31458 – Trials@Home

Centre of Excellence – Remote Decentralised Clinical Trials

WP4 – EAGLE

D4.1
Mapping and analysis of the EU legislation on Remote Decentralised Clinical Trials including legal, regulatory, ethical and stakeholder recommendations for the conduct of the pan-EU pilot

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Document History

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Abstract

The Innovative Medicines Initiative (IMI) Trials@Home project is a large multinational private-public partnership launched in 2019 to explore the concept of remote decentralised clinical trials (RDCTs).

Within this project, work package 4 (i.e., EAGLE) was tasked to map and analyse the regulatory, ethical, good clinical practice (GCP) and legal aspects of the current European Union (EU) environment relevant to RDCTs.

Since clinical trials (CTs) are authorised and supervised at the national level in the EU, relevant national legislation and guidance can impact CT conduct differently throughout Europe. This deliverable aims to map and analyse the pre-COVID-19 legal and ethical framework at the EU and Member State (MS) levels to identify opportunities and challenges and provide recommendations to others on conducting RDCTs. The mapping includes EU and national legislations, including legal, regulatory, ethical and GCP aspects that may be relevant to RDCTs.

Eleven EU MSs were included in the mapping following criteria on the number of registered CTs and geographical location within Europe to ensure a suitable representation. Regulations at the national level for some remote trial activities in few countries were found. This type of regulations or guidance might already exist in standard operating procedures, policies or codes of conduct at the site level. Whilst compulsory to adhere to, these rules are much harder to monitor and enforce and might have high variability between sites and countries. The COVID-19 pandemic forced the clinical research community to re-evaluate how to manage CTs. During this period, Health Authorities have allowed sponsors to use alternative methods to ensure CTs' continuation. Even though decentralised clinical trial activities have been commonly conducted in some countries included in the EU mapping, the relevant regulations are still evolving. Provisions need to be incorporated in the regulations to ensure participants' safety and RDCTs' results robustness.

List of abbreviations and acronyms

AMP	Auxiliary medicinal product
ATMP	Advanced therapy medicinal product
CIOMS	Council for International Organizations of Medical Sciences
CRO	Contract research organisation
CT	Clinical trial
CTA	Clinical trial application
CTFG	Clinical trial facilitation group
CTR	Clinical trial regulation
EMA	European Medicines Agency
EU	European Union
EC	Ethics committee
EWG	Expert working group
GCP	Good clinical practice
GDPR	General Data Protection Regulation (EU) 2016/679
HCP	Healthcare provider
HTA	Health technology assessment
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMI	Innovative Medicines Initiative
IMP	Investigational medicinal product
MDR	Medical Device Regulation
MS	Member state
NB	Notified body
NCA	National competent authority
RDCT	Remote decentralised clinical trial
rSDV	Remote source data verification
SAB	Scientific advisory board
VHP	Voluntary harmonisation procedure
WP	Work package
EAGLE	**E**thical regul**a**tory, **G**CP and **le**gal aspects.

Link to the Trials@Home glossary: https://trialsathome.com/trialshome-glossary/

1. Introduction

Clinical trials (CTs) involving human subjects are an integral part of the development and approval of new treatments, medical devices and vaccines. The current challenges facing those working in CTs are numerous: from participant recruitment to the adoption of technology and regulatory requirements. Several challenges that are well known to those familiar with the conduct of CTs must be addressed and overcome. These include the increasing complexity of CT designs and compliance with the corresponding regulatory framework; participant recruitment and retention; the increasing use of technologies that should be fit for purpose and acceptable to participants, healthcare providers (HCPs) and regulators; the need to identify strategic partnerships with vendors, study sites and/or contract research organisations (CROs); and the development of complex medicinal products, such as cell and gene therapies, and other advance therapy medicinal products (ATMPs) and personalised treatments.

In a conventional CT, participants are required to make regular trips to the trial site for study visits to monitor their overall condition and perform study-related activities. With the advent and use of several technologies, including wearable devices, it is now possible to assess trial participants remotely, which reduces their time spent traveling to visit the clinic.[1] Participants' time investment is essential because their recruitment and retention rely upon their compliance with travelling to the clinic. Travel times and logistical barriers to the trial site can discourage overall participation and waiting times at clinics can affect participants' retention.[2,3] In the last two decades, there have been a number of new innovations and developments within the CT space that increase the feasibility to conduct decentralised trials (Figure 1). Technological improvements, amongst other factors, have been pushing the current site-based traditional trial approach towards one that incorporates features of remote and decentralised design.

In Europe, the first entirely remote trial was conducted for diabetes management (i.e., the VERKKO trial), and it was sponsored by Sanofi in 2015. The objective of this trial was to assess the utility of a 3G-enabled, wireless blood glucose meter for diabetes management. To participate in this trial, participants had to register themselves on a clinical research platform. The participants' information materials were reviewed, and the selected participants then signed the informed consent electronically. The study materials were sent directly to participants' homes. Participants reported high levels of satisfaction, which was also reflected in higher participant retention rates. The coordination activities were lowered by 66% compared to a traditional on-site trial since primarily a single investigator and a study nurse managed the entire study.[4]

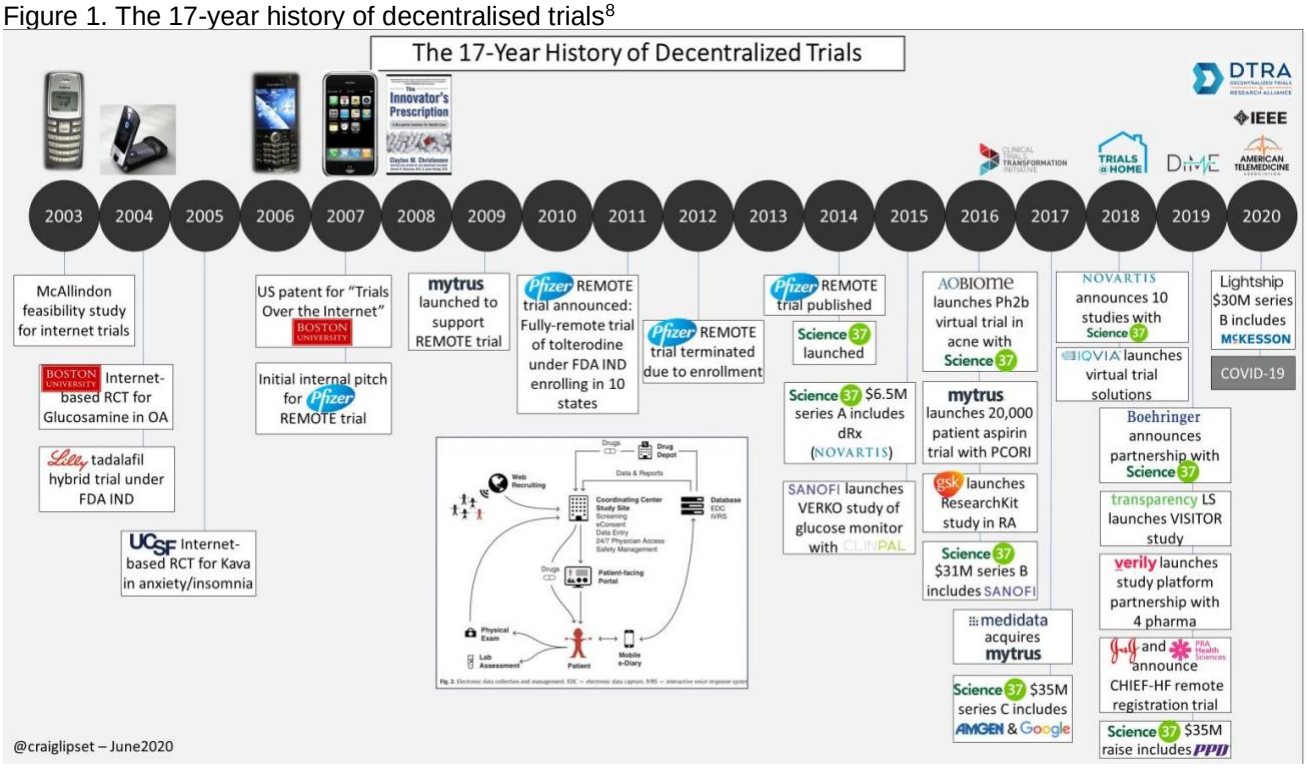
Since the VERKKO study, there have been other CTs that have included decentralised features (Figure 1). In 2017, a survey conducted with pharmaceutical companies and CROs showed that 37% were using mobile technologies in CTs, and 68% of these were using mobile applications. The principal advantages that companies reported for using mobile technologies were real-time data acquisition (36%), improved data quality (25%) and higher participant

[1] Izmailova ES, Wagner JA, Perakslis ED. Wearable Devices in Clinical Trials: Hype and Hypothesis. Clin Pharmacol Ther. 2018 Jul 1;104(1):42–52..
[2] Unger JM, Vaidya R, Hershman DL, Minasian LM, Fleury ME. Systematic Review and Meta-Analysis of the Magnitude of Structural, Clinical, and Physician and Patient Barriers to Cancer Clinical Trial Participation. JNCI J Natl Cancer Inst. 2019 Mar 1;111(3):245–55.
[3] Fogel DB. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review. Contemp Clin Trials Commun. 2018;11:156–64.
[4] eClinicalHealth Announces Successful Results for an Entirely Remote Online Clinical Trial | Business Wire. Available from: https://www.businesswire.com/news/home/20160621005604/en/eClinicalHealth-Announces-Successful-Results-Remote-Online-Clinical

compliance (30%).[5,6] More recently, the COVID-19 pandemic has caused many on-going trials to switch to remote visits midstream, despite it being unchartered territory for many. The information on how the stakeholders across the CT ecosystem are adapting, overcoming challenges and discovering new best practices for conducting clinical research via remote visits will be useful for the performance of CTs in the future.

Well-structured remote decentralised clinical trials (RDCTs), whether fully decentralised or partly decentralised/partly traditionally site-based (hybrid) RDCTs, are expected to use fewer resources in the long run and to optimise participants' involvement. If successful, RDCTs could make it easier to recruit and retain larger numbers of participants, including people living distant from traditional investigational sites and people from groups that are often under-represented in CTs.[7] Moreover, as data collection would be more or less continuous in the participants' natural setting, the data collected could be richer and more reliable, thus providing a better representation of the real world.

Figure 1. The 17-year history of decentralised trials[8]



In 2019, the Innovative Medicines Initiative (IMI) Trials@Home project, a large multinational private-public partnership, was initiated with the aim to explore the concept of RDCTs. The main objective of this multinational partnership is "to reshape clinical trial design, conduct and operations, by developing and piloting standards, recommendations and tools for the definition and operationalisation of RDCTs in Europe".[7] Within this project, work package (WP) 4 (i.e., EAGLE) was tasked to map and analyse the regulatory, ethical, good clinical practice (GCP) and legal aspects of the current European Union (EU) environment relevant to RDCTs.

[5] MHealth in Clinical Trials Report: Just 37% of companies utilize technologies. Available from: https://informaconnect.com/mhealth-clinical-trials-adoption/
[6] von Niederhäusern B, Saccilotto R, Schädelin S, Ziesenitz V, Benkert P, Decker ML, et al. Validity of mobile electronic data capture in clinical studies: a pilot study in a pediatric population. BMC Med Res Methodol. 2017 Dec 8;17(1):163.
[7] Trials@Home – Centre of Excellence Remote and Decentralised Clinical Trials. Available from: https://trialsathome.com/
[8] Drugs in a Virtual World: The rise of digital health solutions in clinical trials · Bessemer Venture Partners. Available from: https://www.bvp.com/atlas/drugs-in-a-virtual-world-the-rise-of-digital-health-solutions-in-clinical-trials

Clinical trials are regulated via directives and regulations, two forms of law that can be passed by the EU. A directive "is a legislative act that sets out a goal that all EU countries must achieve. However, it is up to the individual countries to decide how".[9] An EU directive is issued to establish a policy, to assign responsibilities, to define objectives and/or to delegate authority. A directive may establish or describe a policy, a program and/or an organisation. The EU directive lists certain objectives that must be achieved in every member state (MS). The responsibility of achieving the objectives is in the hands of the national authorities; however, the manner in which they achieve them is in the hands of the MS. In addition to the objectives, an EU directive also lists the date by which the objectives must be completed (i.e., when the framework laid down in the directive has to be implemented in the national law). The main use of a directive is to standardise different national rules and laws. An EU directive issued to all the MSs will ensure that they have the same guidelines and laws while dealing with each other, especially relating to a single market, such as product safety standards.

A regulation "is a binding legislative act. It must be applied in its entirety across the EU".[8] While a directive is an order with a list of objectives to be completed, a regulation is a rule or a law. It is a legal binding force that must be followed and abided in every MS, similar to any other national law. Regulations are law, and the national governments do not have to take any actions to implement them. Every citizen must follow regulations like a law. Regulations may be passed by the European Commission or jointly by the Council of the European Union and the European Parliament. Therefore, MSs have the duty to make the necessary arrangement to implement the Clinical Trials Regulation (CTR).

Since in the EU CTs are authorised and supervised at the national level, relevant national legislation and guidance can impact CT conduct differently throughout Europe. The aim of this deliverable is to map and analyse the pre-COVID-19 legal and ethical framework at the EU and MS levels to identify opportunities and challenges and provide recommendations to others on how to perform RDCTs. This includes mapping the EU and national legislations, including legal, regulatory, ethical and GCP aspects that may be of relevance to RDCTs.

[9] Regulations, Directives and other acts | European Union. Available from: https://europa.eu/european-union/law/legal-acts_en

2. Mapping the European legal, regulatory, ethical and GCP landscape

2.1 Methodology

2.1.1 Country selection

In Europe, Directive 2001/20/EC, reinforced by Directive 2005/28/EC of the European Parliament and the European Council, regulates the implementation of GCP to conduct CTs in the EU. Despite harmonisation efforts, the MSs can and do vary when it comes to implementing the directives in their national laws. As CTs are authorised and supervised at the national level in the EU, relevant national legislation and guidance can impact CT conduct differently on the national level.

The mapping of the European legal, regulatory, ethical and GCP landscape included collecting documentation that exists both at the EU level and the national level in selected EU MSs. The selection of the eleven EU MSs that were included in the mapping was based on the following criteria:

1) The MS is an EU country that belongs to the countries with the highest number of CTs in the EU as per ClinicalTrials.gov website in January 2020.[10]

2) The geographical location in Europe ensures a suitable representation, namely representation from Northern, Western, Central and Southern Europe.

