for IMP redistribution<br>Sponsor responsible for cost reimbursement and logistical assistance<br>Oral consent by patient required | Change of IMP delivery to be notified to CA/EC<br>ICF addendum to be signed by patient (sub. AM required for ICF addendum) | PI decision since PI remains finally responsible for drug accountability<br>No information on patient consent<br>Strategy in line with protocol (home delivery in general possible in USA), sub. AM if update required can be part of cumulative AM |

| Mitigation measure | EU COVID-19 recommendations | Swiss COVID-19 guideline | FDA COVID-19 conduct guideline |
|---|---|---|---|
| REMOTE MONITORING | | | |
| Reduction/Postponement of on-site visits | Risk-based-approach and assessment of possible mitigation strategies<br>On-site monitoring visit require approval by site | Based on risk and mitigation strategy assessment | Risk-based approach to conduct |
| Phone/video monitoring visits | To be used to replace on-site visits for follow up on: study progress, issue resolution, review of procedures, status of patient, site selection, and training purpose<br>Alternatively, status report via email or other online systems | Focus on patient safety topics | Focus on critical site and SDs relevant for safety and data integrity<br>To be used to replace on-site visits for review of study procedures, patient status, study progress<br>Delayed identification of GCP non-compliance – therefore documentation of missed monitoring activities required, including justification to be accessible by sponsors/inspectors<br>Frequency as close as possible to initially planned |
| Central monitoring | To be used to replace on-site visits | Focus on patient safety topics | To support identification of urgently required remote monitoring visits |
| Remote SDV | Only in exceptional cases: COVID trials and final data cleaning steps before database lock for pivotal trials investigating serious or life-threatening conditions with unmet medical needs<br>Risk assessment justifying urgent rSDV<br>Focus on primary efficacy and safety data, secondary efficacy data if covered by same SDs | Not allowed | In line with monitoring plan, ICF, SOPs, and other sponsor policies and procedures. If not in place, to be created |
| Specific instructions for rSDV process set-up | Access only within EEA/EU<br>Site and monitor training required<br>Secure access to be guaranteed to ensure that data are only shared between site and monitor<br>Monitor need to provide written CDA to confirm destruction of any hardcopy or electronic copy | Not allowed | Remote monitoring activities should be documented in the same detail as on-site and finding to be followed-up and documented per monitoring plans |
| Remote SDV: sharing of copies | Sharing of redacted documents<br>Written request by monitor t listing required SDs<br>Site to redact copies, addition of patient number<br>Second review of successful redaction at site<br>Copied of redacted SDV and communication with monitor to be filed in ISF<br>Secure exchange with monitor<br>Monitor to confirm local copy destruction to site | Not allowed during first wave [A] | Sharing of certified copies in sponsor controlled or cloud-based respiratory<br>Blinding to be maintained<br>Certified copies do not need to be maintained as long as sites keep originals |
| Remote SDV: direct access to eRecords | Limited access of monitors to applicable data only<br>Read-only access | Not allowed during first wave [A] | If enough site resource available<br>Access to site and patient records in secure remote viewing portal |

| Mitigation measure | EU COVID-19 recommendations | Swiss COVID-19 guideline | FDA COVID-19 conduct guideline |
|---|---|---|---|
| Remote SDV: video access to records | Over the shoulder review – SDs shared via video from site to monitor<br>Ensure quality of secure video streaming<br>No involvement of servers in third countries<br>Since time-consuming for site, restricted to critical SDs | Not allowed during first wave [A] | |
| Follow-up actions | Increase amount of on-site monitoring after emergency situation has been normalized<br>Reconfirmation of remote SDV activities on the original source data | Not allowed during first wave [A] | |
| (Regulatory) requirement | Update of monitoring plan for frequency, strategy, follow-up actions, list of SD for rSDV,<br>Information to be added in monitoring reports<br>Decision with PI in agreement with site's DPO<br>Approval as sub. AM needed<br>Patient consent required | Update of monitoring plan to be notified to EC; delayed submission accepted | Update of monitoring plan, SOPs, or other procedures required |

[A] updated in V3 issued begin of November but not included here due to focus of this thesis on COVID-19 recommendations during the first EU wave of the pandemic

Table 07.M SUMMARY TABLE B - Overview of the recommended mitigation measures given by the country-specific COVID-19 guidelines for Italy, Spain, Germany (recommended, not accepted, no country-specific informationaddressed in guideline, *but accepted following EMA guideline*)

| Mitigation measure | ITALY | SPAIN | GERMANY |
|---|---|---|---|
| CONDUCT OF TRIALS | | | |
| New trial initiation | *In line with EMA guideline* | *EMA guideline to be followed* | *EMA guideline to be followed* |
| New trial site initiation | | | |
| Continuation of ongoing trial | | *In line with EMA guideline* | |
| Discontinuation/slowing of enrollment | *In line with EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Halt of recruitment and treatment to be submitted to ECs, also for non-initiated sites. | *EMA guideline to be followed* | *In line with EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Notification to EC/CA |
| Discontinuation of treatment | | *In line with EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Especially for immunosuppressant treatments<br>Alternative treatment to be provided by sponsor if drug shortage is reason for discontinuation<br>CA/EC notification within 15 days | |
| SAFETY REPORTING | | | |
| Safety reporting | *EMA guideline to be followed* | *EMA guideline to be followed* | *In line with EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Changes to be submitted as sub. AM |
| COVID-19 reporting within CT legislation | *No country-specific information provided* | *No country-specific information provided* | *No country-specific information provided* |

| Mitigation measure | ITALY | SPAIN | GERMANY |
|---|---|---|---|
| CONSENT PROCESS | | | |
| ICF to be shared upfront | **COUNTRY-SPECIFIC INFO:**<br>Exchange by email or electronic systems only | *In line with EMA guideline:* email or courier | *In line with EMA guideline:* email or courier |
| Remote reconsent conversation | *In line with EMA guideline:* Phone and video | *In line with EMA guideline:* Phone and video | *In line with EMA guideline:* Phone and video |
| Specific strategy for reconsent of infected patients in isolation | **COUNTRY-SPECIFIC INFO:**<br>Phone and video calls<br>Confirmation of consent via camera/photo through transparent isolation barriers | *Only information for COVID trials provided* | *Only information for COVID trials provided* |
| Oral reconsent | **COUNTRY-SPECIFIC INFO:**<br>In presence of a witness, selection of witness to be documented | **COUNTRY-SPECIFIC INFO:**<br>In presence of a witness | *In line with EMA guideline* |
| Documentation of remote reconsent | *Generally following EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Recording of audio/audiovisual means<br>Digital images of signature<br>Email confirmations<br>Witness needs to sign ICF instead of patient | *Generally following EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Recording of audio/audiovisual means<br>Digital images of signature<br>Scan or photo of signed ICF<br>Originally signed ICF sent back to site by mail<br>Image files need to be filed in ISF | *Generally following EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Hardcopy ICFs to be shared for signature<br>Signed ICF to be shared with site during next on-site visit or mail ASAP |
| eSignature | Explicitly mentioned as interim solution, handwritten reconsent needed | | Not allowed |
| eConsent | Applicable electronic systems are explicitly mentioned as interim solution, handwritten reconsent needed | | Not allowed |
| Reconfirmation of remote reconsent | *In line with EMA guideline* | *In line with EMA guideline* | *In line with EMA* |
| Also applicable for initial consent | | Only information on reconsent provided | Only applicable for reconsent |
| (Regulatory) requirement | *In line with EMA guideline: EC approval required for sub. AM or USM*<br>**COUNTRY-SPECIFIC INFO:**<br>DPO's of all applicable data controller need to approve the process, especially for critical personal data e.g. voice recordings | **COUNTRY-SPECIFIC INFO:**<br>Exceptional measures to be documented in TMF<br>No sub. AM or USM, instead COVID-19 summary 4 months after the end of the COVID-19 first wave health care crises (21Oct2020 ) | *In line with EMA guideline: EC approval required for sub. AM or USM* |
| MEDICAL OVERSIGHT | | | |
| Phone and video visits/telemedicine | *In line with EMA guideline* | *In line with EMA guideline* | *In line with EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Change of type and frequency need submission as USM or sub. AM along with justification and risk assessment |

| Mitigation measure | ITALY | SPAIN | GERMANY |
|---|---|---|---|
| Transfer to other sites | *In line with EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Only transfer to the closest initiated site for study<br>Transfer of PI responsibility if complete transfer<br>Partial transfer for specific assessment also possible, in this case PI keeps responsibility<br>Update of contract needed in case of transfer | *In line with EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Patient transfer agreement to be signed by both sites; transfer to be documented in both ISFs and in TMF, original site to share a transfer summary report with new site; new sites need approval as sub. AM<br>No sub. AM or USM, instead COVID-19 summary 4 months after the end of the COVID-19 first wave health care crises (21Oct2020 ) | *EMA guideline to be followed* |
| Involvement of other healthcare institutions | **COUNTRY-SPECIFIC INFO:**<br>Only for routine care assessments<br>Public institutions preferred, private if registered for clinical trials in Italy, last option non-certified<br>Safety relevant focus<br>GDPR compliant set-up (external institution either act on behalf of site as data controller as confirmed by a contract or need to be considered as independent data controller) | *In line with EMA guideline:*<br>**COUNTRY-SPECIFIC INFO:**<br>No sub. AM or USM, instead COVID-19 summary 4 months after the end of the COVID-19 first wave health care crises (21Oct2020 ) | *In line with EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Delegation log required<br>Supervision of PI<br>CA/EC sub. AM approval required |
| Homecare treatment | **COUNTRY-SPECIFIC INFO:**<br>Either by site staff or third vendor contracted by sponsor but under supervision of PI<br>Efficient communication routes to be established<br>Delegation log or delegation cover by contract<br>Training of external staff to be guaranteed<br>Set-up in line with data protection requirements for the designation of data controller: contract or other legal act in line with Art. 28 GDPR<br>Insurance needs to cover home care assessment and treatments: Sponsor to confirm | | **COUNTRY-SPECIFIC INFO:**<br>Delegation log required<br>Supervision of PI<br>CA/EC sub. AM approval required |
| Homecare assessment | | | **COUNTRY-SPECIFIC INFO:**<br>Delegation log required<br>Supervision of PI<br>Might need approval as separate site depending on the delegated activities |
| IMP DELIVERY | | | |
| Handover higher amount of IMP | *In line with EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Expiration date to be checked by PI<br>Amount of IMP shared is decision of PI | *In line with EMA guideline* | *EMA guideline to be followed* |
| Drugs for infusions/injection | No limitation for self-administered drug in local guidance, but home care treatment allowed | | *EMA guideline to be followed* |
| Delivery by site | Not allowed – pharmacy to be involved | Not allowed – pharmacy to be involved | *EMA guideline to be followed* |
| Delivery by site pharmacy | *In line with EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Under supervision of PI and pharmacy | *In line with EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Under supervision of PI and pharmacy | *EMA guideline to be followed* |

| Mitigation measure | ITALY | SPAIN | GERMANY |
|---|---|---|---|
| Direct delivery by sponsor/vendor/warehouse | COUNTRY-SPECIFIC INFO:<br>By warehouse or dedicated courier in line with GDPR requirements (delegate of data controller or designation of data controller)<br>Aim: reduction of additional travel and passage as source of COVID-19 spread | *In line with EMA guideline: in exceptional cases* | *EMA guideline to be followed* |
| Delivery to other person than patient | COUNTRY-SPECIFIC INFO:<br>Delivery to family member, caregiver, or other person delegated in writing | COUNTRY-SPECIFIC INFO:<br>Handover by pharmacy to representative authorized by the patient | *EMA guideline to be followed* |
| Other recommendations | COUNTRY-SPECIFIC INFO:<br>Drug accountability, which can not be postponed and usually performed by CRA, can be conducted by site or pharmacy staff<br>Storage of unused medications by pharmacy who can resent IMP to sponsor/CRO | *EMA guideline to be followed* | *EMA guideline to be followed* |
| Documentation | COUNTRY-SPECIFIC INFO:<br>Documentation to be filed in ISF only<br>Recording/filing of all communication | | *EMA guideline to be followed* |
| (Regulatory) requirement | *In line with EMA guideline*<br>COUNTRY-SPECIFIC INFO:<br>EC approval of sub. AM for immediate implementation needed | *In line with EMA guideline*<br>COUNTRY-SPECIFIC INFO:<br>Reference to national law: §4 of SND/293/2020<br>No USM/ separate sub. AM required<br>Instead, summary report submission as report on trial progress as sub. AM for all exceptional measure 4 months after end of COVID-19 health care crises (21Oct2020 for first wave) | *In line with EMA guideline*<br>COUNTRY-SPECIFIC INFO:<br>GDPR conform consent required, no update of ICF mandatory |
| REMOTE MONITORING | | | |
| Reduction/Postponement of on-site visits | *In line with EMA guideline* | *In line with EMA guideline*<br>COUNTRY-SPECIFIC INFO:<br>Update of monitoring plan for 4 months (during first wave/national lockdown as starting point) | *In line with EMA guideline*<br>COUNTRY-SPECIFIC INFO:<br>Update of monitoring plan does not require approval by EC/CA |
| Phone/video monitoring visits | *In line with EMA guideline* | *In line with EMA guideline* | *In line with EMA guideline* |
| Central monitoring | *In line with EMA guideline* | *In line with EMA guideline* | *In line with EMA guideline:* |
| Remote SDV | COUNTRY-SPECIFIC INFO:<br>Limitation of EMA for exceptional cases not present<br>Agreement of all stakeholders incl. site's DPO<br>Limitations mentioned in EMA guideline not listed in Italian guideline | *In line with EMA guideline (exceptional cases)* | *In line with EMA guideline (exceptional cases)* |

| Mitigation measure | ITALY | SPAIN | GERMANY |
|---|---|---|---|
| Specific instructions for rSDV process set-up | *EMA guideline to be followed* | *EMA guideline to be followed* | *In line with EMA guideline* |
| Remote SDV: sharing of copies | Not accepted since additional workload for sites | | *In line with EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Definition of minimum quality criteria of scans<br>Measure to ensure completeness<br>Corrective actions in case of data breaches<br>Tracking of exchange |
| Remote SDV: direct access to eRecords | *In line with EMA guideline* | | *In line with EMA guideline*<br>Name and version of software<br>Encryption used<br>Written confirmation by sponsor that set-up is in line with consent given by patient and limited access granted to monitor only |
| Remote SDV: video access to records | Not accepted since additional workload for sites | | *In line with EMA guideline*<br>Name and version of software<br>Involved parties<br>Sponsor and monitor written confirmation that data are not stored, temporary data delete, process is in line with patient consent, |
| Follow-up actions | *In line with EMA guideline: increased on-site visits* | | *In line with EMA guideline: increased on-site visits* |
| (Regulatory) requirement | **COUNTRY-SPECIFIC INFO:**<br>Sub. AM approval by EC required for updates to monitoring frequency and procedures | **COUNTRY-SPECIFIC INFO:**<br>No explicit patient consent required since considered as legally regulated necessary action, and patient agreed before to access of monitor to health care records<br>No approval of CA/EC as sub. AM required<br>Instead, updated monitoring plan to be filed along with PIs and site's DPO agreement in ISF and available for CA on request<br>Update of monitoring plan for 4 months during the first/wave national lockdown | **COUNTRY-SPECIFIC INFO:**<br>GDPR conform consent required, no update of ICF mandatory for rSDV and remote monitoring<br>Implementation of rSDV requires EC/CA approval as sub. AM<br>rSDV procedures to be added to the sites data protection register with start and end date<br>Process to be approved by DPO and might require approval by local DPA<br>Detailed information to be shared for amendment submission e.g. used systems, encryptions |

Table 07.N SUMMARY TABLE C- Overview of the recommended mitigation measures given by the country-specific COVID-19 guidelines for France, the Netherlands, Austria (recommended, not accepted, no country-specific information addressed in guideline, *but accepted following EMA guideline*)

| Mitigation measure | FRANCE | THE NETHERLANDS | AUSTRIA |
|---|---|---|---|
| CONDUCT OF TRIALS | | | |
| New trial initiation | *In line with EMA guidance* | *In line with EMA guidance* | *EMA guideline to be followed* |
| New trial site initiation | | | |
| Continuation of ongoing trial | | | |

| Mitigation measure | FRANCE | THE NETHERLANDS | AUSTRIA |
|---|---|---|---|
| Discontinuation/slowing of enrollment | *In line with EMA guidance*<br>**COUNTRY-SPECIFIC INFO:**<br>Notification to EC/ANSM | *In line with EMA guidance*<br>**COUNTRY-SPECIFIC INFO:**<br>Due to safety: direct notification to EC<br>Due to other reason: within 15 days | *EMA guideline to be followed* |
| Discontinuation of treatment | *In line with EMA guidance*<br>**COUNTRY-SPECIFIC INFO:**<br>Justification required, USM, and sub. AM after 15 days of implementation to CA/EC | *In line with EMA guidance*<br>**COUNTRY-SPECIFIC INFO:**<br>Due to safety: direct notification to EC<br>Due to other reason: within 15 days | |
| SAFETY REPORTING | | | |
| Safety reporting | *Generally In line with EMA guidance:* safety reporting remains unchanged<br>**COUNTRY-SPECIFIC INFO:**<br>DSUR: deferral of handwritten signature, instead scanned signatures or email confirmation accepted, postponement of 2 months may be granted by CA on request by email.<br>Safety committees: postponement of regular meetings need risk-assessment, notification to CA and EC and informationincluding consequences need to be shared with all stakeholders, halt of recruitment might be considered | *EMA guideline to be followed* | *EMA guideline to be followed* |
| COVID-19 reporting within CT legislation | To be done in line with country standard testing, to be documented in patient records, to be reported as SUSAR or SAE reporting to CA | | |
| CONSENT PROCESS | | | |
| ICF to be shared upfront | *EMA guideline to be followed* | *EMA guideline to be followed* | *EMA guideline to be followed* |
| Remote reconsent conversation | *EMA guideline to be followed* | *EMA guideline to be followed* | *EMA guideline to be followed* |
| Specific strategy for reconsent of infected patients in isolation | | **COUNTRY-SPECIFIC INFO:**<br>Possibility of deferred reconsent under emergency situation following national memorandum after EC approval is possible | |
| Oral reconsent | *EMA guideline to be followed* | *EMA guideline to be followed* | *EMA guideline to be followed* |
| Documentation of remote reconsent | *EMA guideline to be followed* | *EMA guideline to be followed* | *EMA guideline to be followed* |
| eSignature | | | |
| eConsent | | | EMA guideline to be followed |
| Reconfirmation of remote reconsent | *EMA guideline to be followed* | *EMA guideline to be followed* | *EMA guideline to be followed* |
| Also applicable for initial consent | *EMA guideline to be followed* | **COUNTRY-SPECIFIC INFO:**<br>Possibility of deferred consent under emergency situation following national memorandum after EC approval is possible | EMA guideline to be followed |