2.1.2 Mapping approach

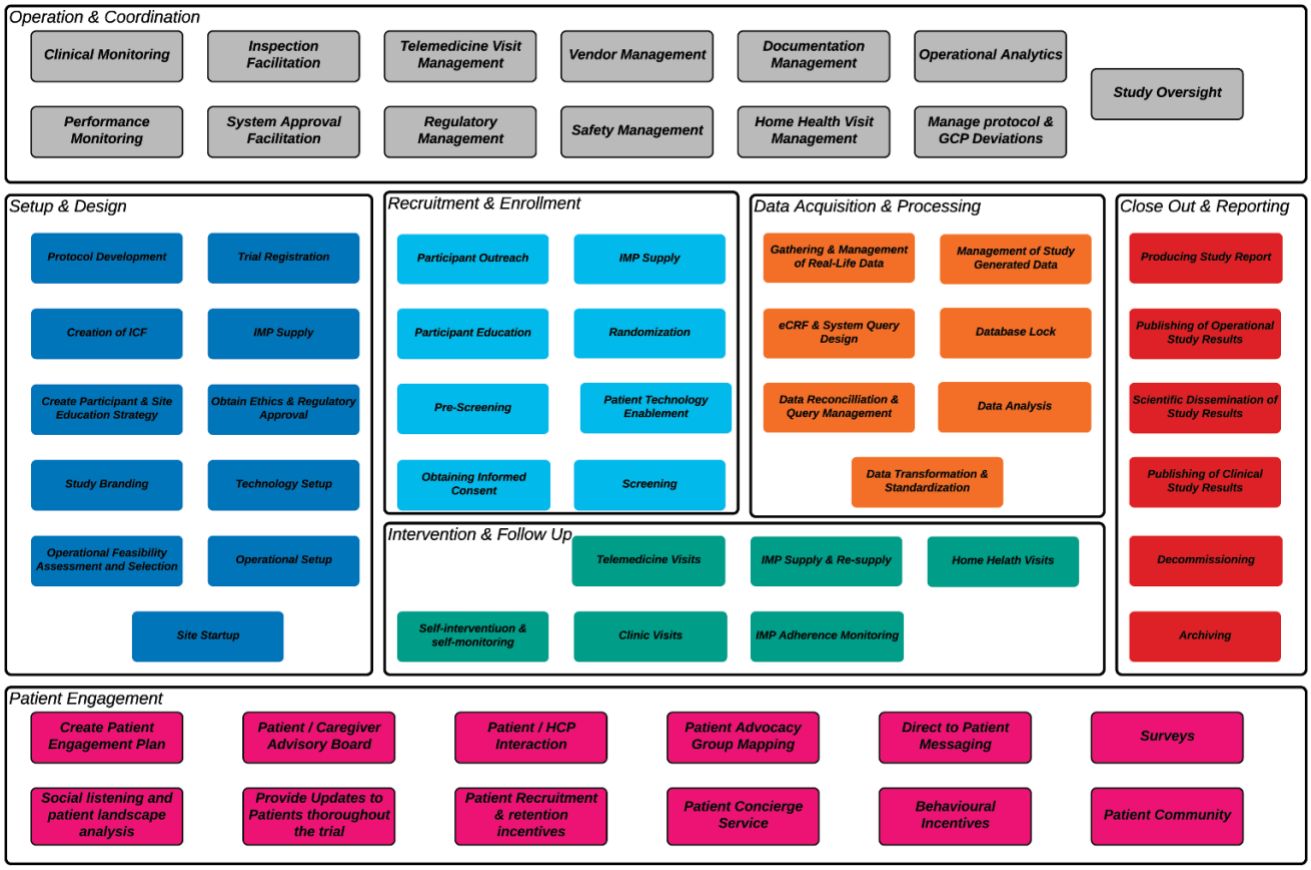
The mapping methodology was based on the Trials@Home building block classification scheme developed by WP2 TECH (Technologies – barriers, enablers and data management) and can be seen in Figure 2. The building blocks overview aims to divide the design, the conduct, the data collection and closing of a CT into different phases.

Taking into account their expertise, WP4 divided their members into three different sub-teams to carry out the mapping for each of the selected trial activities at the MS and European levels. These trial activities were selected based on how frequently they are discussed by the regulatory authorities.

The sub-teams conducted the mapping by building a list of all publicly available documentation on the subject of RDCTs from the European Medicines Agency (EMA) and national institutes. The sub-teams focused on identifying laws and regulations that contain specific provisions relevant to the performance of RDCTs.

[10] Home - ClinicalTrials.gov. Available from: https://clinicaltrials.gov/

Figure 2. Trials@Home building blocks classification scheme



2.1.3 Document review process

The objective was to map and analyse the ethical, regulatory, GCP and legal aspects (i.e., the regulations and guidelines) existing in Europe and in the MSs for RDCTs. To this effect, the sub-teams gathered information from the EMA and national authorities' websites, as well as from international and national industry organizations where guidance and regulations are (publicly) available. Searches were conducted in the local language, and the results were translated to English where necessary. These were then corroborated with in-country regulatory affairs personnel of the Trials@Home consortium who speak the local language.

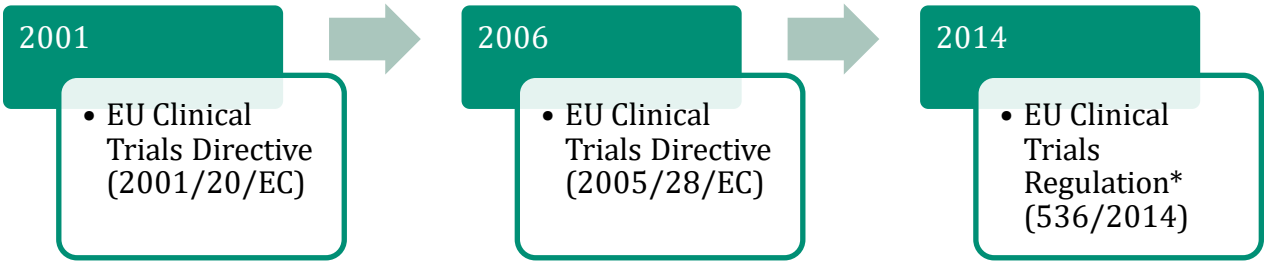
Once the documentation of guidelines and regulations was complete, the results were gathered in a Microsoft Excel format. This was then reviewed by all WP4 EAGLE members and revised where necessary. The mapping document was subsequently shared with the Trials@Home consortium for review.

3. Results

3.1 The European regulatory framework

The European Commission has released a number of directives and regulations related to drug development and the conduct of CTs since 2001 (Figure 3). Directives, regulations and guidance of interest are detailed further below.

Figure 3. Evolution of the legislative framework concerning CTs in the EU



* The Clinical Trials Regulation (CTR) is scheduled to be implemented in December 2021

Directive 2001/20/EC

Directive 2001/20/EC[11] of the European Parliament and the Council of the EU on the approximation of the laws, regulations and administrative provisions of the MSs relating to the implementation of GCP in the conduct of CTs on medicinal products for human use was published in April 2001. It aims at facilitating the internal market in medicinal products within the EU, while at the same time maintaining an appropriate level of protection for public health. It seeks to simplify and harmonise the administrative provisions governing CTs in the European Community by establishing a clear and transparent procedure. The introduction of the Clinical Trials Directive 2001/20/EC has updated pharmaceutical law in such a way that multicentre CT projects had to be evaluated by an ethics committee (EC) only once in each MS. Multicentre trials involving medicinal products or medical devices must be reported to the EC of the country in charge of the coordination of the multicentre trial. The sponsor of the multicentre CT appoints the national coordinator of the multicentre CT, who is one of the investigators involved, including the principal investigator. The EC, to which the national coordinator is subject to, assesses the multicentre CT project. Other ECs can only raise objections to the regional centres or to researchers who intend to participate in the multicentre CT project. The implementation of the Directive 2001/20 can differ between MSs; for example, in some MSs, more than one EC approval is required if there are regional differences in regulations. No information on RDCTs is included in this regulation.

[11] Directive 2001/20/EC of the European Parliament and of the Council. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

Directive 2005/28/EC

Directive 2005/28/EC,[12] released in 2005, strengthens the provisions included in Directive 2001/20/EC. It also establishes principles and detailed guidelines for GCP as regards investigational medicinal products (IMP) for human use, as well as the requirements for the authorisation of the manufacturing or importation of such products. Moreover, the directive refers to the 1995 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) consensus paper that provided a harmonised approach for GCP for the ICH regions (i.e., an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects).

In the context of the implementation of Directive 2001/20/EC and to harmonise the conduct of CTs within EU MSs, the following actions were taken:

1. The European Commission issued detailed guidance and information regarding major aspects of CTs, such as the format of requests to competent authorities (CAs) and of CT information to be submitted to ECs; the reporting of adverse reactions arising from CTs; the documentation on the quality, safety and efficacy of the IMP; and the CT database EudraCT (see section “Clinical trial guidelines” in the next page).

2. The EU Heads of Medicines Agencies (HMA) set up the Clinical Trial Facilitation Group (CTFG) in 2004 to coordinate the implementation of Directive 2001/20/EC across the MSs at an operational and national level.

3. The voluntary harmonisation procedure (VHP) was established in 2008 within the current legal framework for CTs to help address the issues encountered by sponsors with their clinical trial applications (CTA) and to optimise the organisation of coordinated assessment of multinational CTs. The VHP comprises three phases: 1) the request for the VHP and validation of the application; 2) the assessment step, which includes a review of CTA by the national competent authorities (NCAs) of the participating MS; and 3) the national step, with formal CTAs to all concerned NCAs.[13] The Paul Ehrlich Institute, Germany, coordinates the VHP. The list of MSs participating in the VHP as of October 2020 can be found in the following: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_10_CTFG_EUMS_participation_in_VHP_activities.pdf

Notably, the CTFG issued a revised “guidance document[14] for sponsors for a VHP for the assessment of multinational CTs” in 2016. Among other revisions to the VHP, the VHP-plus was implemented, providing the opportunity to involve ECs in the VHP in some MSs. For the VHP, the CTA is divided into two parts: Part I is assessed on a European level by the reporting MS (e.g., protocol, investigator brochure and IMP dossier), and Part II is assessed by each MS individually (e.g., subjects' information sheet, the informed consent form and information

[12] Commission Directive 2005/28/EC of 8 April 2005. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32005L0028&from=FR

[13] Clinical Trials Facilitation Groups Guidance document for sponsors for a Voluntary Harmonisation Procedure (VHP) for the assessment of mul-tinational Clinical Trial Applications Version 3.1. 2013. Available from: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2013_06_CTFG_VHP.pdf?sc_site=website

[14] Clinical Trials Facilitation Groups Guidance document for sponsors for a Voluntary Harmonisation Procedure (VHP) for the assessment of mul-tinational Clinical Trial Applications Version. 2016. Available from: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2016_06_CTFG_VHP_guidance_for_sponsor_v4.pdf

on the informed consent procedure).[15] The list of the NCAs that involve ECs and the specific conditions to do so is publicly available.[16,17]

The VHP project will end with the implementation of the EU regulation 536/2014 on clinical trials. Hence, starting 60 days before the new regulation's effective date, initial clinical trial applications and substantial modifications applications via VHP will no longer be accepted and processed by the VHP administrator.[18]

Clinical Trial Regulation (EU No. 536/2014)

The CTR[19] released in 2014 should facilitate harmonisation of the assessment of CTs on medicinal products and supervision processes for CTs throughout the EU via a CT information system (CTIS) expected to be effective in December 2021.[20] When the CTR becomes applicable, it will repeal the existing Directive 2001/20/EC and national legislations put in place to implement the CT directive. The authorisation and oversight of CTs will remain the responsibility of the MSs, with the EMA managing CTIS and supervising CTIS content and information that will be made public (e.g., CT summary results, clinical data, study and inspection reports). The goal of the CTR, while addressing the challenges of Directive 2005/28/EC, is to create an environment that is favourable to conducting CTs in the EU with the highest standards of **safety** for participants and increased **transparency** of trial information.

Notably, to facilitate the implementation of the CTR, some EU MSs[21] have started pilot projects at a national level. Moreover, the VHP will disappear with the implementation of the CTR.[22]

[15] Clinical Trials Regulation (EU) NO 536/2014 Draft Questions & Answers Version 3. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf
[16] Clinical Trials Facilitation and Coordination Group CTFG. European Union Member States participation in VHP and VHP-related activities. 2019. Available from: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_10_CTFG_EUMS_participation_in_VHP_activities.pdf
[17] VHP-plus: List of Participating National Competent Authorities. Available from: https://www.pei.de/SharedDocs/Downloads/DE/regulation/klinische-pruefung/liste-vhp-plus-members.pdf?__blob=publicationFile&v=2
[18] Conclusion of the Voluntary Harmonization Procedure project. Available from: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2021_01_CTFG_Conclusion_of_the_Voluntary_Harmonization_Procedure_project.pdf
[19] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Available from: https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf
[20] Clinical Trial Regulation | European Medicines Agency. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation
[21] Clinical Trials Facilitation and Coordination Group CTFG. Available from: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_01_EUMS_national_pilot_projects_intro___VHP-plus_2020.pdf
[22] Clinical Trials Regulation (EU) NO 536/2014 Draft Questions & Answers Version 3. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

Clinical trial guidelines

Volume 10 of the European Commission, "The rules governing medicinal products in the European Union", contains guidance documents applying to CTs. A number of documents in Volume 10 are currently being revised and updated to bring them in line with the changes required by the CTR. Additionally, new documents were prepared to cover new aspects introduced by the CTR. To make a distinction between documents applicable to CTs authorised under Directive 2001/20/EC (i.e., the current applicable documents) and documents relevant to CTs authorised under CTR, these documents will be listed in two separate pages on the Eudralex Volume 10 website. However, until the CTR becomes applicable, sponsors should follow the documents and guidelines[23] relevant to the CT directive. These documents and guidelines provide all the information to be submitted to the MS competent authorities in a CTA and consist of administrative information and the necessary demonstration of quality, safety and efficacy of the IMP.

While waiting for the full implementation of the CTR, although it is not mandatory, stakeholders are encouraged to take into consideration a number of aspects that are outlined in the new or updated documents. These aspects should be applied to those CTs authorised under current national laws (following the EU directive) to the extent possible and with compatibility with the legal framework of the directive. During the transitional period, which will last for three years starting from when the CTR becomes applicable (e.g., likely to occur in Q4-2021), both sets of documents will apply accordingly and should be referred to respectively according to the legislation under which the CT is conducted. At the end of the transitional period, all CTs should be conducted under the CTR and should follow only the set of documents applicable to the regulation.

The Medical Device Regulation

Until now, two directives have regulated medical devices: the 1990 Directive 90/385/EEC on Active Implantable Medical Devices (AIMDD) and the 1992 Directive 93/42/EEC on Medical Devices (MDD).