| Mitigation measure | FRANCE | THE NETHERLANDS | AUSTRIA |
|---|---|---|---|
| (Regulatory) requirement | *EMA guideline to be followed* | *EMA guideline to be followed* | *EMA guideline to be followed* |
| MEDICAL OVERSIGHT | | | |
| Phone and video visits/telemedicine | *In line with EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>primary focus on safety follow-up | *In line with EMA guideline:*<br>**COUNTRY-SPECIFIC INFO:**<br>Considered as administrative change – no EC/CA submission needed | *EMA guideline to be followed* |
| Transfer to other sites | *In line with EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>No EC/CA submission needed, agreement of patient and both PIs required, if applicable: new sites of specific institutions can be opened based on notification instead of sub. AM | *EMA guideline to be followed* | *EMA guideline to be followed* |
| Involvement of other healthcare institutions | *EMA guideline to be followed* | *EMA guideline to be followed* | *EMA guideline to be followed* |
| Homecare treatment | **COUNTRY-SPECIFIC INFO:**<br>Delivery of IMP for parental administration in exceptional cases; CA sub. AM approval needed | | |
| Homecare assessment | No country information provided | No country information provided | No country information provided |
| IMP DELIVERY | | | |
| Handover higher amount of IMP | *In line with EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Notification to CA required including information for additional measure to FU drug accountability and patient safety, not allowed for narcotics | *EMA guideline to be followed* | *EMA guideline to be followed* |
| Drugs for infusions/injection | **COUNTRY-SPECIFIC INFO:**<br>IMP delivery for parental administration in exceptional cases based on CA sub. AM approval | *EMA guideline to be followed* | Only drugs applicable for self-administration |
| Delivery by site | *In line with EMA guideline* | Not allowed | *In line with EMA guideline* |
| Delivery by site pharmacy | *In line with EMA guideline* | *In line with EMA guideline* | *EMA guideline to be followed* |
| Direct delivery by sponsor/vendor/warehouse | *EMA guideline to be followed* | Not allowed | *In line with EMA guideline: in exceptional cases* |
| Delivery to other person than patient | Only trial subject mentioned | Only trial subject mentioned | Only trial subject mentioned |
| Other recommendations | *EMA guideline to be followed* | IMP to be shared by hospital/clinical trial pharmacy with public pharmacy if required<br>In case of drug shortage due to COVID-19 treatment with substance link to separate instruction by CCMO provided: | **COUNTRY-SPECIFIC INFO:**<br>Support of site team by sponsor-contracted vendor for IP delivery<br>Trained and qualified vendor staff<br>Delegation log |

| Mitigation measure | FRANCE | THE NETHERLANDS | AUSTRIA |
|---|---|---|---|
| Documentation | *EMA guideline to be followed* | *EMA guideline to be followed* | *In line with EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Tracking documentation to be filled only in ISF, only in exceptional cases eTMF filing of redacted documents expected e.g. for PDs |
| (Regulatory) requirement | *In line with EMA guidance*<br>**COUNTRY-SPECIFIC INFO:**<br>Packaging and labels to be provided by sponsors if requested by site<br>Simplification of process to releasing sites and pharmacies<br>Separate guidance available in French for data protection requirements to be followed<br>USM plus sub. AM to CA/EC specifying procedure, conditions, monitoring, and information shared with patient within 15 days, COVID-19 protocol addendum expected for temporary changes | *In line with EMA guidance*<br>**COUNTRY-SPECIFIC INFO:**<br>No submission to EC/CA since considered as administrative change, instead written documentation and filing thereof required<br>Oral patient consent should be confirmed by email and documented in patient record, retrospective reconfirmation in writing not needed | **COUNTRY-SPECIFIC INFO:**<br>Sub. AM require written confirmation of PI that delivery by site no longer possible even with involvement of external vendor staff at site |
| REMOTE MONITORING | | | |
| Reduction/Postponement of on-site visits | *Generally following the EMA guidance*<br>**COUNTRY-SPECIFIC INFO:**<br>Focus on safety data and primary endpoints<br>Missing visits not considered as reason for discontinuation or major protocol deviation but need to be reported in CSR<br>USM plus sub. AM for follow-up procedures within 15 days, COVID-19 protocol addendum for temporary changes | In line with EMA guidance | *In line with EMA guideline* |
| Phone/video monitoring visits | *In line with EMA guidance* | *EMA guideline to be followed* | *In line with EMA guideline* to replace on-site visits |
| Central monitoring | *In line with EMA guidance* | *EMA guideline to be followed* | *In line with EMA-guideline* |
| Remote SDV | Not allowed | *Limitation in line with EMA guideline* | *Limitation in line with EMA guideline* |
| Specific instructions for rSDV process set-up | Not allowed | **COUNTRY-SPECIFIC INFO:**<br>Reference to country DPA recommendation<br>Documentation of monitor names<br>Reading aloud SDs during calls is not allowed | *EMA guideline to be followed* |
| Remote SDV: sharing of copies | Not allowed | Not allowed | |

| Mitigation measure | FRANCE | THE NETHERLANDS | AUSTRIA |
|---|---|---|---|
| Remote SDV: direct access to eRecords | Not allowed | *Generally in line with EMA guideline:*<br>**COUNTRY-SPECIFIC INFO:**<br>Preferred to be accessed from CRO office and logged one-person space: to be documented by video or photograph<br>Using logged PC/laptops ensuring that only monitor can access: to be documented by screenshots<br>No recording allowed – functionality should be disabled<br>Reportable data protection breach for all accesses to SDs not critically needed | |
| Remote SDV: video access to records | Not allowed | *Generally in line with EMA guideline:*<br>**COUNTRY-SPECIFIC INFO:**<br>Preferred procedure | |
| Follow-up actions | *EMA guideline to be followed* | *In line with EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Gradual restart of monitoring activities need approval by site institution, to be conducted in line with institution and local governmental policies, restart of trial activities do not necessarily allow restart of all on-site monitoring activities, restart of on-site monitoring should also follow risk-based approach for prioritization | *In line with EMA guideline* |
| (Regulatory) requirement | **COUNTRY-SPECIFIC INFO:**<br>Justification required, USM, and sub. AM within 15 days, COVID-19 protocol addendum expected for temporary changes | **COUNTRY-SPECIFIC INFO:**<br>No submission to EC/CA since considered as administrative change, instead written documentation and filing thereof required<br>Updated patient ICF giving explicit consent to rSDV needed<br>Recommendation of DPA for privacy and video calls to be followed<br>Data protection breached to be reported to DPA e.g. in case SDs not critically needed are reviewed | *In line with EMA guideline*<br>**COUNTRY-SPECIFIC INFO:**<br>Sub. AM approval required before implementation |

AM = amendment, CA = Competent Authority, COA = Clinical outcome assessment, CSR = Clinical Study Report, DPA = data protection authority, DPO = date protection officer, EC = Ethic Committee, HCP = Health Care Provider, ICF = Informed Consent Form, IMP = Investigational Medicinal Product, IRB = Institutional Review Board, ISF = Investigator Site File, LAR = Legally Authorized Representative, PD = protocol deviation, PI = Principle investigator, QP = Qualified Person, rSDV = remote source data verification, SDs = source data documents, sub. = substantial, TMF = Trial Master File, USM = urgent safety measure

signed hardcopy to be shared with sites by mail or during the next study visits. While the above refers to the confirmation of the given patient signatures on printed ICFs, the FDA allows the signature on a blanc document by adding the protocol title and number on the document prior to the signature. Proper documentation and justification of the alternative processes are expected to be filed in the patient records. Besides the Spanish CA, other European authorities consider oral consent as an intermediate solution that needs reconfirmation by the standard process as soon as possible during on-site visits.

In difference to the FDA and Italian guidelines, no recommendations on reconsenting procedures for isolated COVID-19 infected participants are provided in the Swiss, EMA and the other local guidelines. The Dutch authorities added instead a reference to the national guidance for the deferral of (re)consent for emergency situations when patients' health condition do not allow the routine consent procedures, which might also be applicable for COVID infected patients.

Contrarily to other countries, the Swissethics published a COVID-19 ICF addendum that should be used to receive reconsent to COVID-19 mitigation measures listed in the Swiss guidance. Country-specific differences are also visible for the acceptance of alternative strategies for initial consents. While the FDA and Italian CA accepts EC approved consent procedure for both, the EMA and Swiss guidance expect alternative methods only for reconsent with the exceptions for COVID trials.

Differences are also evident in the acceptance of electronic signatures and eCONSENT procedures. While the FDA supports the conduct of eCONSENT by sponsoring an applicable APP, electronic consent is not possible in most EU countries. Out of the investigated EU guidelines, only the Italian authorities accept esignatures as an interim solution. Contrarily, German ECs considered esignature as non-acceptable since not legally binding in Germany.