The adoption of Regulation (EU) 2017/745 on Medical Devices[24] (MDR; 2017) will change the EU legal framework for medical devices. The regulation, which entered into force in May 2017, will supersede existing directives and was expected to be applied on 26 May 2020. However, on 23 April 2020, the European Parliament and the Council of the EU adopted a proposal to extend the transitional period of the MDR by one year – until 26 May 2021. This measure aims to avoid shortages of medical devices during the on-going COVID-19 pandemic due to the limited capacity of NCAs or notified bodies (NBs) to implement the regulation. The MDR amends Directive 2001/83/EC, Regulation (EC) No. 178/2002 and Regulation (EC) No. 1223/2009 and repeals Council Directives 90/385/EEC and 93/42/EEC.

Medical devices are products or equipment intended generally for a medical use and are regulated at MS level. Article 2(1) of the MDR provides, among other definitions, a definition of medical devices as:

[23] EudraLex - Volume 10 - Clinical trials guidelines | Public Health. Available from: https://ec.europa.eu/health/documents/eudralex/vol-10_en#fragment0

[24] Regulation (EU) 2017/ 745 of the European Parliament and of the Council - of 5 April 2017 - on medical devices, amending Directive 2001/ 83/ EC, Regulation (EC) No 178/ 2002 and Regulation (EC) No 1223/ 2009 and repealing Council Directives 90/ 385/EEC and 93/42/EEC. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN

'Medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

1. *diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,*
2. *diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,*
3. *investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,*
4. *providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.* [25]

The following products shall also be deemed to be medical devices:

1. *devices for the control or support of conception;*
2. *products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.*

The MDR has introduced new responsibilities for the EMA and NCAs in the assessment of certain categories of medical device.

In the EU, medical devices must undergo a conformity assessment to demonstrate that they meet legal requirements and to ensure that they are safe and perform as intended. European Union MSs can designate accredited NBs[26] to conduct conformity assessments. The conformity assessment usually involves an audit of the manufacturer's quality system and, depending on the type of device, a review of technical documentation from the manufacturer on the safety and performance of the device. Manufacturers can place a CE (Conformité Européenne) mark on a medical device once it has passed a conformity assessment.

The EMA has published a question and answer (Q&A) document that provides practical considerations concerning the implementation of the MDR as well as guidance to applicants as regards aspects falling within the scope of the EMA's activities.[27] The Q&A should be read in conjunction with the new MDR.

Notably, the French Medicines Agency (ANSM) launched a "pilot phase" in 2019 to simulate the new organisation imposed by the MDR while continuing to comply with current regulations in France. The primary aim of this "pilot phase" for clinical investigations conducted on MDs is to ensure that the agency and its stakeholders will be ready once the MDR applies on 26 May 2021. The ANSM launched this experimental procedure on 16 September 2019 with the collaboration of the 39 existing ECs, and they released a practical information guide for

[25] MDR - Article 2 - Definitions - Medical Device Regulation. Available from: https://www.medical-device-regulation.eu/2019/07/10/mdr-article-2-definitions/
[26] Notified bodies | Internal Market, Industry, Entrepreneurship and SMEs. Available from: https://ec.europa.eu/growth/single-market/goods/building-blocks/notified-bodies_en#:~:text=Notified bodies: 1 are free,in question More items...
[27] Q&A Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations EU2017745 and EU2017746.pdf. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/questions-answers-implementation-medical-devices-vitro-diagnostic-medical-devices-regulations-eu/745-eu-2017/746_en.pdf

applicants.[28] It is essential to acknowledge that the scope of the pilot is rather limited; for example, it does not include drug-device combinations.

General Data Protection Regulation (GDPR; EU No. 2016/679)

The General data protection regulation (GDPR)[29] became fully applicable on 25 May 2018. It is concerned with the protection of personal data inside the EU and of EU residents.

Personal data is defined in Article 4 of the GDPR as "any information related to an identified or identifiable natural person". Persons can be identifiable if they can be directly or indirectly identified, especially by reference to an identifier such as a name, identification number, location data, online identifier or one of several unique characteristics, which expresses the physical, physiological, genetic, mental, commercial, cultural or social identity of these natural persons. In practice, these also include all data, which are or can be assigned to an identifiable person in any way. For example, the telephone, credit card or personnel number of a person, account data, number plate, detailed appearance, customer number or address are all personal data. The GDPR gives expression to the right to personal data protection within and beyond the EU, as long as an EU subject's data or data collected in the EU are processed.

According to Article 9 of the GDPR, health, biometric and genetic data (among others) are regarded as "sensitive personal data", the GDPR in principle forbids the processing of such data however there are exemptions for this prohibition and requirements for further compliance steps for any entity processing them. The GDPR acknowledges the need to facilitate different research types, citing scientific and historical research, statistical research, and archiving in the public interest (Article 89 GDPR). In the research context, Article 9(1) of the GDPR offers derogations to the principle of informed consent to process sensitive personal data that may be introduced under EU or MSs' national law. However, MSs may also maintain or introduce hurdles in the form of specific limitations to the processing of genetic, biometric or health data (Article 9[4] GDPR). Therefore, MSs have leeway to open or restrict the processing of these categories of data under the GDPR, which has a potentially large impact on the way research is conducted both within the MS and multi-centre, cross-national studies.

Article 89 of the GDPR functions by establishing a baseline that requires that safeguards and derogations relating to processing for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes is subject to the existence of appropriate safeguards for the rights and freedoms of data subjects. Here, the GDPR stresses that those safeguards shall include the following:

1. Data minimisation.
2. Technical and organisational measures.
3. Privacy by design and by default.
4. Pseudonymisation/further processing.

It is important to note that in the case of the application of any derogation to the points listed above; this must be undertaken by taking into account the principles of proportionality and

[28] Practical information guide for applicants. Medical Device Clinical Investigations submitted to the ANSM and Ethics Committee within the PILOT phase. 2019. Available from: https://archiveansm.integra.fr/content/download/164021/2144083/version/2/file/AEC_DOC025_V01_Guide_PP_DM_Juillet-2019_En.pdf

[29] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2016.119.01.0001.01.ENG#d1e1384-1-1

necessity. Such assessment must be conducted before the derogations are applied and must be documented. Next to the derogations listed above, the EU or MS law may allow for derogations on the following points:[30]

1. The rights to access.
2. The right to rectification.
3. The right to erasure (right to be forgotten).
4. The right to restrict processing.
5. The right to object.

The application is restricted by the requirements to also apply the safeguards mentioned above. A further qualifier is added in that any derogation must be justified by the fact that the full application of any of the rights listed above is "likely to render impossible or seriously impair the achievement of the specific purposes" and that such derogations "are necessary for the fulfilment of those purposes". Lastly, where processing personal data serves multiple purposes, one of which falls within the ambit of derogations for research as per Article 89 GDPR, the processing operations that do not fall within the scope of research cannot benefit from these derogations.

GDPR coverage

The GDPR covers all the EU MSs: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, and Sweden. Countries for which the EU so far has recognized an adequate data protection level are: Andorra, Argentina, Canada (only commercial organisations), Faroe Islands, Guernsey, Israel, Isle of Man, Jersey, New Zealand, Switzerland, Uruguay and Japan. Therefore, data transfers to these countries are permitted without additional safeguards in relation to international data transfer. A third country is a country other than the EU member states and the three additional the European Economic Area (EEA) countries (Norway, Iceland, and Liechtenstein) that have adopted a national law implementing the GDPR.

GDPR and Brexit

Following the departure of the United Kingdom (UK) from the EU and with the end of the transition period in December 2020, the GDPR will remain applicable to the UK for a maximum period of six months (minimum four months, if either party objects to the additional period of two months). These six months are called "the bridge" and allow the UK government to seek adequacy decision from the European Commission. The adequacy decision is a formal decision, whereas the European Commission decides if the UK's personal data protection regime provides data protection safeguards "essentially equivalent" to those in the EU.

During the bridge, entities that plan to continue transferring personal data to the UK will not need to take further steps and continue complying with the general principles of the GDPR.
After the bridge, in case of an adequacy decision adopted by the European Commission, no specific authorization will be required, and personal data will continue to flow without additional restrictions from the EEA to the UK.
In contrast, in the absence of an adequacy decision at the end of the bridge, UK will be considered "third country" requiring the implementation of relevant safeguards for data transfers from the EEA to the UK. EU data protection law will continue to apply to particular

[30] For a full list with discusión see: GDPR and research. A basic overview. Available from: http://www.medlaw.nl/wp-content/uploads/2018/01/GDPRrshexemptionsv.1.4.pdf

"legacy" personal data. "Legacy" personal data is the data of individuals outside the UK that was transferred from the EU to the UK during EU membership or the transition period. Transfer of personal data form the UK to the EEA can be considered unproblematic, as the UK has given adequacy to the EEA.

The relation between informed consent to participate in a clinical trial and the GDPR

There can be no objection to the principle that informed consent is a necessary condition to participate in a CT, except in the case of minors, incapacitated persons and emergencies, where substitute consent can be obtained if other conditions have also been met.

Informed consent in the GCP's sense is not the same as consent in the sense of data protection. The latter (data consent) is one of the six legal bases described in Article 6 of the GDPR. Personal data has to be processed fairly and lawfully, following one of the Article 6 lawful bases, and, where sensitive personal data is involved, based on an Article 9 exemption. The GDPR allows for exemptions to this principle based on national or EU law. One of those exemptions is when the data processing is necessary for reasons of public interest in the area of public health, such as ensuring high standards of quality and safety of healthcare and of medicinal products or medical devices (Article 9.2.i GDPR).

After consultation of the European Data Protection Board, the European Commission made an attempt to explain the interplay between the CTR and the GDPR. In essence, the guideline states that many aspects of the data processing during a CT are regulated by the CTR.[31] All data processing following from the trial protocol are hence subject to the CTR and additional trial regulations. The legal basis for the sensitive data is then Article 9.2.i GDPR. However, for activities based purely in the context of research, a different legal basis is necessary. The guidelines do not give a clear answer as to what constitutes the research following for the protocol and “purely research activities”. It should be mentioned that the CTR contains a provision that a research participant may give additional consent to research outside the protocol (Article 28.2 CTR).

The World Medical Association (WMA). The Declaration of Helsinki (2013)

The Declaration of Helsinki[32] (DoH) is a set of general ethical principles; it is widely regarded as a landmark document on human research ethics. The DoH is not a legally binding instrument but instead draws its authority from the degree to which it has been codified in legislation and regulations all over the world. The DoH is relevant to all medical research involving humans. Similar to previously detailed directives and regulations, there is no specific information in the DoH concerning the use of digital technologies or remote aspects of CTs.

The ICH E6 GCP Guideline

Good Clinical Practice (GCP) is "an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and

[31] See: Question and Answers on the interplay between the Clinical Trials Regulation and the General Data Protection Regulation. Available from: https://ec.europa.eu/health/sites/health/files/files/documents/qa_clinicaltrials_gdpr_en.pdf
[32] WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects – WMA – The World Medical Association. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the CT data are credible"[33] GCP enforces tight guidelines on clinical research ethical aspects.

The ICH-GCP Guideline presents a unified standard for the EU, Japan, United States, Canada, Brazil, China, Taiwan and Switzerland to help the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.[34] The first version of the ICH E6 GCP Guideline was published in 1996 and describes all participants' responsibilities and expectations in CTs' conduct, including investigators, monitors, sponsors, and Institutional Review Boards. GCP covers CTs' monitoring, reporting, and archiving and incorporates addenda on the Essential Documents and the Investigator's Brochure.[35]

The ICH E6 GCP is composed of core principles, stating that all CTs should be conducted following ethical principles; sound scientific evidence and detailed protocols; the benefits of conducting CTs should outweigh the risks; the rights, safety and well-being of CT participants are important, and these should be protected by obtaining informed consent and keeping confidentiality; care must be provided by appropriately qualified personnel with adequate experience; patient's records should be easily accessible and retrievable for reliable reporting, verification and interpretation; the IMPs should be manufactured, handled and stored following applicable Good Manufacturing Practice (GMP) and should be used per the approved protocol.

When the original ICH E6(R1) text was prepared in 1996, CTs were conducted in a paper-based process. Progress in electronic data recording and reporting aids the implementation of other approaches, such as centralised monitoring. Therefore, the ICH E6(R1) was revised in 2016, resulting in the ICH E6(R2) to encourage the implementation of improved and more efficient approaches to design, conduct, oversight, recording, and reporting of CTs, while ensuring that human subject protection and data integrity are maintained. Standards on electronic records and essential documents aimed to increase CTs' quality and efficiency were also updated.[36]

The ICH E6(R2) did not address CTs design innovations, emerging technologies or other circumstances that might affect CTs' conduct, such as the COVID-19 pandemic. Five years after the latest ICH E6 addendum, there are new questions and concerns about data security and patient privacy. As a result, currently, and in line with the ICH reflection paper[37] on "GCP renovation", the ICH E6 (R3) expert working group (EWG) is working on the revision of the ICHE6 (R2) GCP guideline. This includes addressing the application of GCP principles to the increasingly diverse trial types and the data sources being employed in drug development to support regulatory and healthcare-related decision-making on drugs and provide flexibility whenever appropriate to facilitate the use of technological innovations in CTs.

It is expected that the ICH E6(R3) will be a complete rewrite of E6 (R2). New topics will include decentralised clinical trials (DCTs) and guidance on incorporating real-world data

[33] ICH GCP - Introduction [Internet]. Available from: https://ichgcp.net/introduction
[34] Guideline for good clinical practice E6(R2). Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf
[35] ICH Official web site : Efficacy Guidelines. Available from: https://www.ich.org/page/efficacy-guidelines
[36] International Council for Harmonisation of technical requirements for pharmaceuticals for human use (ICH) ICH harmonised guideline integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). 2016. Available from: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
[37] ICH Reflection on “GCP Renovation”: Modernization of ICH E8 and Subsequent Renovation of ICH E6. 2017. Available from: https://admin.ich.org/sites/default/files/2019-04/ICH_Reflection_paper_GCP_Renovation_Jan_2017_Final.pdf

appropriately. "The ICH E6(R3) will include more specific discussions and refinement to E6 principles in the context of different trial types and data sources in two annexes:

> Annex 1 - Interventional CTs. Will include the use of unapproved or approved drugs in a controlled setting with the future allocation of treatment to participants and collection of trial data.
>
> Annex 2 - Additional considerations for non-traditional interventional CTs. Will include pragmatic CTs and DCTs and those trials that incorporate real-world data sources"[38]

As per their concept paper[38] and work plan, the ICHE6 (R3) EWG should release their revised guideline by the end of 2022.