***Alternative IMP delivery procedures:***

IMP delivery to the patient's home is recommended in all guidelines if sufficient control mechanisms are set-up to monitor drug stability, the chain of custody, the explicit patient consent for this process and appropriate training. Two procedures are possible (a) delivery by the local institution to the patient and (b) direct delivery of IMPs by sponsors via the involvement of warehouses or vendors. For the latter, following the ICH-GCP requirements, all guidelines highlight that the responsibility of drug accountability remains with the investigator. Therefore, supervision and agreement by the PIs need to be guaranteed in these set-ups.

While direct IMP delivery by sponsors is prohibited in Switzerland and the Netherlands, the process is accepted by the FDA, EMA and other European countries on a case to case decision. The Swiss and EMA guideline reference to IMPs suitable for safe drug self-administration at home. Instead, the FDA, French and Italian CAs also allow, in exceptional cases, delivery of infusions for treatment at home or

other healthcare institutions. The French guideline limits this to parental administered drugs only. A rigorous approach was established by the BASG requesting a written PI statement confirming that IMP delivery is no longer feasible at the site. Thus, direct IMP delivery by the sponsor is needed. In the USA, IMP delivery to the patient's home is possible also under Non-COVID times if outlined by protocol. If the approved IMP delivery process needs to be changed, study modification approval is required. Single case deviations will be accepted if documented as PDs. For trials investigating already approved drugs, local prescription and sourcing has been mentioned as measure by the FDA, even if this will result in off-label use. Neither of the European or Swiss guidelines comments on this, and therefore, this is considered not applicable.

Handover of a higher number of IMP during on-site visits is only mentioned in the European recommendations and not present in the Swiss and FDA guidance and should therefore be discussed with the applicable authorities before the implementation.

Differences are also seen for IMP distribution by local site institutions. Based on the national standard process, IMP delivery is either handled by trial site s(Switzerland), the site's pharmacy (Italy, Spain and The Netherlands) or can be performed by both (Germany, Austria, France and USA).

The IMP handover to patient representatives other than authorized caregivers has been outlined by the Italian and Spanish agency that will accept this based on a written delegation by the patient. No information in this context has been shared by the other countries, and the recommendations given reference to the trial subject only. Therefore it has been classified as not allowed.

***Remote monitoring and remote SDV (rSDV)***

All of the analyzed guidelines commonly recommend the reduction of on-site visits and the implementation of remote and centralized monitoring instead. Changes are considered to be added to the monitoring plan, or at least a COVID-19 addendum to the monitoring plan is expected. Information on the type of monitoring visit, the data already monitored, and a list of monitoring actions that could not be performed remotely must be documented, preferable in monitoring reports.

While the FDA encourages the usage of rSDV, the EMA limits these to exceptional cases. At the beginning of the pandemic, the acceptance of rSDV differed mainly across the EU countries. In the course of the pandemic, this section mainly changed, and national CAs started to accept rSDV in limited cases. Being not accepted in France and Switzerland during the first pandemic wave, most of the analyzed EU countries follow the general recommendation of the EMA. Only limited to COVID trials or pivotal trials investigating new therapies for conditions with unmet medical needs near the database lock for which delayed SDV might result in delayed marketing approvals.

The EMA guidance recommends three alternative routes: (a) remote access to electronic site systems, (b) in-time video-sharing and (c) exchange of redacted SD copies. The latter is not accepted in the Netherlands and Italy since it is considered critical in terms of data protection or will provide an additional burden for sites. For Italy, the same applies for in-time video-sharing by the site. In summary, rSDV can be implemented in Germany, Austria, the Netherlands, Italy and Spain.

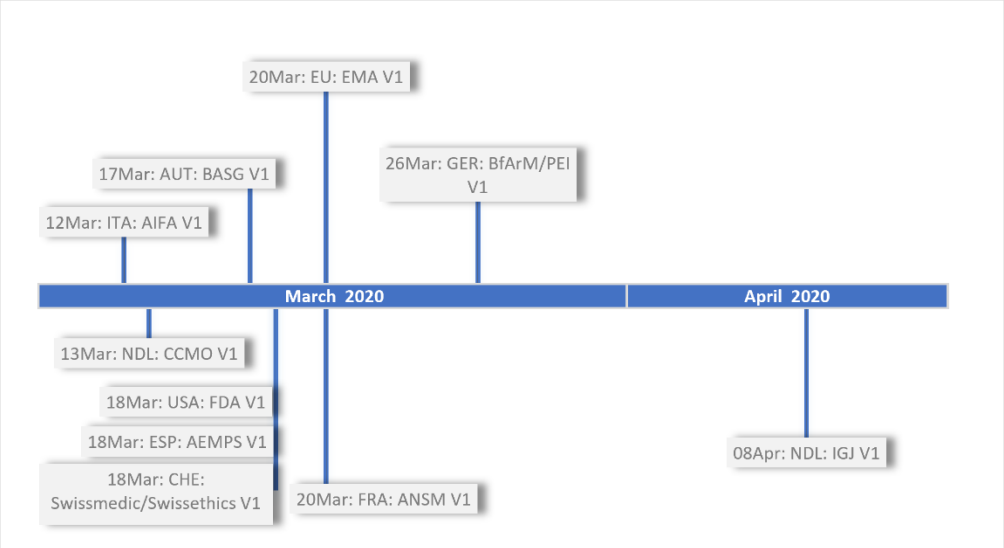
The national guidelines also differ in the regulatory requirements, the required documentation and the details that need to be shared by the authorities to receive approval for rSDV procedures. While the FDA requires documentation of delays or approval for the changes in the monitoring strategies, the majority of the EU countries require substantial amendment applications. They consider rSDV as critical in terms of data protection and consequently request explicit patient consent to this process. One exception is made by the Spanish authority, which neither needs EC/RA approval nor an explicit patient consent since rSDV is considered as legally authorized by its listing in the country COVID-19 recommendation.

# VIII. DISCUSSION

## A. COMPARATIVE ANALYSIS OF THE COVID-19 GUIDELINES FOR ONGOING CLINICAL TRIALS

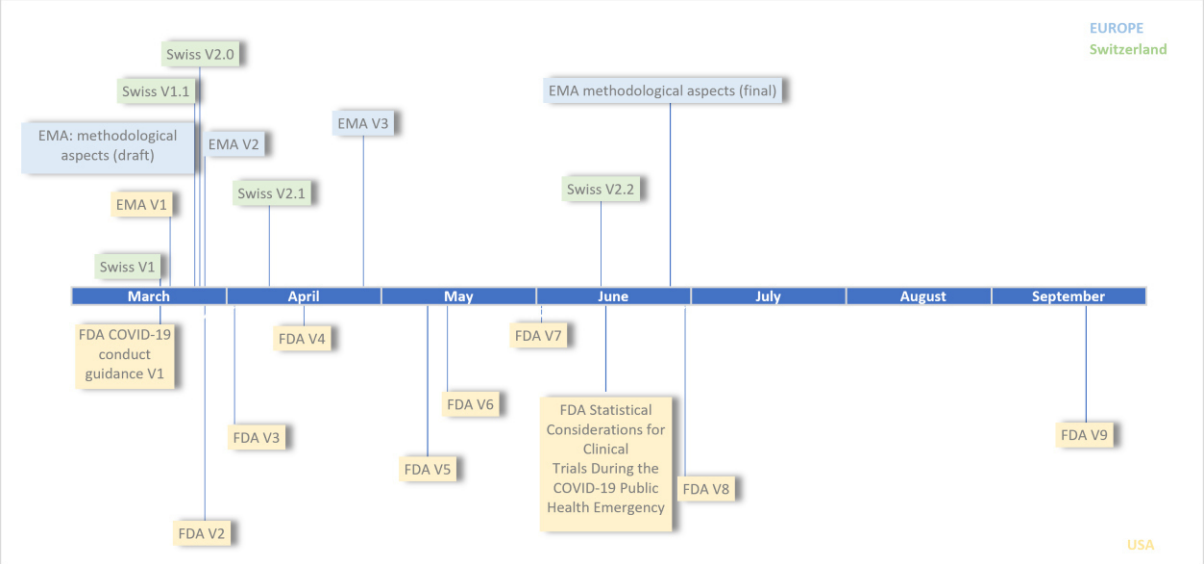
The COVID-19 recommendations published by the EMA, FDA, and the national guidelines issued in Austria, the TOP5 EU countries, and Switzerland were analyzed for country-specific discrepancies and their evolvement during the first six months of the pandemic. The authorities quickly reacted to this unique situation in publishing the first COVID-19 guidance within days after the WHO declaration of the pandemic. Following the European trend of harmonizing the CT regulatory network across the member states, a common set of exceptional measures for the conduct of ongoing CTs was released by the European Commission on behalf of the EMA and the HMA on 20 March (fig. 8.1).

Fig. 8.1 Release of the first versions of the COVID-19 recommendations in the USA, EU, and Switzerland



First national guidelines were published in Italy, the Netherlands, Austria, and Spain up to eight days before the release of the harmonized EU guidance. In contrast, the French and German recommendations were published as supplemental guidance afterward. In line with the date of the first releases, reference was made to the harmonized EU guideline or the release triggered an update of the local guidance. Due to the highly flexible situation, the COVID-19 recommendations published by the EMA, FDA and Swiss Authorities were updated several times. The majority of the revisions occurred end of March to June during the acute phase of the first pandemic wave and the lockdowns (fig. 8.2).