The World Medical Association (WMA). The Declaration of Taipei (2016)

In 2016, the WMA also adopted a set of ethical considerations regarding health databases and biobanks: the Declaration of Taipei.[39] This guideline applies to the collection, storage and use of identifiable data and biological material beyond the individual care of participants. Biological material refers to a sample obtained from an individual human being, living or deceased, that can provide biological information, including genetic information, about that individual. The Taipei declaration states that research should pursue science advancement and public health development while respecting the dignity, autonomy, privacy and confidentiality of individuals. Moreover, the collection, storage and use of data and biological material from individuals must be voluntary. The rights of individuals include the protection against direct risks for individuals of being re-identified as well as the rights to autonomy, privacy and confidentiality. Furthermore, the provisions in the Declaration of Taipei state that individuals are entitled to exercise control over the use of their personal data and biological material. Law must lay down any exceptions. The declaration requires that health databases and biobanks are governed by internal and external mechanisms based on the principles of protection of individuals, transparency, participation and inclusion and accountability. An independent EC must approve the establishment of health databases and biobanks used for research and other purposes. In addition, the EC must approve the use of data and biological material and check whether the consent given at the time of collection is sufficient for the planned use or if other measures must be taken to protect the donor. The committee must have the right to monitor on-going activities.

The Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Health-Related Research Involving Humans. Geneva 2016

This ethical guideline publication applies to activities designed to develop or contribute to generalisable health knowledge.[40] Among the 23 guidelines, there is one specific guideline on the “Online Environment and Digital Tools in Health-Related Research” (Guideline 22). It requires researchers to anticipate, control, monitor and review interactions with their data

[38] Final Concept Paper ICH E6(R3): Guideline for Good Clinical Practice Dated 17 November 2019. Available from: https://database.ich.org/sites/default/files/E6-R3_FinalConceptPaper_2019_1117.pdf
[39] WMA Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks – WMA – The World Medical Association. Available from: https://www.wma.net/policies-post/wma-declaration-of-taipei-on-ethical-considerations-regarding-health-databases-and-biobanks/
[40] International Ethical Guidelines for Health-related Research Involving Humans. Biomedical Research. 2016. Available from: https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

across all stages of the research. Researchers must describe in the protocol how data obtained from online environments and digital tools will be treated, along with the potential risks of the research and how the potential risks are mitigated.

e-Signature (eIDAS)

The e-Signature Directive (Directive 1999/93/EC) establishes the legal framework at EU level for electronic signatures and certification services. The aim is to make electronic signatures easier to use and help them become legally recognised within the MSs. This directive was repealed by Regulation (EU) No. 910/2014 of the European Parliament and of the Council of the EU, of 23 July 2014, on electronic identification and trust services for electronic transactions in the internal market.[41] This framework is under consultation (until October 2020; no new information is expected until early 2021) with the aim to collect feedback on drivers and barriers to the development and uptake of electronic identification (eID) and trust services in the EU. After the consultation, the European Commission will evaluate which parts of the eIDAS framework can remain and, if appropriate, they will modify the scope of the regulation or its specific provisions.[42]

It should be mentioned that eIDAS is, first of all, intended as a unique identifier for citizens accessing public services. The national identification with a high level of certainty should also be used when accessing cross-border public services. It is doubtful whether eIDAS can be used to uniquely identify participants in CTs, especially in those countries, such as the Netherlands, where the civic registration number cannot be used for research. The eIDAS tool for public services will be based on that number. In addition, the eIDAS Regulation sets standards for mutual recognition of electronic signature systems in commercial services.

Digital policies and other EU legislations of potential relevance to RDCTs

The European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Pharmaceutical Research and Manufacturers of America (PhRMA), Principles for Responsible Clinical Trial Data Sharing: Our Commitment to Patients and Researchers (2013)[43]

This document, which is currently being revisited, comprises a joint policy on data sharing for pharmaceutical industries in the EU and the United States of America (USA). Since 1 January 2014, it is possible to access patient-level data, clinical study protocols and reports for new medicines approved in the EU and the USA. This document summarises the biopharmaceutical sector's commitment to data sharing while maintaining participant privacy and the integrity of national regulators. This policy aligns with agencies' transparency policy (e.g., EMA Policy 0070 for the publication of clinical data[44] of medicinal products).

[41] Regulation (EU) No 910/2014 of the European Parliament and of the Council of 23 July 2014 on electronic identification and trust services for electronic transactions in the internal market and repealing Directive 1999/93/EC. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0910&from=en
[42] Trust Services and Electronic identification (eID) | Shaping Europe's digital future. Available from: https://ec.europa.eu/digital-single-market/en/policies/trust-services-and-eidentification
[43] Principles for Responsible Clinical Trial Data Sharing. Available from: https://www.efpia.eu/media/25189/principles-for-responsible-clinical-trial-data-sharing.pdf
[44] Clinical data publication | European Medicines Agency. Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication

European Commission High-level expert group on Artificial Intelligence. Ethics guidelines for trustworthy AI (2019)[45]

The guidelines put forward a set of key requirements that artificial intelligence (AI) systems should meet in order to be deemed trustworthy. A specific assessment list aims to help verify the application of each of the following key requirements: human agency and oversight; technical robustness and safety; privacy and data governance; transparency, diversity, non-discrimination and fairness; societal and environmental well-being; and accountability.

The Organisation of Economic Co-operation and Development (OECD). Recommendation of the Council on Health Data Governance, OECD/LEGAL/0433 (2017)[46]

The recommendation calls upon countries to develop and implement national health data governance frameworks. These should set the conditions for greater harmonisation so that more countries are able to benefit from statistical and research uses of data in which there is a public interest and from international comparisons.

Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use Annex 11: Computerised Systems

Annex 11 is part of the EU Guidelines to Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use (EU GMP Guidelines).[47] It enables the European regulatory agencies to establish the requirements for computerised systems that relate to pharmaceutical products and medical devices. Among other things, Annex 11 defines the management criteria for electronic records and electronic signatures.

Annex 11 is not legally binding but is strongly recommend it to follow it since it provides a practical procedure in three fundamental areas: risk management, personnel and supplier and service providers. The Annex 11 states that computerised systems involved in GMP-regulated activities should be validated. The validation consists of demonstrating that the software design, use, and analysis of data is accurate and reproducible following a key to the data's reliability, robustness, and integrity. Besides data integrity, software tools face many issues, including reimbursement methods, patient confidentiality and data privacy concerns, which can be addressed by national decision-making and collaboration across regulators.

The Annex 11 only applies to the production and distribution of medicinal products and not medical devices. Electronic systems that qualify as medical devices should independently comply with all the medical device legislation's responsibilities. However, after the Global Harmonization Task Force's dissolution, the EU takes a centralised approach and eventually apply its guidance more broadly to all regulated areas. Annex 11 represents the clearest thinking yet from the EU on electronic record keeping and electronic signatures in a regulated environment. Annex 11 compliance can help medical device manufacturers go a long way toward meeting future European medical device expectations.

The EMA published on April 7, 2020, a "Notice to sponsors on validation and qualification of computerised systems used in clinical trials" and accordingly updated the Good Clinical

[45] Ethics guidelines for trustworthy AI | Shaping Europe's digital future. Available from: https://ec.europa.eu/digital-single-market/en/news/ethics-guidelines-trustworthy-ai
[46] Recommendation of the Council on Health Data Governance. Available from: https://www.oecd.org/health/health-systems/Recommendation-of-OECD-Council-on-Health-Data-Governance-Booklet.pdf
[47] EudraLex The Rules Governing Medicinal Products in the European Union Volume 4 Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Annex 11. Available from:https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/annex11_01-2011_en.pdf

Practice (GCP) Q&As, Questions 8 and 9. The EMA's GCP Inspectors Working Group (IWG) and the Committee for Medicinal Products for Human Use (CHMP) jointly produced the Notice.

The usage of digital tools such as wearables for patient monitoring, electronic consent and data collection and analysis and collection of safety information has become part of the new CT landscape, where the remote operation of parts of a CT is becoming the norm. The software must be validated to guarantee that the generated data is robust, reliable, and accurate. Although the sponsor is responsible for conducting a CT, third-party providers must facilitate compliance and ensure the suitability of the software used in a CT.

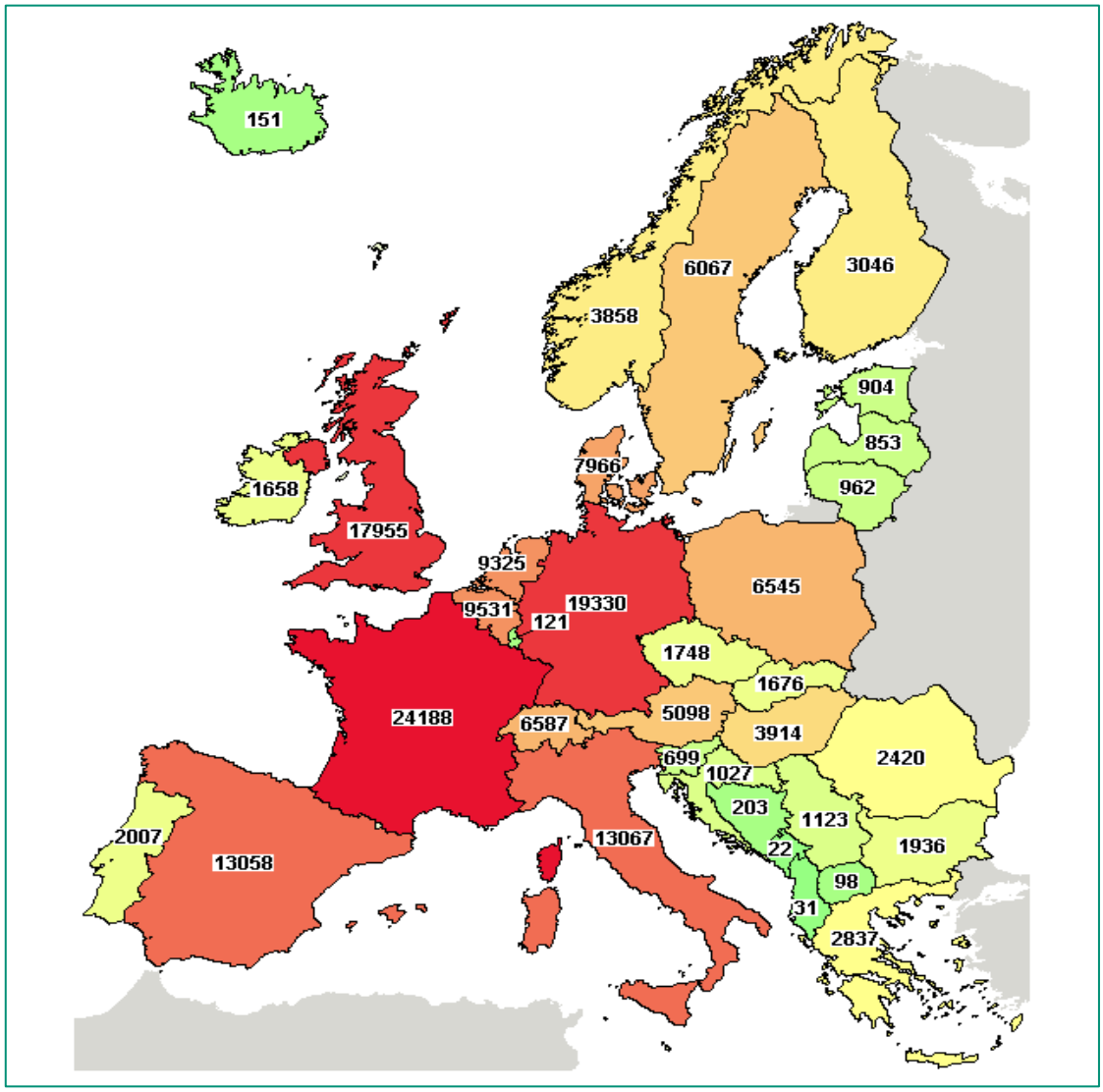
3.2 The national regulatory framework

In line with the predefined documentation methodology, the analysis focuses on eleven selected EU countries to understand how CTs are approved at the national level. This included documenting possible country specificities and whether there are already known specific legal and regulatory requirements and challenges for the conduct of RDCTs.

The number of registered CTs per country according to the registry of the National Institutes of Health (NIH) U.S. National Library of Medicine, ClinicalTrials.gov,[48] is presented in Figure 4.[49]

[48] ClinicalTrials.gov. Available from: https://clinicaltrials.gov/
[49] The same search was carried out on the EudraCT website, obtaining similar results in the ranking of the number of clinical trials per country.

Figure 4. Number of CTs registered at ClinicalTrials.gov as January 2020[49]



3.2.1 Overview of selected member states

Since CTs are embedded in healthcare and healthcare system structures vary between countries, the characteristics of the health systems of the countries being mapped are presented in the following table.

Table 1. Overview of the EU countries selected to be included in the mapping

Country	Number of inhabitants in 2019 (mln)	Number of registered CTs*	Geographical location in Europe	Health Service Provision
Belgium	11.5	9,531	North	Private
Czech Republic	10.6	1,748	East	Private
Denmark	5.8	7,966	North	State
France	67.0	24,188	West	Private
Germany	83.0	19,330	Central	Private
Italy	60.4	13,067	South	Private
Netherlands	17.3	9,325	North	Private
Poland	38.0	6,545	East	Private
Spain	46.9	13,058	South	State
Sweden	10.2	6,067	North	State

*Number of registered CTs in January 2020. The health systems information is taken from "Classifying OECD Healthcare Systems: A Deductive Approach".[50]

In the following section, the main characteristics of the health systems of the countries in focus are described. A brief overview of the regulations relevant to CT is also presented.

- **Belgium**

The Belgian healthcare system is arranged in two levels, the federal and the regional. The Federal Government, the Federal Public Service Social Security, the National Institute for Sickness and Disability Insurance (INAMI) and the Dutch, French, and German-speaking community Ministries of Health share the responsibility for healthcare policy.

The co-payments to finance healthcare can be either a reimbursement system or a third-party payer system. In case of the reimbursement system, the patient pays the full costs of services and afterwards obtains a refund for part of the expense from the sickness fund, which covers ambulatory care. For the third-party-payer system the sickness fund directly pays the provider, and the patient only pays the co-payment covering inpatient care and pharmaceuticals.

The federal government regulates and finances the compulsory health insurance by determining accreditation criteria and financing hospitals and medical care units. The regional governments are responsible for the financing of hospital investment, the implementation of hospital accreditation standards, health promotion, maternity and child health services and some aspects of elderly care.

The Federal Agency for Medicines and Health Products (FAMHP) grants or refuses the marketing authorisation of medicinal products falling outside the scope of the centralised procedure. Like all

[50] Katharina Böhm, Achim Schmid, Ralf Götze, Claudia Landwehr, Heinz Rothgang: Classifying OECD Healthcare Systems: A Deductive Approach (TranState Working Papers, 165) Bremen: Sfb 597 „Staatlichkeit im Wandel", 2012 ISSN 1861-1176

other competent authorities, FAMHP and its assessors and experts are actively involved in EMA committees and the assessment of products that fall within the scope of the centralised procedure.

The 2004 Act on Experiments on Humans covers CTs with medicine and any other research that aims at "the development of the knowledge that is proper to the exercise of healthcare professions". Both this act and the royal decree include specific provisions for CTs with medicine. These provisions implement the EU Clinical Trials Directives 2001/20/EC and 2005/28/EC. Clinical trials for medicinal products in humans are generally only permitted with the CT authorisation given by the FAMHP and a favourable opinion from the EC.

The new law on clinical trials with medicines for human use, of 7 May 2017, was adopted in response to the adoption of the EU regulation on CTs, which will repeal the current Directive 2001/20/EC once it becomes applicable. The scope of the new law is restricted to CTs that are covered by the EU regulation and will exist in parallel with the law of 7 May 2004, which has a broader scope. The law was implemented by the Royal Decree on clinical trials with medicines for human use, of 9 October 2017, with some aspects of the new law and of the new royal decree becoming applicable in November 2017. These aspects relate, for instance, to the organisation of the CAs for ECs. Some of these rules were updated in November 2019. The other provisions will be implemented when the regulation becomes applicable.

- **Czech Republic**

The health system in the Czech Republic is financed by health insurance (zdravotní pojištění). Healthcare is provided to anyone insured in the country. Employers pay insurance contributions for employees as a separate payment and an amount deducted from employee wages. Self-employed persons pay this insurance themselves. Persons who are not working and who are not insured by the state must pay their insurance contributions as those with no taxable income.

The medical and health law in the Czech Republic was altered by the social changes after 1989 and the restoration of a democratic political system and the rule of law. The conduct of CTs is currently governed by Directive 2001/20/EC as implemented by the Czech Pharmaceuticals Act and related decrees and guidelines.

On 25 July 2019, the Czech Senate discussed a draft amendment to Act No. 378/2007 Coll., Pharmaceuticals Act. The primary purpose of the amendment was to facilitate the digitalisation of healthcare services by setting up detailed rules on the "eRecept System", which enables physicians to access current and historic information about patients, such as the medication that has been prescribed or dispensed to a patient. This amendment provides an "opt-out" option under which the patient can revoke their consent for physicians to access such information at any time.

- **Denmark**

The Danish Ministry of Health is accountable for determining the overall structure of the Danish healthcare; this includes the legislation on healthcare services, medicinal products and medical devices. Denmark has various private hospitals operating alongside public hospitals within many therapeutic areas. Private pharmacies are privately owned and have a monopoly on the sale of prescription-only medicinal products and some over-the-counter medicinal products.

Denmark is divided into five regions, each responsible for their public hospitals, general practitioners and hospital pharmacies. A large part of the medicinal products and medical devices dispensed at public hospitals are acquired through a company named Amgros. Amgros is a partnership between

the five regions and carries out tenders and acquisitions of medicinal products and medical devices for public hospitals.

The CA for the approval of marketing medicinal products is the Danish Medicines Agency (DMA). A medicinal product is here defined as a product presented as having properties for treating or preventing disease in human beings or animals; a product that may be used in or administered to human beings either to restore, to correct or to modify physiological functions by exerting a pharmacological, immunological or metabolic action; or a product that makes a medical diagnosis (section 2 of the Danish Medicines Act).

The Danish Medicines Act is the main legislation regarding medicinal products; it sets general criteria (i.e., safety, efficacy and quality) for the approval of the marketing of medicinal products. The Danish Executive Order on Marketing Authorisation for Medicinal Products (No. 1239, of 12 December 2005) covers the regulations on the requisites of marketing authorisations for medicinal products. Under the Danish Act on Research Ethics Review of Health Research Projects (No. 1083, of 15 September 2017), CTs must be reported to the National Committee on Health Research Ethics. The Danish Act on Research Ethics Review of Health Research Projects stipulates that CTs cannot start without authorisation from the competent scientific EC. Furthermore, CTs must also be authorised by the DMA. The DMA implemented a multi-stakeholder forum to address DCT opinions, experiences and problems in Denmark.

- **France**

The healthcare system in France is funded in part by mandatory health contributions taxed on all salaries and paid by employers, employees and the self-employed; the central government finances another part; the final part is contributed by users who usually have to pay a small fraction of the cost of healthcare that they receive. The French healthcare system is made up of an integrated network of public and private hospitals, medical doctors and other medical service providers. Healthcare is a universal service for every citizen, irrespective of wealth, age or social status.

The French Public Health Code[51] (Code de la Santé Publique) was created in 1953 by law. It was revised by ordinance in 2000 for the legislative part and by five important decrees for the regulatory part between 2003 and 2005. The Public Health Code contains both statute law and regulatory provisions governing the professions and the healthcare facilities that are qualified to deliver healthcare or medical goods. In addition, the Public Health Code contains the rules regarding healthcare products, healthcare industries and operators. It also establishes relationships between these actors and healthcare professionals – in particular, the code of medical ethics[52] – which health professionals must comply with when administering healthcare in France.[53]

The social security code contains other important provisions, such as the regulation for public tenders (Ordinance No. 2015-899).[54] The Ministry of Health is responsible for the enforcement of regulations and laws that apply to healthcare, and they oversee the implementation of the national health policy through the French Health Directorate (DGS) and the French Directorate-General for Health Services (DGOS).

Administrative bodies supervise and control healthcare delivery. These bodies also issue interpretative guidelines, offer support to physicians and investigate malpractice suspicions.

[51] https://www.legifrance.gouv.fr/codes/texte_lc/LEGITEXT000006072665/
[52] https://www.conseil-national.medecin.fr/sites/default/files/external-package/edition/168yke7/code_de_deontologie_version_anglaise.pdf
[53] https://www.cleiss.fr/particuliers/venir/soins/ue/systeme-de-sante-en-france_en.html
[54] https://www.legifrance.gouv.fr/loda/id/JORFTEXT000030920376/2020-12-01/

Furthermore, it is important to take into account the soft laws issued by the Ministry of Health and other competent agencies, such as the National Agency for the Safety of Medicines and Health Products [Agence Nationale de Sécurité du Médicament et des Produits de Santé; ANSM].[55] Soft laws are rules that are not legally binding but are indirectly enforceable; they principally set standards of conduct, such as the rules of good practice. The European legislation contains fundamental principles in regulations and directives specific to CTs, medicinal products, medical devices and related good practices.

The ANSM is an independent administrative body. It is funded by the state and was created by the law of 29 December 2011 on strengthening the safety of medicines and health products. It replaced the former agency, the French Agency for the Safety of Medicines and Health Products (AFSSAPS). The ANSM is responsible for the regulation of medicines, medical devices, biological products of human origin (such as blood components, tissues and cells), therapeutic products and cosmetics and tattoo products (under Article L5311-1 CSP). The ANSM authorises CTs and the marketing of medical products, controls advertising and conducts some inspections, notably on manufacturing sites. The agency also centralises data vigilance and controls products' benefits-to-risks ratios. The ANSM has health policing powers and collaborates with other MSs' agencies and European bodies.

The Law 2004-806, of 9 August 2004, on health policy, implemented directive 2001/20/EC into the French Public Health Code. Directive 2005/28/EC was implemented by governmental acts of 8 November 2006, 19 May 2006, 24 May 2006 and 24 November 2006. On 5 March 2012, France adopted a new law (Jardé's law) on research involving human subjects. This Law No. 2012-300 entered into force at the end of 2016 with the publication of implementing decrees. Notably, prior to its finalisation, the Jardé Law was revisited to render the regulatory framework that it creates compatible with the new European CTR.

- **Germany**

Germany has a nationwide multi-payer social health insurance (SHI) system that is mainly organised by the statutory health insurance system (gesetzliche Krankenkasse; GKV). The healthcare system is a dual public-private system funded by statutory contributions, and coverage is nearly universal. Furthermore, it is possible to hire private health insurance (Private Krankenversicherung; PKV) to either replace or top up the coverage of the GKV.

The Federal Ministry of Health has the responsibility of developing health policy at the federal level, and this involves developing laws and drawing up administrative guidelines for the self-governing activities within the healthcare system. The most relevant decision-making body in the system of the GKV is the Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA),[56] an association representing all relevant parties of the healthcare sector, such as physicians, hospitals, sickness funds and patients. The G-BA issues directives and determines the benefits package of the GKV.

The G-BA is responsible for healthcare quality assurance together with the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; IQWiG)[57] and other institutions. The IQWiG assesses the benefits and risks associated with treatments and diagnostic procedures by analysing the available scientific data on selected topics.

The organisation of the GKV, the responsibilities of the G-BA and the other self-governing bodies and the provisions for medical care are contained in the Social Code Book V (SGB V). There are

[55] https://www.ansm.sante.fr/L-ANSM/Une-agence-d-expertise/L-ANSM-agence-d-evaluation-d-expertise-et-de-decision/(offset)/0
[56] https://www.g-ba.de
[57] https://www.iqwig.de/en/

two German laws dealing with details about medicine: the Medicinal Products Act (The Drug Law; AMG) and the ordinance on the implementation of good clinical practice in the conduct of CTs on medicinal products for use in humans (GCP Ordinance – GCP-V).

Section 2, paragraph 1 of the AMG states that drugs are substances or preparations of substances that are intended to alleviate, cure or prevent diseases or pathological complaints (presentation drugs); to restore, correct or influence the physiological functions by a pharmacological, immunological or metabolic effect; or to make a medical diagnosis.[58]

The GCP-V ordinance aims to "guarantee compliance with Good Clinical Practice in the design, conduct and documentation of CTs in humans and reporting on such trials. It aims to ensure that the rights, safety and well-being of the trial subject are protected and that the results of the clinical trial are credible". The GCP-V serves to transpose the Directive 2001/20/EC.[59]

Several authorities in Germany are responsible for drug monitoring due to the federal structure. These authorities work together in the Central Office for Health Protection of Medicinal Products and Medical Devices to monitor the manufacture of medicinal products and ongoing CTs on site. According to the AMG, central tasks are assumed by various higher federal authorities: the Federal Institute for Drugs and Medical Devices (BfArM) is liable for the approval and monitoring of low-molecular and biotechnologically manufactured drugs and medical devices;[60] the Paul Ehrlich Institute (PEI) is liable for biological drugs, such as vaccines, advanced therapy drugs (e.g., gene therapies and cell therapies) and blood and tissue preparations;[61] and the Federal Office of Consumer Protection and Food Safety (BVL) is liable for the approval and monitoring of veterinary drugs.[62]

Directive 2001/20/EC was implemented by the 12th Amendment to the Pharmaceutical Drug Act and so-called GCP Regulation in 2004. The General Administrative Provision for the Execution of the Pharmaceutical Drug Act in 2006 implements Directive 2005/28/EC.

- **Italy**

In Italy, access to healthcare is universally granted under the principles outlined in Article 32 of the constitution. Several sources fund the Italian public healthcare:

- regional taxation (IRAP) and municipal income tax (IRPEF)
- prescription revenues charged to patients
- the state budget (particularly the National Health Fund and shares in VAT income)

Every region defines its own legal and regulatory framework for the organisation and management of healthcare services in compliance with the general principles set by the state legislation (Legislative Decree 502/1992). Furthermore, each regional system must ensure essential levels of assistance (livelli essenziali di assistenza; LEAs) through services provided by public and private providers.

The Italian Medicines Agency (AIFA) is the national authority in charge of the marketing authorisation of medical products. The AIFA is a public body operating autonomously and transparently under the direction and monitoring of the Ministry of Health. The Ministry of Economy also monitors the AIFA.

[58] https://www.gesetze-im-internet.de/englisch_amg/englisch_amg.html
[59] https://www.pei.de/SharedDocs/Downloads/EN/regulation-en/clinical-trials/gcp-ordinance.pdf?__blob=publicationFile&v=2
[60] https://www.bfarm.de/EN/BfArM/_node.html
[61] https://www.pei.de/EN/institute/official-duties/duties-node.html
[62] https://www.bvl.bund.de/EN/Home/home_node.html

The Ministry of Health is responsible for the regulation of medical devices. The National Institute of Health (ISS), operating under the control of the Ministry of Health, is in charge of research, experimentation, consultancy and educational activities in public health matters. The AIFA, in cooperation with the EMA, monitors compliance with the legal requirements of medicinal products, including good manufacturing and delivery practices and pharmacovigilance.

A new law on CTs of medicine came into effect on 15 February 2018 (Law No. 3, of 11 January 2018, on the Delegation of Power to the Government over Clinical Trials of Medicines and on Provisions for Reorganising the Health Professions and on the Health Directorate at the Ministry of Health).[63] The new law delegates powers to the government to amend the existing legislation on CTs of medications for human use, introducing specific references to gender medicine and paediatric patients (Law No. 3, Article 1[1]). To that effect, the law creates a national coordinating centre of territorial ECs for CTs of medicine for human use and medical devices (Article 2[1]).

- **Netherlands**

The Dutch healthcare system is based on guaranteeing universal access while still maintaining a certain limited level of competition between healthcare insurers and providers and hence a broad choice for citizens and patients. The Dutch Health Authority oversees this system of "managed competition".

Four basic acts govern the access of citizens to the Dutch healthcare system: the Health Insurance Act (Zorgverzekeringswet), the Long-Term Care Act (Wet langdurige zorg), the Social Support Act (Wet maatschappelijke ondersteuning) and the Youth Act (Jeugdwet). The national government oversees the first two acts, but health insurers execute them. The local government executes the latter two acts.

The Health Insurance Act institutes a system of compulsory insurance for all essential healthcare and regulates the reimbursement of healthcare services in the Netherlands since January 2006. This scheme is supported by a risk equalisation program to avoid risk selection by insurers based on age and health status as insurers can compete on the market for the compulsory insurance within narrowly defined margins. No insurance premium is required for the insurance of children younger than 18 years old, and there is special assistance for those with a limited income.

The major act regulating the position of patients is the Dutch Medical Treatment Contracts Act (WGBO) of 1995, which has become part of the Dutch Civil Code. As follows from the title, the relationship between doctor and patient is seen as a contractual relationship where the weaker party, the patient, is protected by compulsory clauses. Amongst other factors, the treatment contract regulates informed consent to treatment, medical confidentiality and the position of minors and incapacitated persons.[64]

The Medical Devices Act aims to protect patients with regards to the safety of medical devices and is based on the EU directives. The current act will remain valid until the new MDR enters into force. The Medicines Act and decrees under it regulate the production, trade, distribution and prescription of medicines. It is largely based on EU directives and regulations. It contains a number of clauses making an exception to the regular distribution of pharmaceutical products in the context of research involving human subjects.

[63] https://www.gazzettaufficiale.it/eli/id/2018/1/31/18G00019/sg
[64] https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/laws/dutch-medical-treatment-contracts-act

Moreover, with regard to medical research involving human subjects in the Netherlands, there are several laws. The law most important to CTs is the WMO (Wet medisch-wetenschappelijk onderzoek met mensen; the Medical Research involving Human Subjects Act), which governs the conduct and ethical review of CTs. The WMO also established the CCMO (Centrale Commissie Mensgebonden Onderzoek; the Central Committee on Research Involving Human Subjects). The CCMO is responsible for the recognition of ECs and oversees their functioning. Most of the ECs are vested at university medical centres. An EC must authorise a CT unless the trial type is within the remit of the CCMO itself. The CCMO can also issue binding guidelines regarding the execution of research, which is within the remit of the WMO. One of these guidelines is that concerning the review of multi-centre research and external review. The latest version of these guidelines dates from June 2015.[65] Amongst other statements, this decree stipulates that a protocol that has been authorised by an EC should not be subject to review by another EC, except to ascertain the local conditions to perform the trial. The decree also stipulates which research will be vetted by the CCMO, namely research involving genome editing, animal to human embryo transfer, the use of illicit drugs, reproductive cells, the development of vaccines, cell therapy and genetically modified organisms.