Fig. 8.2 Release of the revised COVID-19 recommendations in the USA, EU, and Switzerland




By comparing the different revisions per guideline, it became apparent that more details, especially for practical solutions for the daily trial conduct, were added or updated for clarification with each revision. The national guidelines were generally adapted after the release of new EMA revisions to also cover the updates and provide additional country-specifics. Information previously shared in national guidelines were introduced in a later revision of the EMA guideline. This fact demonstrates the authorities' intention to regularly adapt and evolve the COVID-19 recommendations with more detailed and latest instructions to guide sponsors and investigators through the highly flexible daily challenges and hurdles caused by COVID-19. In general, guidelines including a FAQ section, such as the French and FDA guidance, provided more detailed instructions. In this context, it needs to be considered that the current situation is unique in modern history, not only for sites, sponsors, and CROs but also for regulatory authorities and ECs.

Clinical research is controlled by a complex and robust regulatory network that has been continuously harmonized in several reforms in the last three decades, especially in the EU. The challenges associated with COVID-19, practically overnight, changed this situation by opening various regulatory bottlenecks. The difficulty is compounded by the dynamic of the pandemic, the high number of guideline

revisions and the different country-specific requirements for the implementation of the same mitigation measures, even across the European countries. This fact requires a regular review of the regulatory landscape at a higher frequency than under pre-COVID-19 conditions to ensure regulatory compliance and oversight. The majority of country guidelines do not include a summary of changes, nor are they issued in tracked change mode. The latter is of particular interest as the EMA explicitly recommends the exchange of documents with highlighted changes between sponsors and sites for a more effortless follow-up and faster implementation. In addition, in most cases previous guidance documents are replaced on the webpages by revised versions so that overdue versions were no longer available for comparison. Since the instructions shared by responsible authorities e.g. for rSDV mainly changed during the first months, this would be helpful for sponsors and CROs in particular for a retrospective analysis of the actions taken versus the recommendations given at this time.

The guidelines also differ in their general structures, the information provided, the level of details shared for the set-up of mitigation measures and the route of publication. As seen for the Netherlands, official guidelines and their revisions separately published by national CT authorities and committees involved, resulting in the situation that several regulatory documents even within the same country need to be compared. These facts make it very complicated for sponsors, CROs, and investigators to catch the differences between the national recommendations and the different revisions. Thus, CROs, pharma consultants, and clinical research networks and organizations have developed regular webinar sessions, COVID-19 regulatory summaries tables, and overviews or publicly available COVID-19 guidance repositories to support and guide sponsors in these regulatory highly flexible times. Unfortunately, in most cases, these databases and repositories also provide links that directly refer to the latest guidance on the CA/EC webpages. Consequently, already superseded guidelines are often no longer accessible in these databases as well.

As highlighted in the results part, the main differences between the guidelines are seen for the set-up of the reconsenting process, remote monitoring, rSDV and the IMP delivery. Another discrepancy across the guidelines of the different regions and also within the EU was identified for recommendations published on the revocation of the exceptional measures and the restart of standard clinical trial activities during the relaxing situation in the EU in summer 2020. Neither the FDA nor the EMA so far published detailed recommendations on this topic, whereas France, the Netherlands, and Spain updated their guidelines with instructions on the gradual restart of CTs in line with the relaxing burdens for the sites and the return to standard health care procedures in summer. One reason for this is that the COVID-19 crisis was and is still not solved, and the situation for the local sites is very diverse. As seen in the USA in July, further pandemic waves will additionally challenge the conduct of trials. Consequently, all of the temporary mitigation guidelines are still in place until further notice.

Although not part of the EU, the Swiss guideline follows the European recommendations in significant aspects. This fact follows the general trend of Swiss authorities to align national policies and laws for the development of clinical products and devices to the European legal framework to ensure the consistency of collected data in line with the bilateral relationship and mutual agreements of Switzerland and the EU [108,109,110]. In contrast to the Netherlands, a joint guideline of the responsible authority and committee, Swissmedic and Swissethics, were published to streamline the country recommendations.

Interestingly, details on the specific country set-up of mitigation measures shared by the Italian and Spanish CAs refer to recommendations issued by the FDA, which are not covered in the EMA guideline. These include, among others, the recommendation of strategies for the reconfirmation of remotely given patient consents. This discrepancy indicates that, besides the European Commission, EMA and HMA intended to streamline the COVID-19 recommendation across Europe, deviating instructions are provided on country-level. In this context, the German authorities strictly followed the harmonized process and issued only country-specifics recommendations. Contrarily, other EU authorities repeated recommendations already covered by the EMA, but different levels of details were shared.

The varying level of information on the planned set-up, the differences in the required documentation, and the diverse regulatory requirement for implementing the same extraordinary COVID-19 measure in the different countries also challenge sponsors and CRO in preparing CTA application dossiers. In this context, it was noted that although the majority of the guidelines were issued in English, critical national guidelines and laws, e.g. on data protection requirements, are only available in local languages. As a result, follow-up for pharmaceutical companies, particularly small entities, conducting CT in multiple countries is complicated and requires local input and expertise on a larger scale than usual, resulting in increased time efforts and costs.

While most of the EU countries analyzed follow the EMA guidance and require an individual or collective application per mitigation measure, the Spanish authorities request the submission of one single summary report per study for all COVID-19 measures implemented following the national guidance. This is an exciting approach as it relieves the burden on CAs and ECs and also on CROs and sponsors during the health crises. With the risk of trials being impacted by further waves and lockdowns in the coming months, an additional burden on national authorities is very likely, so that similar approaches should be considered in the other countries as well. This shows that although the CT regulatory and ethical framework has been substantially harmonized across Europe by several reforms, the current regulatory requirements for implementing COVID-19 measures appeared to vary across EU member states. This is of particular interest in view of the Clinical Trial Regulation 536/2014, which will come into force at the end of 2021. The current situation makes it clear that further harmonization is urgently needed. It can be speculated that an earlier release of the repeatedly postponed European

portal (Clinical Trials Information System, CTIS) would have positively impacted the harmonization of COVID-19 measures across the EU and would have at least streamlined the application process. For the latter it can be highlighted that in contrast to the other countries the German CAs recommended the usage of the HMA Common European Submission Portal (CESP) for CTs applications. This portal represents a secure method of communicating with the EU CAs via one platform to "*reduce the burden for both Industry and Regulators of submitting/handling applications on CD-ROM and DVD*" [111]. The CESP platform is already in use for submissions related to e.g. drug authorization and variations since 2013. While Germany accepts submission of clinical trial applications via the CESP already since 2019, none of the other investigated EU countries highlighted this system as alternative route for CA applications during the pandemic.

Taking all the above COVID-19 triggered challenges together, establishing a common structure for the national guidelines of European countries and a European database containing the supplementary guidelines of all EU states in clean and track-change versions would support the ongoing trend towards harmonization of the European CT regulatory network. A similar approach was taken to provide clarity and visibility for country-specific CTs requirements involving genetically modified organisms on the European Commission's homepage [112]. Besides, further harmonization of the currently diverse regulatory requirements and the general acceptance of mitigation measures such as rSDV and eCONSENT procedures is also needed. In this context, the generation of a pandemic preparedness guideline by the EMA or the ICH would allow sponsors, CROs, trial sites, ECs, and CAs to implement harmonized rules and strategies in their business continuity plans, protocols, and standard operating procedures concerning the risks of additional COVID-19 waves or the spread of pandemics in future.

## B. NEGATIVE IMPACT OF COVID-19 ON ONGOING AND FUTURE CLINICAL TRIALS

Following the international ICH standards, the priority of all issued COVID-19 recommendations remains first, patient safety and second, clinical data integrity [8,23]. Challenges raised by COVID-19 impact diverse processes and parties involved in clinical research. As a result, even well-established processes currently require continuous re-assessment and revision, both at the sponsor-, country-, and site-level. Especially in March to May, this caused additional work and required prioritization of essential tasks. With particular attention to the site situation, unanimous statements were added to guidelines to ensure that the measures taken should not provide additional workload to trial sites. Instead, the guideline urges sponsors and CROs to reduce the burden for the sites, whenever possible.

### (1) NEGATIVE IMPACT OF THE ONGOING CLINICAL TRIALS DURING THE PANDEMIC

The database search identified 14 713 ongoing trials within the EEA. Most of these are conducted in Spain, Germany, France, the Netherlands, and Italy, consequently determined as TOP5 EU countries for a detailed analysis of the COVID-19 guidance above. For the USA, a total of 13 903 trials and 24

853 investigational CTs worldwide were identified. Neither of these databases allows a retrospective search for the overall study status. Therefore, the results only include trials with an ongoing status on 02 July 2020, the database search's date. CTs that were terminated, completed, withdrawn, or suspended before this date are not included. Consequently, ongoing trials identified in these searches are considered trials with a favorable risk-benefit profile even under the risk associated with COVID-19. For these trials, specific COVID-19 measures were required to ensure that the CTs participants have (a) continued access to study medications and (b) are adequately monitored for their health conditions to ensure the safety of the study participants and the clinical data integrity. Because the registration of phase 1 trials and trials outside of the US is not mandatory, the number of investigational trials identified in the ClinicalTrials.gov database does not represent the exact number of affected sites. Still, it provides the best estimate based on publicly available CT registries.

The impact of COVID-19 on the health care system, including CTs, and the mitigation measures are temporary disruptions that are expected to be mainly minimized once an effective vaccination strategy will be in place. Although all authorities prefer the safe continuation of much-needed clinical research during the pandemic, for some trials, the suspension of study treatment or enrollment was the only option to ensure patient safety. In this context, the FDA and EMA guidance recommend a temporary halt or the slowing down of the study enrollment and study treatment for trials with a negative benefit-risk profile due to higher risk from the pandemic.

To quantify the pandemic's impact on the number of CTs stopped for COVID-19 reasons, the dataset published by Benjamin Carlisle was modified for additional investigation focusing on investigational drugs and biologics [33,35]. As of August 2020, 42% of the stopped trials identified by B. Carlisle were stopped due to COVID-19, with 84% of these being investigational trials. As expected, the vast majority of trials classified as stopped due to COVID-19 were temporarily suspended, with the most suspension occurring during the first hot phase of the pandemic in the EU and the US in April and May. The first study was suspended in Denmark on 16 March 2020, even before the first version of the EMA/FDA guidance was issued. This trend suggests that sponsors decided, in a first reaction, to temporarily halt ongoing CTs for a detailed evaluation of the risk-benefit profile and the set-up of robust and reliable procedures, mitigation measures and new concepts to allow a restart, if applicable, later on also during the continuous risk associated with the pandemic. Less than 10% of the studies stopped were terminated or withdrawn, the majority of these in June and July 2020 indicating that for these trials the reevaluation of the risk-benefit-profile and the impact on the trial seen by the pandemic in March to May has been considered as unfavorable and not sufficient to complete the trials under these challenging circumstances.

With respect to the indication category introduced by Carlisle, the majority of the trials stopped were cancer trials, which is in line with the general observation that the highest proportion (32%) of all trials conducted worldwide are cancer trials [113]. The database analysis indicated a higher impact of COVID-19 on ongoing clinical trials funded by non-commercial sponsors, represented mainly by universities and organizations, such as non-profit research organizations. The same trends were described in publications issued by the charity cancer organization in the United Kingdom in April 2020. The organization announced that the funding for clinical research would have to be cut by more than 50 million Euros based on the COVID-19 pandemic [114.] The main reason for this is a massive drop in donations caused by the cancellation of fundraising events. This is also prompted by a shift in focus on COVID-19 treatment and vaccination. Charlie Swanton, the organization's chief clinician in the UK, estimates that "*we may have lost five years in the worst-case scenario*" since 90% of the non-commercial research has been paused in the UK. In contrast, approximately 50% of the commercially-funded research is still ongoing [114]. Non-commercially funded studies, including investigator-initiated trials (IITs), often investigate alternative treatment options, changed application schemes, or indication extensions of already approved drugs. Although supported by the pharma-industry, non-commercial sponsors such as investigators, hospitals, or universities might not have the full picture of the risks associate with the drugs, and consequently, the legally required benefit-risk re-assessments might be challenging also with a view on the limited personal and financial resources and the general impact of the pandemic on the health care sector. Consequently, a rapid adaptation of the management of IITs to allow ongoing conduct even under this highly flexible situation might not be sufficiently covered by these sponsors, and consequently, the trials are temporarily suspended.

In the database analysis performed, 68 commercial sponsors were identified to be affected by trial terminations and suspensions worldwide. The data analysis of the trials stopped by these sponsors indicated that 7 to 38 substances and 11 to 25 indications are affected, suggesting a broader impact on several development programs. Of the TOP5 pharmaceutical companies conducting trials worldwide, only Novartis was also identified based on the dataset analyzed as mainly impacted. In addition, Boehringer Ingelheim, Eli Lilly, UCB Pharma, and GSK appealed as TOP5 sponsors with the highest number of COVID-19 stopped trials. Consequently, the number of trials conducted in general, did not align with the number of trials stopped due to COVID-19. This can be explained by the fact that the authorities do not expect a general trial suspension, and each study needs to be individually assessed. In this context, all guidelines commonly expect the sponsors to be responsible for the final assessment of study continuation or suspension based on a risk-based approach.

Phase I trials aim to determine the risk potential of a new drug to confirm the pharmacokinetic and pharmacodynamic effects in the human body derived from the preclinical test results [20]. If not

targeting cytotoxic substances such as cancer treatments, phase 1 trials are conducted with healthy volunteers. Since healthy volunteers have no personal benefit, but drug treatment and on-site hospitalization in phase 1 units during the pandemic crises lead to higher risks, a less balanced benefit-risk profile is expected [115]. Only the Dutch guideline provides specific guidance on this topic and expects a general suspension of phase 1 trials except COVID-19 and trials covering diseases with an unmet medical need. Consistent with this, the database analysis performed in this thesis indicated a higher COVID-19 impact of the termination and suspension of trials in the early phase of clinical development.

By comparing the numbers of ongoing interventional trials to the number of trials stopped due to the pandemic, it becomes evident that a limited number of trials have been stopped (5.6%; ratio stopped to ongoing 1:17.8), indicating that the majority of trials are still ongoing. Contrarily, other publication and clinical research experts reported much higher numbers of suspended or terminated trials, impacting more than 50% of commercial and 90% of non-commercial studies [114]. Also, EvaluatePharma estimated in May 2020 a 15-fold increase in the number of suspended CTs in spring 2020 compared to 2019, indicating that COVID-19 triggered a higher number of trial suspensions [116]. The reason for this discrepancy might be (a) that the entry of the stopping reasons is not mandatory in the database and (b) delays in the reporting of changed overall study status due to COVID-19 prioritization. In addition, the suspension of individual trial sites is also not covered in the database.

The author B. Carlisle demonstrated an overall increase of the number of stopped studies in spring and summer 2020 in comparison to an non-COVID comparator arm [33,35]. This data analysis covers all studies registered in the ClinicalTrials.gov database and consequently also covers (non)-interventional studies with medical devices, dietary supplements and other investigations. Nevertheless, the general trend of a higher number of stopped trials is expected for clinical drug trials, indicating a destruction of the clinical research landscape by the pandemic.

The reduction in recruitment rate must also be considered for significant effects of COVID-19 on ongoing studies [35.] This could have an even more significant impact of COVID-19 on the clinical research landscape than the temporary suspension of studies. As highlighted in the COVID-19 guidelines investigated in this thesis, the ongoing risk assessment should cover estimated COVID-19 effects at study-, site- and where appropriate patient-level, particularly in light of the highly dynamic and diverse situation at local trial sites across the regions. Consequently, closer cooperation and more frequent communication between sponsors, CROs, and the sites are needed during these times to ensure that appropriate measures and actions are taken. For future inspections, a primary focus on the review of relevant communications is expected to verify that (1) sponsor/CRO/investigator oversight was maintained during the crises and (2) all involved parties managed the exigent circumstances in the best interest of patients and in accordance with the COVID-19 recommendations. This refers not only to

the study conduct during the pandemic but also to the clean-up of outstanding tasks, such as obtaining wet-ink signatures for reconfirmation of patient reconsent and additional in-situ monitoring visits, once the pandemic will be overcome [117]. In particular, ISF filing may require further investigations by sites and CRAs after the end of the health care crises since this is likely to be delayed and incomplete due to postponed on-site visits and staffing issues at the sites.

In a survey conducted from late March to early April 2020, the CRI (Cancer Research Institute) and CRO IQVIA, 60% of the interviewed investigators reported a moderate or high impact of COVID-19 on the conduct of patient visits at the onset of the pandemic [118,119]. A significant decrease in patient enrollment in oncology trials, particularly in the USA and Europe, was reported [120]. Only 20% (USA) and 14% (EU) of participating trial centers disclosed that patient recruitment was at the usual scale. In both regions, most sites were still recruiting patients, but to a lower extent than expected (60% in the USA and 86% in the EU). Patient safety and resourcing issues were cited as the most critical factors and reasons. In this context, the IMP type and route of IMP administration were mentioned as the most critical factors for the determination of whether or not patient recruitment would be sustained. The complexity of trial designs did not appear to be a crucial factor in this decision.

A similar trend was published by Medidata Solutions, one of the most important technology companies for software and devices for CTs [121]. The company posted an analysis of its real-time patient recruitment data collected during the first six months of the pandemic. This analysis confirmed a decline of more than 60% in patient recruitment worldwide compared to the data of 2019 in March and early April. Same values were identified for Italy, Spain, France, and the USA, while Germany was less affected (32%) at this time. A comparison of the enrollment rates per indication showed that cancer studies were less affected than studies investigating cardiovascular, CNS, or endocrine diseases. The highest impact on enrollment rates was seen in April when patient recruitment numbers fell by an average of 75% at the global level. From late May to June, a trend toward increased patient recruitment was visible, resulting in a 30% global decline at the end of June [122]. The recovery trend remained with the data released for July, showing a global decrease of 6% of study enrollment compared to the pre-COVID data. European countries, including Germany, returned roughly to the pre-COVID numbers, while the USA remained at a 16% decline in patient recruitment due to higher infection rates, as in Europe [123]. At this time, enrollment rates per indication showed that all categories were still below the enrollment rates of the pre-COVID-19 baseline besides cancer trials. Contrarily, an increase of 20% was noted for cancer trials, which is consistent with the European authorities' expectations to focus on the continuation of trials to explore therapies for life-threatening diseases. This increase of enrollment in July is likely caused by the restart of suspended cancer trials as indicated in the database analysis above and the catch-up of the lower recruitment rates at the trial sites. Similar effects are

expected for the restart of the other Non-COVID trials at the end of the health care crises to catch back up the lost time. The preparedness and an accelerated restart will be crucial for sites, sponsors, and CROs. In this context, additional revisions of the Swiss, FDA, and EMA guidelines are expected, as updates of national guidelines were already seen in some European countries during the relaxing of the COVID-19 impact on Europe's health care systems in summer 2020.