The decree of 24 November 2014 contains rules for compulsory insurance in medical research involving human subjects (Medical Research [Human Subjects] Compulsory Insurance Decree). In Dutch, this is called the “Besluit Verplichte Verzekering bij Medisch-Wetenschappelijk Onderzoek met Mensen”. In essence, the sponsor of the CT should insure the subject against damages that are caused by participation in the trial and which were not explained as being inherent to that participation or which were explained but were more severe than expected.

Directive 2001/20/EC was implemented by amendments to the Act on Medical-Scientific Research involving Human Subjects (WMO) on 1 March 2006 (last amendment of 4 June 2015). Directive 2005/28/EC was implemented in the Decree on Research with Medicinal Products (1 March 2006). Furthermore, the Decree on the Obliged Insurance with Medical-scientific research involving Human Subjects is relevant here.

- **Poland**

The National Health Fund covers approximately 70% of healthcare expenditures in Poland, with the remaining 30% coming from private health insurance. Residents are required to pay an insurance fee (redistributed tax), which is 9% deducted from their personal income. The national budget covers around 5% of all healthcare expenses.

The Ministry of Health has legislative and supervisory powers over the pharmaceutical market. The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych; URPL) is the Polish NCA for the evaluation of quality, efficacy and safety of medicinal products, medical devices and biocidal products. It is subordinated directly to the Minister of Health. The manufacture and import of medicinal products and medical devices as well as the quality and advertising of medicinal products and medical devices sold by pharmaceutical wholesalers, pharmacies, pharmaceutical outlets and other sales points are supervised within the State Pharmaceutical Inspection (Państwowa Inspekcja Farmaceutyczna) system.

[65] Staatscourant 2015, 17447: https://zoek.officielebekendmakingen.nl/stcrt-2015-17447.html

- **Romania**

The main legislation overseeing medicinal products in Romania comprises of the Healthcare Reform Law (95/2006) and the Pharmacy Law (266/2008). The Ministry of Health Order 1295/2015 establishes rules for the authorisation to manufacture medicines, while the Ministry of Health Order 131/2016 determines rules on the authorisation to distribute medicine for human-use.

The Government Decision 734/2010 explains the organisation and functioning of the National Agency for Medicines and Medical Devices. The Ministry of Health regulates medicinal products through the National Agency for Medicines and Medical Devices. The Ministry of Health is liable for setting national priorities in public healthcare and coordinating the allocation of the funds. The National Agency for Medicines regulates the medicines and supervises their marketing. They take responsibility for the issuance of marketing authorisations, the supervision of CTs and the assessment and approval of laboratories to market supervision. However, specific authorisations (e.g., for the manufacture of psychoactive substances) also require approval from the ministry.

According to the National Agency for Medicines and Medical Devices Scientific Council Decision 2/2014, CTs must be conducted in authorised sites only. The National Agency regulates the authorisation procedure for conducting CTs for medicine and medical devices under the Scientific Council Decision 6/2014. As stated by the Ministry of Health Order 904/2006 on the implementation of GCP in the conduct of CTs, such activities are not permitted without a favourable opinion from the National Agency for Medicines and Medical Devices' EC. The procedure and the required documents for obtaining the EC's opinion are regulated by the National Agency for Medicines and Medical Devices Scientific Council Decision 55/2006.

- **Spain**

Spain is divided into seventeen autonomous regions that hold ample powers concerning both the provision of publicly funded healthcare and the regulation, oversight and inspection of private healthcare. The Spanish National Health System is based on the principles of universality and is mainly funded from general taxation. The system provides healthcare based on need and is free at the point of delivery, except for a cost-sharing scheme for pharmaceuticals dispensed in hospitals.

This decentralised system has led to the concurrence of national rules that determine the core principles that must be observed and guaranteed throughout the country with the different rules approved by the autonomous regions within the scope of their health competences.

The seventeen regional departments of health have primary jurisdiction over strategic and operational planning at the regional level, resource allocation, purchasing and provision. Each regional health system is organised geographically into primary healthcare districts, which are embedded in healthcare departments. Each regional health system is responsible for collecting and archiving its information. All regional authorities, without exception, are equipped with electronic (or digital) health (or medical) record (EHR) systems in primary healthcare, and the information between regions is heterogeneous.

At the state level, the primary laws and regulations affecting the provision of healthcare in Spain are the General Health Law 14/1986, of 25 April, which has the objective to regulate all the actions necessary to make the right to health protection effective as recognised and stated in Article 43 of the Constitution;[66] Law 41/2002, of 14 November, which regulates patient autonomy and the rights

[66] https://www.boe.es/eli/es/l/1986/04/25/14

and obligations of clinical information and documentation;[67] Law 44/2003, of 21 November, which examines healthcare professions;[68] Royal Decree 1277/2003, of 10 October, which establishes the general basis for the authorisation of health centres, services and establishments;[69] and Royal Decree 1907/1996, of 2 August, which discusses the advertising and commercial promotion of products, activities or services intended for health purposes.[70] Before the current law (Royal Legislative Decree 1/2015 of 24 July), entered to action, the Act 29/2006 regulated human medicines and medical products and their clinical research, evaluation, authorisation, registration, manufacture, preparation, quality control, storage, distribution, circulation, traceability, marketing, information and advertising, importation and exportation, prescription and dispensing, the monitoring of the benefit-risk ratio, their rational use and the procedure for public funding.[71].

The Royal Legislative Decree 1/2015 references that the provisions to Law 29/2006, which address the guarantees and rational use of medicines and health products, will be understood to be made to the corresponding precepts of the revised text that is approved, and therefore repealing, any provisions of equal or lower rank that oppose the provisions of this law and, in particular, Law 29/2006 on the guarantees and rational use of medicines and health products, with the exception of its second, third and fourth provisions.[72]

CTs conducted in Spain are subject to Royal Decree 1090/2015, of 4 December, on CTs and ECs on medicine research,[73] which implements Regulation (EU) 536/2014. The document "Instructions of the Spanish Agency of Medicines and Medical Devices (AEMPS) to conduct CTs in Spain", of 10 December 2019, provides a practical approach on the regulation. According to Royal Decree 1090/2015, three requirements must be met to perform CTs in Spain: the single, binding and favourable decision of an EC; the resolution of authorisation issued by the competent authority (AEMPS); and conformity of the site where the CT is going to be performed, through a Clinical Trial Agreement.[74]

Directive 2001/20/EC was implemented by Royal Decree 223/2004 on CTs. Directive 2005/28/EC was implemented by Ministry of Health Regulation No. SCO/256/2007 concerning GCP and the monitoring and importation of investigational medicinal products (IMPs) for human use. Both documents have been abrogated by Royal Decree 1090/2015, of 4 December, on Clinical Trials and Ethic Committees on Medicines Research and the Spanish Clinical Trials Registry, which implements Regulation No. 536/2014 of the European Parliament and of the Council on CTs on medicinal products for human use.

- **Sweden**

The Swedish government share responsibility for healthcare in Sweden with the county councils and the local municipalities. The Ministry of Health and Social Affairs is accountable for all policies related to social service in Sweden, including the delivery of healthcare. The National Board of Health and Welfare is responsible for all social services, health and medical services, patient safety and epidemiology. Moreover, the Health and Social Care Inspectorate is in charge of supervising healthcare and social care, as well as healthcare staff. The Swedish county councils are responsible on a regional level for the financing and delivering of healthcare services to citizens. The Medical Products Agency (MPA) is liable for the regulation of manufacturing and marketing of medicinal

[67] https://www.boe.es/eli/es/l/2002/11/14/41
[68] https://www.boe.es/eli/es/l/2003/11/21/44
[69] https://www.boe.es/eli/es/rd/2003/10/10/1277
[70] https://www.boe.es/eli/es/rd/1996/08/02/1907
[71] https://www.boe.es/eli/es/l/2006/07/26/29
[72] https://www.boe.es/eli/es/rdlg/2015/07/24/1
[73] https://www.boe.es/eli/es/rd/2015/12/04/1090
[74] https://www.aemps.gob.es/investigacionClinica/medicamentos/docs/Instrucciones-realizacion-ensayos-clinicos.pdf

drugs, medical devices and cosmetics. Furthermore, the MPA is the CA for the approval of the marketing of new medicinal products and market entry for medical devices.

The Medicinal Products Act (2015:315) and the Medicinal Products Ordinance (2015:458) are the principal regulatory frameworks for medicinal products. These regulations are based on EU Directives 2001/83/EC and 2001/82/EC (the Medicinal Products Directives). The definition of "medicinal product" used in Sweden, corresponds with the definition in the Medicinal Products Directives.

The Medicinal Products Act, the Medicinal Products Ordinance, the Ethical Review Act (2003:460) and MPA Regulation LVFS 2011:19 on CTs, which refers to Directives 2001/20/EC and 2005/28/EC regarding GCP, apply to ECs' approval and the execution of CTs. Clinical trials for medicinal products and medical devices require prior approval from both the MPA and an EC (the Swedish Ethical Review Authority).

All CTs of medicinal products must follow the EMA guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products. To implement the new regulation on CTs (no. 536/2014), the Swedish government prepared the Additional Provisions on Ethical Review for the EU Regulation on Clinical Trials Act 2018:1091, which is ready to come into force.[75]

Sweden is already examining the condition and requirements to conduct safe and effective RDCTs in the long term after the MPA received, in April 2020, a grant of SEK1.8 million from Vinnova (a Swedish government agency).[76,77]

3.2.2 Results per building blocks and MSs

In the following sections, the information from the regulations identified through the mapping is presented. The results are organised per building blocks, as illustrated in Figure 2. Notably, a lack of specific legislation for a specific trial activity for RDCTs in a given MS does not imply that RDCTs (or some hybrid form of RDCT) have not been conducted or are not permitted; it only means there are so far no specific legal or regulatory considerations.

3.2.2.1 Recruitment enrolment – Patient engagement

Remote recruitment

No specific regulations for RDCTs were found in any of the MSs or at the EU level. For any CT, recruitment activities must be approved by competent authorities including ECs.

Remote consenting

Informed consent is deemed to be expressed in writing, and it must be dated and signed by the study participant. Using electronic signatures to collect consent to participate in a CT raises legal doubts and has not been widely introduced.

There are no specific regulations about e-consent in the EU legislation. In the **Netherlands**, the bill to allow e-consent or an e-informed consent form (e-ICF) for WMO research has been submitted to

[75] Guide to EU Pharmaceutical Regulatory Law. Seventh Edition. 2017. Edited by Sally Shorthose, Bird & Bird LLP
[76] https://www.vinnova.se/en/p/virtual-clinical-trials/
[77] https://www.lakemedelsverket.se/sv/tillstand-godkannande-och-kontroll/klinisk-provning/lakemedel-for-manniskor/virtuella-kliniska-lakemedelsprovningar#hmainbody1

Parliament. The bill stresses that the sponsor and the EC reviewing the protocol should be responsible for deciding whether an e-ICF is appropriate in the given situation.[78] In **Denmark**, the requirement to provide a signature according to Article 29 of the regulation on informed consent can be met by using a technique that ensures the unique identification of the person who is signing the document. It is possible to use an e-signature; however, this is not specific for e-consent.

During the COVID-19 pandemic, remote consenting has been possible according to the EMA and Belgian, Dutch and Italian guidelines. However, the informed consent form (ICF) must be signed when possible at the trial site together with the investigator. Note also that this guidance mostly concerns COVID-19 related CTs or "re-consenting" (e.g., for changes in IMP supply). Therefore, the guidance during COVID-19 is not "generalizable".[79]

Remote screening

No specific regulations for RDCTs were found in any of the MSs or at the EU level. Competent authorities, including the EC, have to approve the procedures performed to screen participants according to well defined inclusion and exclusion criteria. In the case of conducting remote screening, it is important to ensure that data privacy aspects are evaluated.

Remote participant education

The information that a CT participant needs changes in the different CT stages, from obtaining the informed consent through the course of study until end of the CT. Participant education plays an essential role in influencing treatment adherence. When educating participants about their disease and treatment options, health literacy can play an important role in helping participants to comprehend and consider the benefits and risks of study treatment. Although no regulations were found in any of the MSs or at the EU level, it is important to note that independently of the CT design, the EC is responsible for approving all the documentation or information given to the CT participants.

Participant outreach

No specific regulations for RDCTs were found in any of the MSs or at the EU level. However, in any participant outreach campaign, the EC must review all recruitment materials for potential trial subjects (e.g., in the Netherlands, this is stated in the standard research file).[80]

According to advertising policies from Google, "Promotions for clinical trial recruitment may not promote prescription drugs or create misleading expectations or effects of a product being tested or imply that the product being tested is safe". The promotion of CT recruitment is possible in Belgium, France, Germany, Italy and the Netherlands.[81]

[78] https://www.internetconsultatie.nl/wijzigingwmo
[79] https://www.boe.es/diario_boe/txt.php?id=BOE-A-2017-8393 https://www.aemps.gob.es/informa-en/exceptional-measures-applicable-to-clinical-trials-to-manage-problems-arising-from-the-covid-19-emergency/?lang=en
[80] https://www.ccmo.nl/onderzoekers/standaardonderzoeksdossier/e-informatie-proefpersonen/e3-wervingsmateriaal-proefpersonen
[81] https://support.google.com/adspolicy/answer/176031?hl=en

Table 2. Summary of key findings: Recruitment enrolment – Patient engagement

	Remote recruitment	Remote consenting/eICF	Remote Screening	Remote participant education	Participant outreach
EU					
BE					
CZ					
DE					
DK					
ES					
FR					
IT					
NL					
PL					
RO					
SE					

EU: European Union, FR: France, DE: Germany, NL: Netherlands, PL: Poland, ES: Spain, BE: Belgium, IT: Italy, RO: Romania, CZ: Czech Republic, DK: Denmark, SE: Sweden. e-ICF: electronic informed consent form; RDCTs: remote decentralised clinical trials.
Colour code: Red: Regulation found, and activity not allowed. Yellow: regulations under discussion. Green: Regulation found, and activity is allowed. Grey: No regulation found.

3.2.2.2. Operations

Notably, although restricted for use during the COVID-19 pandemic, useful information on the management of CTs during the pandemic is included in the EC guidance.[82] In addition, the EMA Q&A webpage,[83] which provides useful information on GCP, was recently updated to provide further related guidance on computerised systems to ensure the integrity, reliability and robustness of the data generated in CTs.