Additional changes in the management of CTs are expected to re-adapt ongoing and suspended trials to the post-COVID conditions. This will include investigations for a gradual restart of trials and the implementation of catch-up actions to compensate missed data and activities, e.g. on-site SDV, inspections, audits, and patient assessments that could not entirely be conducted during the pandemic. This will also require updates and adaption of local policies, protocols, and study manuals triggering additional EC/CA applications and risk-assessments by the sponsors and sites. Required updates are expected to include (a) regular COVID-19 test for enrolled and new study participants, (b) a change in the eligibility criteria including a COVID-19 vaccination as mandatory screening assessment as seen for other infectious diseases such as hepatitis, meningococcal and pneumococcal vaccination, in particular for CTs enrolling immunosuppressed patients. Here, the availability of the COVID-19 vaccine might also be a critical factor for the restart of the trials in 2021.

#### (2) NEGATIVE IMPACT OF COVID-19 ON FUTURE/PLANNED CLINICAL TRIALS

Challenges posed by the spread of COVID-19 will also influence the planning and start of new CTs. As outlined by the European COVID-19 guideline, a primary focus on COVID trials and trials investigating unmet medical needs is expected for any new trial started during the pandemic. In this context, pharmaceutical companies reported delays in their clinical development programs, especially for new studies. As of 23 March 2020, Eli Lilly confirmed the postponement of new study starts caused by COVID-19 [124]. Similar information was published by the Bayer Healthcare company confirming that 10 out of 20 clinical trials were postponed in the first months of 2020 [131].

The set-up of protocols already in development and planning will be impacted here. Updates to the benefit-risk section and the re-evaluation of the study design by statisticians and medical monitors might be required. Based on the current situation, COVID-19 specific assessment and mitigation measures will need to be implemented. This will cause massive changes in protocols and study manuals. This could be more challenging than before, as country-specific protocol amendments or addendums may be required to cover all local COVID-19 requirements, not only for the start of new studies under COVID-19 but also for the gradual revocation of exceptional measure.

The postponement of site selections will also trigger further delays in the start-up phase. In this context, a survey conducted by Medidata in April 2020 showed that 78% of the investigators/study teams worldwide indicated that COVID-19 had impacted their ability to start new trials [121.] Delays could also

result from data required from previous studies that will not be available in time. On top of this, a shift in the focus of the company's clinical development program to COVID studies or studies with higher relevance could impact the continued conduct of non-COVID studies by, for example, diverting financial and human resources. The latter could also be exacerbated by an increased number of infected employees and the disruption of research teams through home office solutions and travel restrictions.

In addition, delays in the start-up phase might also be caused by longer review timelines for CT applications. In this context, all reviewed COVID-19 guidelines emphasized that national authorities and committees prioritize COVID-trials and amendments associated with pandemic mitigation strategies. In July, the Swissethics published an analysis on the impact of COVID-19 on the EC review processes in Switzerland from March to June 2020 [125]. Three significant challenges were identified (1) a drastic increase in clinical research applications, (2) an increased workload for ECs to support the COVID-19 challenged hospitals in finding quick and pragmatic solutions, and (3) restructuring of the EC working processes to comply with the COVID-19 contingency measures, such as the establishment of teleconferences to replace regular in-person meetings. In comparison to 2019, more than twice as many applications were submitted. In April and May, the majority of these were related to COVID-19 projects or COVID-19 triggered changes. Based on preliminary evaluations, the Swissethics confirmed that the Swiss ECs worked very quickly despite the higher workload and met the regular deadlines while maintaining the quality standard. Nevertheless, further analysis will be required to investigate long-term effects also in case of additional pandemic waves.

To quantify the impact of COVID-19 on the start of new trials, a database analysis was done by comparing the numbers of new interventional COVID-19, and Non-COVID trials started per month from beginning January to August 2020 with a pre-COVID arm (Jan 2018 – Dec 2019). Less non-COVID trials were registered in the database during the hot phase of the pandemic in March to May 2020, representing 56-73% of the average number of trials started in pre-COVID-19 times. At the same time, the highest numbers of newly-initiated COVID trials were registered. From June to August 2020, considered as less COVID-19 impacted period for Europe, the number of started non-COVID trials was higher in comparison to the average in pre-COVID times and even exceeded the maximum value identified under pre-COVID conditions. This indicates indeed a clear shift from Non-COVID to COVID trials at this time. In addition, this trend suggests that several sponsors decided, in a first reaction, to put the initiation of new trials on hold for a detailed evaluation of the risk-benefit profile and for the establishment of robust and reliable procedures, mitigation measures and hygiene concepts to allow a safe start of the trials in summer.

Keeping in mind that, unlike the EudraCT database, the trial registration in the US registry is not part of the initial application procedure, but instead should occur within 21 days of the first enrollment,

this shift might be triggered by a delay in (a) the start of the enrollment, (b) delayed registration and (c) the restart of previously suspended trials. For the latter, a database analysis based on the dataset from Carlisle was performed to examine the number of suspended trials that returned to active status until October 2020 since the author did not publish the data for the restart of trials until October 2020. Out of these, 62 % of the identified investigational drug trials that were suspended due to COVID-19 were restarted and mainly returned to active recruitment. This already shows an improvement of the situation during the relaxing of COVID-19 restrictions and lower infection numbers in summer 2020. In addition, it can be considered that the temporary halt of the these trials sponsors and sites was used to establish sufficient mitigation measures to ensure a proper restart of the trial even with the remaining challenging situations caused by the pandemic in the next months. Here again, a higher impact of COVID-19 on clinical investigations funded by non-commercial sponsors was visible. This might be triggered by the fact that commercial sponsors have the higher personal and financial power to evaluate and oversee challenging regulatory situations and, therefore, can quicker react and adapt the conduct and management of CTs to the changed conditions.

CTs are the most important, time- and cost-intensive step in the development of new drugs.[126, 21]. As discussed above, the COVID-19 pandemic will trigger delays for ongoing as well as future trials. Delays in the study preparation and start-up phase, delayed patient recruitment, reduced patient retention, and the disruption of the conduct of the trial compared to the initially planned study design and statistic evaluation resulting in a bias and lack of collected study data will trigger further delays in key study milestones such as database locks and the completion of the study end reports [16,14]. The slowing of successful completion of clinical development programs and the unexpected implementation of measures to minimize the pandemic impact will increase the study budget. As a consequence, urgently needed new therapeutics will be significantly delayed. Therefore, experts expect COVID-19 to decrease the number of marketing authorization for new drugs in the next years, which are likely to reach the drug market at higher prices [134,126.]

## C. POSITIVE EFFECT OF COVID-19 ON THE CLINICAL TRIAL LANDSCAPEs: LESSONS LEARNED AND THE IMPLEMENTATION OF INNOVATIVE TECHNOLOGIES

Besides the negative impacts of the pandemic outlined above, the experience gained with innovative technologies recommended as COVID-19 measures also have the potential to promote digitalization in clinical research. Several innovative technologies were developed but were often not accepted by CAs and ECs for CTs in the past.

One example of a step forward in the digitalization of clinical research triggered by COVID-19 is the broader acceptance of digital submissions of initial and amendment CT applications. In countries such

as Germany, Italy, and Switzerland, where hardcopy submission was still standard for at least parts of dossiers in pre-COVID-19 times, the submission pathways were quickly converted to electronic means.

Many of the COVID-19 mitigation strategies now recommended in the guidelines differ from the standard pre-pandemic processes, particularly in Europe. While rSDV was already accepted in the USA prior to the pandemic, this was not the case in many EU member states, including Germany [127]. The exceptional acceptance of this strategy under COVID-19 is an excellent example of how regulatory requirements can change based on the experiences gained under the challenging situations of the pandemic. In 2017, the German Central Office of the Federal States for Health Protection for pharmaceuticals and medical devices (ZLG) issued a guidance document for inspectors on this topic [128]. The ZLG classified rSDV as unacceptable for SDs containing personal patient data since redacted copies cannot be considered SDs as defined in the ICH-GCP guideline (section 1.52) [23.] In contrast, they are classified as already processed data. Thus, SDV is possible only on-site by monitoring the original data. In this context, the authors Sather and Lawyer commented that although the EMA and some national COVID guidance allow rSDV in exceptional cases, the requirement of an on-site reconfirmation on-site will lead to an enhanced on-site monitoring approach. Consequently, they consider that the general understanding and acceptance of rSDV based on the GDPR requirement will not change in the EU in the future [129]. Instead, the FDA does not request a reconfirmation of the rSDV. Consequently, this might be an additional advantage for future clinical trials in the USA.