Direct-to-participant drug supplies and management

According to the provisions of ICH GCP 4.6, the investigator or institution is responsible for the correct handling of the IMP at the trial site, in particular for IMPs dispensing to trial subjects. They are also responsible for adequate documentation thereof, based on respective instructions by the sponsor (see ICH GCP 5.14). Therefore, under the system as laid down in ICH GCP guidelines, the investigator (or a qualified delegate under principal investigator's supervision) is fully responsible for the supply of IMP and the respective documentation.

In **France**, it was found that the IMP shipping directly to a patient's home is not possible according to French regulation. The delivery of products to patients should be made by the site according to Article R5124-3-1 of French Health Public Code, which states, "Distributors of investigational products can distribute these products only to pharmacists listed in law (L. 5126-11 and L. 5126-12)

[82] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf
[83] https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp

the hospital pharmacist, the armed hospital or in other cases to Investigator and/or to pharmacist of authorized area". Similarly, local sources in Belgium confirmed that direct shipments from sponsor to patient are not allowed in **Belgium**.

In **Poland**, the regulations allow the delivery of medicines via courier. Pharmacists dispense some medicines, and an e-prescription system for drugs has been introduced. At site, which has a hospital pharmacy, the investigational medicinal product must be registered by the pharmacy (Article 86 of the Pharmaceutical Law).

In **Spain**, during the COVID-19 pandemic, a document was released detailing how to ship IMPs to homes or local pharmacies.[84] Prior to the pandemic, no regulations about shipping IMPs were found.

In the **Netherlands**, a manufacturer may only deliver an IMP to pharmacists; these pharmacists must practice their profession in a pharmacy (Medicines Act, Article 61, second paragraph). It is therefore not possible for a manufacturer to supply an IMP directly to, for example, a doctor or a researcher.[85]

In **Denmark**, IMPs can be delivered directly to trial participants' homes. However, there are certain conditions that must be met, and a justification must be presented clearly in the CTA. In addition, the procedure must be described clearly in the participant information to be approved by the National Committee on Health Research Ethics. The investigator may send IMPs to patients' homes, but the sponsor may not deliver IMPs directly to the participants' homes.[86]

In the **Czech Republic**, **Germany**, **Italy**, **Romania** and **Sweden**, no regulations regarding direct-to-participant IMP supply were found.

Direct-to-patient interactions – Telemedicine (e.g., video calls)

There are regulations on telemedicine in France, Italy, Spain, Germany, the Netherlands and Romania. No regulations on telemedicine were found in Poland, Denmark and the Czech Republic.

In **France**, Article 78 of Law No. 2009-879, of 21 July 2009, called HPST (hospital, patients, health and territories) was the first to define telemedicine (Article L6316-1 of the Public Health Code). Five telemedicine acts are then defined in decree No. 2010-1229, of 19 October 2010, as well as their conditions of implementation: teleconsultation, tele-expertise, remote monitoring and remote assistance.[87]

In **Germany**, physicians should not exclusively treat patients remotely but may do so in certain circumstances. The Federal Medical Association has issued guidelines under which physicians may resort to telemedicine solutions to treat patients. According to § 7 Abs. 4 MBO-Ä, virtual treatment can even be conducted without prior physical contact between patient and physician, if appropriate.[88]

Due to the COVID-19 pandemic, the **Spanish** regulatory agency has approved temporary exceptional measures applicable to CTs.[89]

[84] https://2opfle1yeg2f3zqyqbpfbx76-wpengine.netdna-ssl.com/wp-content/uploads/2020/04/Procedimiento-Sefac-entrega-a-domicilio.pdf
[85] https://english.igj.nl/medicines/clinical-trials-gcp/rules-for-clinical-trials/investigational-medicinal-product
[86] https://laegemiddelstyrelsen.dk/en/licensing/clinical-trials/clinical-trials-questions-and-answers/
[87] https://www.legifrance.gouv.fr/loda/id/JORFTEXT000022932449/
[88] https://www.bundesaerztekammer.de/fileadmin/user_upload/downloads/pdf-Ordner/Recht/2015-12-11_Hinweise_und_Erlaeuterungen_zur_Fernbehandlung.pdf
[89] https://www.aemps.gob.es/informa-en/exceptional-measures-applicable-to-clinical-trials-to-manage-problems-arising-from-the-covid-19-emergency/?lang=en

In the **Netherlands**, the government officially encourages telemedicine, albeit without implementing specific regulations.[90] Similarly, although there are no specific regulations on telemedicine, it is also utilised in **Sweden, Denmark and Poland.**[91]

Italy has national guidelines on telemedicine. These state that telemedicine is subject to the verification of the possession of the minimum requirements that are defined at national level to provide safety to the patient.[92]

In **Romania**, telemedicine became mandatory in 2020 to prevent the spread of COVID-19. The Romanian government issued regulations that allowed the remote provision of medical services during the state of emergency (Government Decision No. 252/2020),[93] and this was extended during the state of alert (Government Emergency Ordinance No. 70/2020).[94] The draft legislation of the adoption of telemedicine will serve as a legal framework for the practice of telemedicine that can be applicable after the state of alert is relaxed.

Home health visits

The responsibility for all trial-related medical decisions lies with a qualified physician (defined in ICH GCP 2.7 and 2.8)[95] who must be an investigator or sub-investigator for the trial (ICH GCP 4.3.1).[96] As can be concluded from ICH GCP 4.1.5, 4.2.5 and 4.2.6, the investigator may delegate trial-related duties, even those that are significant, to appropriately qualified individuals or parties under his supervision (i.e., mobile nurses). However, there is a high risk that under the current wording of the ICH GCP guideline, it may not be possible to perform trial-related activities at the trial subject's home. More specifically, ICH GCP 1.34 defines the "investigator" as "a person responsible for the conduct of the clinical trial at a trial site". The "trial site" is "[t]he location(s) where trial-related activities are actually conducted" (ICH GCP 1.59).[97] If it is mentioned in an approved trial protocol that trial-related tasks may also be performed at the trial subjects' homes without listing them as trial sites, it may be possible to refer to the respective approval in order to argue GCP compliance. However, it remains to be seen whether this is sufficient for health authorities to accept the generated data.

In the **Netherlands**, the general provisions of the health legislation apply, and they are sometimes further interpreted by professional codes. The government's policy is that patients should be given care as much as possible at home, and "neighbourhood nursing has its own quality standards.

Belgium, **Denmark** and **France** follow the EMA Q&A document[98] (topics No. 10 and 11), which states that "sponsor cannot delegate tasks related to the medical care of the subjects that are specific of the Investigator (e.g., IMP dispensing/administration, AE/SAE evaluation), because the Investigator is responsible for all the trial medical activities (…) A contract/written agreement should be in place between the Institution/Hospital/Investigator and the single individual(s) or the organization which will provide the service/personnel".

[90] https://www.government.nl/topics/ehealth/government-encouraging-use-of-ehealth
[91] https://www.oecd-ilibrary.org/social-issues-migration-health/bringing-health-care-to-the-patient_8e56ede7-en
[92] http://www.salute.gov.it/imgs/C_17_pubblicazioni_2129_allegato.pdf
[93] http://www.cnas.ro/cjastm/post/type/local/hg-252-2020-privind-stabilirea-unor-masuri-in-domeniul-sanatatii-pe-perioada-instituirii-starii-de-u.html
[94] http://legislatie.just.ro/Public/DetaliiDocument/225600
[95] https://ichgcp.net/2-the-principles-of-ich-gcp-2
[96] https://ichgcp.net/4-investigator
[97] https://ichgcp.net/1-glossary
[98] https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp

In **Germany**, **Spain**, **Poland** and **Sweden**, where no regulations were found, it is expected that home health visits are assessed by NCAs and ECs on a case-by-case basis.

Laboratories

Home collection of samples by home nurses is permitted in **Belgium** but is not specifically regulated for CTs. No specific regulations were found in other MSs; each case should therefore be separately assessed by NCAs and ECs.

Imaging

No specific regulations were found in other MSs; the health authorities and EC should thus separately assess each case.

Electronic patient-reported outcome (ePRO)

There are currently no laws or regulations in **Belgium** that allow or prevent the completion of ePRO by study participants outside of study site, this was confirmed by local sources. In the situation where a mobile application is used, it should be considered as a medical device and as such should comply with the MDR. No specific regulations were found in other MSs.

Wearables

On 5 April 2017, two new EU regulations on medical devices were adopted: the MDR and Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices (IVDR). The MDR "lays down rules concerning the placing on the market, making available on the market or putting into service of medical devices for human use and accessories for such devices in the European Union".[99]

There are currently no laws or regulations in any of the MSs to allow or prevent the use of wearables. However, it is important to note that a wearable sensor would be considered a medical device only if it is intended to be used for a medical purpose as defined under MDR art 2(1).

Omics (e.g., genomics, transcriptomics, proteomics and metabolomics)

In the **Netherlands**, there are rules for processing genetic data that aim to safeguard patients' confidentiality. In **Sweden**, the law of genetic integrity includes genetic testing, genetic research and gene therapy. However, these two regulations are not specific to RDCTs. No specific regulations were found in the rest of the mapped MSs.

[99] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02017R0745-20170505

Table 3. Summary of key findings: Operations

	Telemedicine		Remote assessments					
	Direct-to-patient drug supplies and management	Direct-to-patient interactions – telemedicine	Home health visits	Labs	Imaging	Patient-reported outcome	Wearables	Omics
EU								
BE								
CZ								
DE								
DK								
ES								
FR								
IT								
NL								
PL								
RO								
SE								

EU: European Union, FR: France, DE: Germany, NL: Netherlands, PL: Poland, ES: Spain, BE: Belgium, IT: Italy, RO: Romania, CZ: Czech Republic, DK: Denmark, SE: Sweden.
Colour code: Red: Regulation found, and activity not allowed. Yellow: regulations under discussion or follow recommendations from other sources. Green: Regulation found, and activity is allowed. Grey: No regulation found.

3.2.2.3. Data collection and quality

Electronic case report form (eCRF)

The EMA guidance (EMA/INS/GCP/454280/2010) does not provide specific instructions for RDCTs. However, it does focus on e-sources and eCRFs, so there is a lot of information relevant to RDCTs as most of RDCT-related activities are undertaken by use of electronic systems.[100]

In **Denmark**, there are no specific regulations, but the use of eCRFs is allowed.[101] In **Italy**, the NCA stipulates eCRF requirements in section 1.1 of its Q&A.[102] In the **Netherlands**, a guideline on research with human subjects applies to research conducted by academic hospitals (UMCs) and states the use of eCRFs.[103] In **Spain**, there is no specific requirement from the NCA. The format or formats that guarantee the correct conservation of the eCRF will be used. It should be noted, however, that eCRFs replacing traditional paper-based CRFs are being used increasingly more often and have not been challenged by authorities now that it is possible to verify the data entered in the eCRFs.

[100] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/reflection-paper-expectations-electronic-source-data-data-transcribed-electronic-data-collection_en.pdf
[101] https://laegemiddelstyrelsen.dk/en/licensing/clinical-trials/gcp-inspection/source-data-list/
[102] https://www.aifa.gov.it/documents/20142/847386/FAQ_generali-Ispezioni_GCP_05.10.2021.pdf
[103] https://www.nfu.nl/sites/default/files/2021-01/21.00023_Richtlijn_Kwaliteitsborging_Mensgebonden_Onderzoek_2020.pdf

Remote monitoring oversight

The EMA reflection paper on risk-based quality management in CTs (EMA/269011/2013) addresses explicitly central (i.e., remote) monitoring, defined as "document review, data review and analysis performed remotely from the investigator site by the sponsor to examine the data collected in order to check compliance, identify unusual data patterns, deviations from protocol or missing or invalid data". Although this encourages new (risk-based) approaches, it does not provide any detailed instructions.[104]

There are no specific local provisions. However, the current interpretation is that the regulations currently allow remote monitoring in many MSs, such as the **Czech Republic**, **Germany**, **Denmark**, **Spain**, **France**, **Italy** and the **Netherlands**. For instance, in the Dutch Quality Assurance Guideline for Human Research 2019, it is explained that there are two types of centralized monitoring: "Remote monitoring: the monitor approaches the research team of a research location by telephone or via an electronic Case Report Form (eCRF) with the request to send coded information to the monitor for verification. These can be screening logs, checklists, but in no case, documents containing personal data. Statistical monitoring: collected data from all participating research locations as predetermined in the research-specific Monitoring Plan are reviewed. The analysis can focus on trends, missing data, and outliers. After this check, the monitor can monitor more specifically and visit research locations that require more attention or where verification of source documentation is necessary. Timely entry of data in an eCRF is a precondition for statistical monitoring"[105]

During the COVID-19 pandemic, in some cases, remote source data verification (rSDV) is allowed but restricted to safety data and primary efficacy data. Remote source data verification can be conducted specifically for COVID-19 CTs, pivotal CTs, CTs for serious or life-threatening diseases, CTs where the absence of SDV would pose unacceptable risks to participant's safety, or CTs with vulnerable participants.[106]

Query management

No specific provisions were found at the EU level or at the MS level.

Audits

At the EU level, the revision on General Considerations for Clinical Studies addresses auditing, but no specific RDCT provisions.[107] There are no specific local RDCT provisions in the countries studied.

[104] https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-risk-based-quality-management-clinical-trials_en.pdf

[105] https://www.nfu.nl/sites/default/files/2021-01/21.00023_Richtlijn_Kwaliteitsborging_Mensgebonden_Onderzoek_2020.pdf

[106] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

[107] https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-guideline-e8-r1-general-considerations-clinical-studies-step-2b_en.pdf

Table 4 Summary of key findings: Data collection and data quality

	Data collection and quality			
	Electronic case report forms	Remote monitoring and oversight	Query management	Audit
EU				
BE				
CZ				
DE				
DK				
ES				
FR				
IT				
NL				
PL				
RO				
SE				

EU: European Union, FR: France, DE: Germany, NL: Netherlands, PL: Poland, ES: Spain, BE: Belgium, IT: Italy, RO: Romania, CZ: Czech Republic, DK: Denmark, SE: Sweden.
Colour code: Red: Regulation found, and activity not allowed. Yellow: Regulation found, see specifications. Green: Regulation found, and activity is allowed. Grey: No regulation found.