Another example of innovative study procedures triggered by the pandemic is the broader establishment of so-called direct to patient services, including direct IMP delivery. MARKEN, a service company, disclosed on 09 April that they received a high number of requests and realized fast set-ups of appropriate procedures in line with the national requirement to support trials worldwide to maintain IMP delivery in regions where this strategy was previously not accepted [130].

Although highlighted as exceptional for the COVID-19 pandemic only, the experiences and advantages gained under these circumstances will accelerating the adoption of innovative technologies and will very likely create acceptance also beyond the current pandemic situation, not only for CTs but also for routine care. Pharma industry sponsors such as Bayer outlined that due to the pandemic, they "*were forced to implement new technologies rapidly and will go on with this*" [131]. Regulatory experts such as the Head of the Spanish CA (AEMPS) Cesar Hernandez Garcia mentioned that the use of new technologies to speed up trial processes had already been under discussion and that the crises may have the power to accelerate this discussion by providing different perspectives [132]. In line with this, the Swissethics commented that based on the lessons learned of the pandemic crisis, in-depth re-evaluations of the existing legal framework should also be undertaken to address the introduction of not yet

recommended but promising innovative technologies such as the implementation of e-consent procedures even in post-COVID-19 times [133].

COVID-19 guidelines strongly recommend centralized monitoring tools to replace and support on-site monitoring during the pandemic. The establishment of dashboards presenting real-time data out of electronic systems used in the trials allows sponsors and CRAs to maintain study oversight, which is particularly important in the absence of on-site monitoring visits for the regular follow-up on the status and progress of the participation of enrolled patients, new study enrollment and the study conduct in line with the protocol [121]. The same applies to the medical oversight by investigators in the absence of on-site patient visits. Real-time dashboards summarizing health and safety data entries of electronic devices or apps will allow the early detection of putative adverse events [123]. The implementation of remote outcome assessment tools, such as electronic investigator, patient or observer reported eQuestionnaires and eDiaries are particularly recommended by the FDA to support the collection of essential outcome data even in case of site closures and travel restrictions. The usage of wearable medical devices and mobile applications such as portable ECG and blood pressure devices representing innovative technologies and promising digital assessment tools are exciting alternatives to on-site assessment. The latter is of particular interest since a general trend in clinical research is seen to more complex trials that require the participation of specialized investigators. This makes a greater local distance between the investigators' location and the patients very likely [134]. In this context, decentralized clinical trial models and the involvement of satellite sites and local health care vendors performing widely used routine protocol assessment outside of trial sites are interesting new concepts [134].

An additional potential positive outcome of the pandemic has been highlighted by Mitchell *et al* [135]. Being present in daily news and social media for the development of new COVID-19 vaccines and treatment options, clinical research, and the general principles of evidence-based medicine have become more visible for the public as well as for the governments. This might improve the CT infrastructure and result in a higher interest of patients in the development of new medicines and medicinal investigations in the future.

In conclusion, although direct and indirect effects of the COVID-19 pandemic have already and will continuously harm several aspects of ongoing and future CTs, the experience gained and lessons learned from the pandemic could also be a key catalyst for innovative, more efficient, and cost-effective clinical research approaches, including decentralized clinical trial models, electronic application submissions procedures and alternative IMP supply processes that have been proven effective during the COVID-19 healthcare crises.

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# X. APPENDIX

**Fig. A.1 Number of trials investigating biological and chemical drug candidates versus non-drug trials**

Out of 24853 CTs, 21843 trials lists the keyword drug in the investigation field (87.9%). For 4225, biologic was added (17%). 2.4% contained the keyword diet, 4.5% devices, and 0.6% diagnostic test.

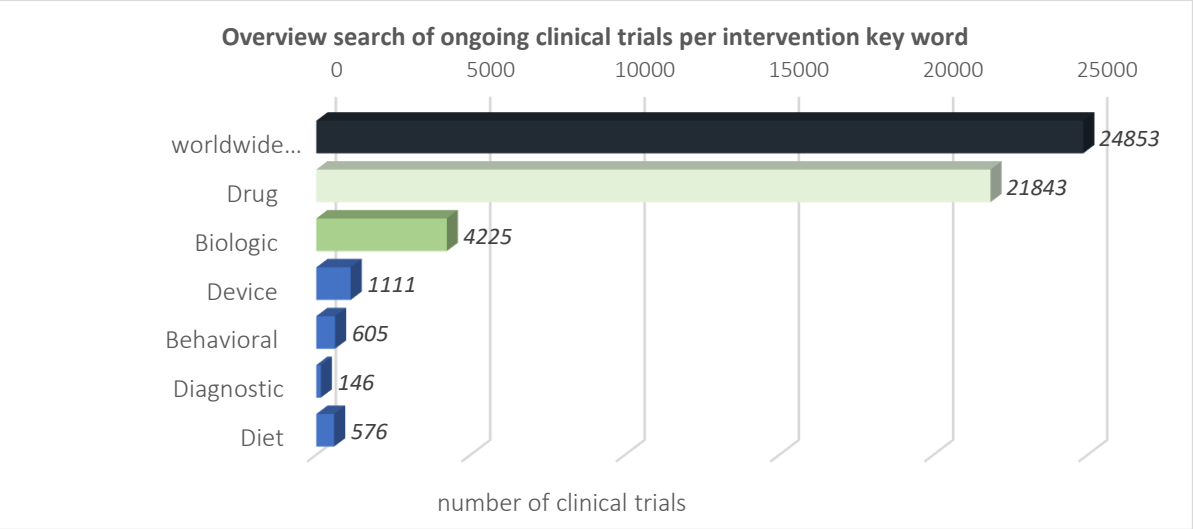



**Fig. A.2: Overview of the database results for ongoing, future and stopped CTs during the pandemic wordlwide**

| | Number of trials | Source | in % | Comment |
|---|---|---|---|---|
| ongoing interventional trials during the COVID-19 pandemic | 24853 | data base search performed in this master thesis in clinicaltrial.gov, started before/on 11Mar2020, ongoing status as of 02Jul2020 | | |
| studies stopped during the pandemic | 4024 | data set published by Carlisle based on daily database search in clinicaltrial.gov, download 02Sep2020, Dec2019 to 31Aug2020 | | |
| interventional trials stopped during the pandemic | 3414 | data set published by Carlisle based on daily database search in clinicaltrial.gov, download 02Sep2020, Dec2019 to 31Aug2020, filtered for interventional trials | 84.8 | of the studies stopped are interventional trials |
| interventional trials stopped due to COVID-19 | 1404 | data set published by Carlisle based on daily database search in clinicaltrial.gov, download 02Sep2020, Dec2019 to 31Aug2020 filtered for interventional, stopped due to COVID-19 | 41.1 | of the interventional trials stopped are stopped due to COVID-19 |
| | | Compared to data base search performed in this master thesis, clinicaltrial.gov, started before/on 11Mar2020, ongoing status as of 02Jul2020 | 5.6 | of the number of ongoing interventional trials are stopped due to COVID-19 (ratio: 1:17.7 for stopped to ongoing) |

| | Number of trials | Source | in % | Comment |
|---|---|---|---|---|
| interventional drug/biologic trial stopped due to COVID-19 | 692 | further analysis of the data set published by Carlisle, download 02Sep2020 in this master thesis, present data set for drug/biologic, reconfirmed in database analysis for the IMP type investigated | 49.3 | of the interventional trials stopped due to COVID-19 are investigating drugs or biologics |
| | | | 20.3 | of the interventional trials stopped are investigating drugs or biologics and are stopped due to COVID-19 |
| | | | 2.8 | of the investigational studies ongoing are stopped due to COVID-19 and are investigating drugs or biologics, but total number contains also other investigations, based on with 87.9% drug and 17 % biologics, combined search not possible in database |

Fig. A.3: Impact of COVID-19 on the number of CTs started per month.

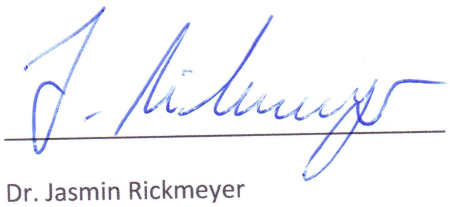
The number of non-COVID CTs started per month before the pandemic (Jan 2018 to Dec 2019) was compared to the data collected during the COVID-19 crises until Aug 2020. The analysis showed a significant decrease in new NON-COVID-19 targeting trials from March to May 2020. The data collected for Jun to Aug 2020 showed an increase in new trial registrations even higher than the maximum number seen for the Pre-COVID-19 phase.

| PRE-COVID-19 | Average Jan2018-Dec2019 | Maximum (Jan19) | Minimum (Feb19) |
|---|---|---|---|
| Number of trials started | 766 (100%) | 911 | 634 |
| **COVID-19** | **Number of trials started** | **NON-COVID-19 trials** | **COVID-19 trials** |
| Jan-2020 | 812 | 807 | 5 |
| Feb-2020 | 679 | 649 | 30 |
| Mar-2020 | 621 | 557 (73%) | 64 |
| Apr-2020 | 717 | 425 (56%) | 292 |
| May-2020 | 737 | 520 (68%) | 217 |
| Jun-2020 | 1018 | 852 (111%) | 166 |
| Jul-2020 | 1132 | 953 (124%) | 179 |
| Aug-2020 | 1123 | 970 (126%) | 153 |

## XI. ERKLÄRUNG

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Jüchen, den 22. Dezember 2020



Dr. Jasmin Rickmeyer