3.2.2.4 Data processing

Electronic health records

The EMA reflection paper[108] on expectations for electronic source data and data transcribed to electronic data collection tools in CTs (EMA/INS/GCP/454280/2010) outlines the current opinion of the EU GCP inspectors working group and provides useful information on the use of electronic data capture in CTs trials and on related inspections. Section 5.5 of the Note for Guidance on Good Clinical Practice (CPMP/ICH/GCP/135/95) describes standards for the use of electronic trial data handling and/or remote electronic data systems. Overall, the guidance does not provide specific instructions for RDCTs. However, as it focuses on e-sources and eCRFs, it contains a lot of relevant information as most of RDCT-related activities will be conducted by use of electronic systems.[109]

We did not find specific regulations for EHR systems in RDCTs. Each country has their own regulations on EHR systems. In **Poland**, access to medical records requires patients' consent, usually expressed in an ICF.[110] In **Spain**, the EHR systems are region independent, and the regional authority governs access, but no regulations were found regarding the use of this data for CTs.[111] In

[108] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/reflection-paper-expectations-electronic-source-data-data-transcribed-electronic-data-collection_en.pdf
[109] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/reflection-paper-expectations-electronic-source-data-data-transcribed-electronic-data-collection_en.pdf
[110] https://www.gif.gov.pl/download/3/5000/pharmaceuticallaw-june2009.pdf
[111] https://www.mscbs.gob.es/organizacion/sns/planCalidadSNS/docs/HCDSNS_English.pdf

France, there is a law that regulates EHR systems (Loi n° 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés).[112] In the **Netherlands**, the act on special provisions concerning sensitive data in healthcare regulates certain aspects of the digital data; from 2020, healthcare providers must keep track of who has viewed which data. Patient consent is required before another healthcare provider may retrieve data that have been previously noted by another healthcare provider.[113]

Data protection

Key regulations are the GDPR and Directive 2002/58/EC. The latter is planned to be replaced by the new e-privacy regulation. These are generic regulations that do not specifically address CTs (remote or not). There are some additional documents that address data protection topics specific to clinical research (e.g., secondary use of data). However, none of them are specific to RDCT.[114] Each country has their data protection law on top the GDPR.

In **Belgium**, on 5 September 2018, the Act of 30 July 2018 on the protection of natural persons with regard to the processing of personal data (the Data Protection Act) [*Wet betreffende de bescherming van natuurlijke personen met betrekking tot de verwerking van persoonsgegevens. Loi relative à la protection des personnes physiques, à l'égard des traitements de données à caractère personnel*] was published in the Belgian Official Gazette. The Data Protection Act addresses the areas where the GDPR leaves room for EU MSs to adopt country-specific rules. It also implements Directive 2016/680 on the protection of natural persons with regard to the processing of personal data by NCAs for the purposes of the prevention, investigation, detection or prosecution of criminal offences or the execution of criminal penalties and on the free movement of such data.[115]

In the **Czech Republic**, the Act on Personal Data Processing [*Zákon o zpracování osobních údajů*] came into effect on 24 April 2019. This act does not include any specific employment law-related provisions. Therefore, employers, as data controllers, must comply primarily with the provisions of the GDPR and the Labour Code, which regulates the monitoring of employees and recruitment rules.[116]

In **Denmark**, the main regulation concerning the processing of personal data is the Data Protection Act, [*Lov om supplerende bestemmelser til forordning om beskyttelse af fysiske personer i forbindelse med behandling af personoplysninger og om fri udveksling af sådanne oplysninger (databeskyttelsesloven)]* which came into force on 23 May 2018. In addition to the rules of the GDPR, the Data Protection Act and national practice implement certain derogations concerning the processing on personal data, particularly in regard to the processing of personal data within the employment sector. Furthermore, the national legislation introduces a fourth type of personal data in form of "confidential" personal data, which may include private, social or economic data that concerns the data subject.[117]

In **France**, the correspondent law is the Data Protection Act, June 2019 [*La loi Informatique et Libertés*].[118]

[112] https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000031912641&categorieLien=id
[113] https://www.rijksoverheid.nl/onderwerpen/digitale-gegevens-in-de-zorg/betere-bescherming-van-digitale-zorggegevens
[114] https://eur-lex.europa.eu/eli/reg/2016/679/oj
[115] https://www.timelex.eu/sites/default/files/pdf/Nieuwe-belgische-privacywet-30-07-2018.pdf
[116] https://www.zakonyprolidi.cz/cs/2019-110
[117] https://www.retsinformation.dk/eli/lta/2018/502
[118] https://www.cnil.fr/fr/la-loi-informatique-et-libertes

In **Germany**, the Federal Data Protection Act [*Bundesdatenschutzgesetz (BDSG)*] governs data protection and supplements the GDPR.[119] Moreover, in Germany, the Federal Data Protection Act governs data protection. The overseeing of the principles of data protection law is assigned to the individual federal states in Germany. Therefore, every state has its own Data Protection Authority (DPA) that is responsible for data monitoring in its territory. The DPA can request any information that is necessary to monitor compliance with the applicable data protection law and can further institute an investigatory (on-site) inspection.

In **Italy,** a specific Italian legislation on data protection [*Codice in materia di protezione dei dati personali*] is set forth in the Personal Data Protection Code (Legislative Decree 196/2003). This decree implements EU Directive 2002/58/EC and has been largely amended by Legislative Decree 101/2018 in order to align its content with the GDPR.[120]

In the **Netherlands**, the General Data Protection Regulation Implementation Act *(UAVG)* [*Uitvoeringswet Algemene Verordening Gegevensbescherming*], which implements the GDPR, also supplements the GDPR.[121]

In **Poland**, the local data protection law is the act of 10 May 2018 on the Protection of Personal Data (PDPA) [*Ustawy o ochronie danych osobowych*].[122]

In **Spain**, the local data protection regulation is the Organic Law 3/2018 (Dec 2018) [*Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos y Garantía de los Derechos Digitales*].[123]

In **Romania**, there are two important laws, besides the GDPR: Law 190/2018 [*LEGE nr. 190 din 18 iulie 2018 privind măsuri de punere în aplicare a Regulamentului (UE) 2016/679 al Parlamentului European*],[124] which implements measures for the GDPR and Law No. 102/2005 [*LEGE nr. 102 din 3 mai 2005 privind înfiinţarea, organizarea şi funcţionarea Autorităţii Naţionale de Supraveghere a Prelucrării Datelor cu Caracter Personal*], which discusses the establishment, organisation and functioning of the National Supervisory Authority for Personal Data Processing (DPA).[125]

In **Sweden,** the Data Protection Ordinance (2018:219) (DPO) [*Förordning (2018:219) med kompletterande bestämmelser till EU:s dataskyddsförordning*] regulates general aspects of data protection where the GDPR permits it, for instance the processing of social security numbers and data referring to criminal offences. The DPO authorises the government and other public authorities that the government designates to issue more detailed regulations concerning several important features of the DPO. The DPO entered into force on 25 May 2018.[126]

Database, access and integration

No specific regulations were found at the European level or at the MS level.

[119] https://www.gesetze-im-internet.de/bdsg_2018/BDSG.pdf
[120] https://www.garanteprivacy.it/web/guest/home/docweb/-/docweb-display/docweb/9042718
[121] https://wetten.overheid.nl/BWBR0040940/2020-01-01
[122] https://uodo.gov.pl/
[123] https://www.pbjuridico.com/the-organic-law-3-2018-of-december-5-on-data-protection-and-guarantee-of-digital-rights-enters-into-force-2/?lang=en
[124] https://www.dataprotection.ro/servlet/ViewDocument?id=1685
[125] https://www.dataprotection.ro/index.jsp?lang=en&page=home
[126] https://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/forordning-2018219-med-kompletterande_sfs-2018-219

Analysis

There are several EU and ICH guidelines (e.g., ICH E10 choice of control group in CTs guideline[127]) that discuss the analysis of CT data. However, there are no specific regulations on RDCTs at the EU level or at the MS level. It is important, however, to ensure data integrity so as to draw appropriate conclusions from the results.

Re-use of data

Notably, the EFPIA position paper on the secondary use of CT data and Opinion 3/2019 concerning the 2019 Q&A document on the interplay between the CTR and the GDPR discuss re-use of data. However, this topic is independent of where and how a CT is conducted.[128,129,130]

In **France**, re-use of data is included in the national interoperability framework by the national agency for shared health information system (ASIP-Sante). The medical file hosts keep the patients' personal health data in a deposit that is available to professionals, health establishments or patients themselves. They cannot use them for other purposes. The accommodation service is the subject of a contract in accordance with legislative provisions.[131]

In the **Netherlands**, Article 7:457 BW, 7:458 BW (WGBO; the medical treatment contracts act) regulates the relation between the patient and the healthcare provider. This contains rules on consent and exceptions to consent for the use of patient data for secondary research (but not for the re-use of CT data).[132] No specific rules for RDCTs were found.

Clinical trial close-out and reporting

There are no RDCT-specific regulations or guidance covering these topics. This is unexpected, at least for now. However, with experience gained, this may change. The reporting is independent from where a study was conducted. For archiving, even in a RDCT, there will still be at least one virtual site. This will then be the entity responsible for archiving "site files" and source documents in line with GCP and relevant standard regulations. No information was found at the MS level.

[127] https://www.ema.europa.eu/en/ich-e10-choice-control-group-clinical-trials
[128] https://edpb.europa.eu/our-work-tools/our-documents/opinion-art-70/opinion-32019-concerning-questions-and-answers_hu
[129] https://www.efpia.eu/media/413227/position-paper-safeguards-framework-for-secondary-use-of-clinical-trial-data-for-scientific-research-september-2019.pdf
[130] https://ec.europa.eu/health/sites/health/files/files/documents/qa_clinicaltrials_gdpr_en.pdf
[131] https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000000886460
[132] https://wetten.overheid.nl/BWBR0005290/2019-11-15/#Boek7_Titeldeel7_Afdeling5

Table 5. Summary of key findings: Data processing

	Data processing				
	Electronic health records	Data protection	Database, access and integration	Analysis	Data re-use
EU					
BE					
CZ					
DE					
DK					
ES					
FR					
IT					
NL					
PL					
RO					
SE					

EU: European Union, FR: France, DE: Germany, NL: Netherlands, PL: Poland, ES: Spain, BE: Belgium, IT: Italy, RO: Romania, CZ: Czech Republic, DK: Denmark, SE: Sweden.
Colour code: Red: Regulation found, and activity not allowed. Yellow: Regulation found, see specifications. Green: Regulation found, and activity is allowed. Grey: No regulation found.

3.3 Regulatory guidance for ongoing CTs during the COVID-19 pandemic in the EU

The COVID-19 pandemic had an enormous impact on ongoing CTs. Regulatory guidance on CT management was vital during the initial phases of the pandemic. While conducting the regulatory mapping presented in this report, some members of the WP4, conducted in parallel a study aimed to provide insights into regulatory authorities' response to the COVID-19 pandemic for ongoing CTs in the EU.

The NCAs' and the European Medicines Agency (EMA) websites were consulted for published guidance on CTs' management during the COVID-19 pandemic. The results of this study were summarised as regulatory readiness and regulatory guidance as a two-fold outcome for the regulatory response.

The number of days from the first European and country-specific COVID-19 case to the first published guidance on CTs' management during the pandemic by the respective NCA was defined as regulatory readiness. The regulatory guidance content, including regulatory flexibilities, was described using 12 pre-defined operational trial activities using the same basic building blocks scheme we used in the present report. (Figure 2)

Twenty-four out of the 27 EU NCAs published country-specific guidance. The specific content of the guidance differed per NCA, but the overall measures aimed at ensuring participant safety and trial integrity. The guidance was provided most frequently for regulatory management, safety management, CT monitoring, and IMP supply. [133]

4. Discussion

Advancements in technology and data generation have significantly impacted drug development over recent years, and this has resulted in an increase in opportunities to implement these in the CT setting. The use of mobile and digital technologies not only increases patients' participation in CTs but also provides an opportunity to generate data on the use of therapies in real-time. These advancements, amongst others, are also slowly but surely prompting the current site-based traditional trial set up to become more remote and decentralised. This swift expansion and implementation of digital technologies in CTs has also resulted in a number of challenges, including those for regulators and ECs that must assess their use within the current regulatory framework in order to safeguard patient safety, privacy and data integrity. The current ethical, regulatory and legal framework for CTs has so far been tailored to site-based, traditional CTs. Switching from site-based, traditional CTs to RDCTs will require all stakeholders' acceptance and adaptation. Changes that can be made within the current regulatory framework will provide some good principles to apply, including GCPs. Some experience has been gained, as reflected, which should help the Trials@Home consortium to clarify the concept of RDCTs and to identify some preliminary recommendations to be used for the pilot study.

The objective of this Deliverable was to map and analyse the ethical, regulatory, GCP and legal aspects (i.e., regulations and guidelines) existing in Europe and in the MSs for RDCTs. To this effect, WP4 focused on EU MSs in which, as the clinicaltrial.gov database demonstrates, a great number of CTs are generally conducted. The selection also took into consideration the need to have an appropriate geographical representation of EU MSs, meaning a suitable number of MSs from Northern, Western, Eastern and Southern Europe. As the UK left the EU on 1 January 2021, it is unclear if it can be considered as one of the countries in which to run the pilot study. Some consortium members based in the UK are involved in the conduct of UK/EU CTs, which brings insight into what remote approaches are currently being implemented in both regions. The UK is one of the countries with highest number of CTs conducted in Europe, and some of the smaller EU countries have often adopted UK-based guidance and examples. The UK Medicines and Healthcare products Regulatory Agency (MHRA) is frequently regarded as one of the top agencies in the world from which to seek quality scientific advice. It is considered a pragmatic agency, open to new ways of conducting CTs and innovative clinical development. Experiences from the UK will certainly be of value in addition to EU experiences.

This topic may even benefit from the pandemic where, under regulators' scrutiny, remote approaches have been required to maintain ongoing CTs. The MHRA has published different statements and guidelines to comply with GCP while adapting to new technologies such as EHRs electronic health records.[134] In 2018, the MHRA published a joint statement with the National Health Service (NHS), where the legal and ethical requirements are stated for seeking and documenting consent using electronic methods.[135] The MHRA Grey Guide, Section 8.2.7 contains some requirements for

[133] de Jong A.J.; Santa-Ana-Tellez Y.; van Thiel G.J.M.W.; Zuidgeest M. G.P.; Siiskonen S.J.; Mistry D.; de Boer A.; Gardarsdottir H. COVID-19 and the Emerging Regulatory Guidance for Ongoing Clinical Trials in the European Union. Clin. Pharmacol. Ther. Epub 2021 February

[134] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/470228/Electronic_Health_Records_MHRA_Position_Statement.pdf

[135] https://s3.eu-west-2.amazonaws.com/www.hra.nhs.uk/media/documents/hra-mhra-econsent-statement-sept-18.pdf

ePROs, such as validation with the protocol requirements, availability of the source data in the site, and the possibility of tracking back the changes in records.[136] Additionally, during the COVID-19 pandemic, the delivery of IMP to a participant's home supply was permitted. [137] It is important to note that after leaving the EU, data protection between UK and EU might change depending on the agreements reached after a transition period after 1 of July 2021 (for more details see section GDPR and Brexit).

When starting the mapping, it became evident that despite a great interest in remote approaches, experience is limited in the EU.

4.1 Implications of the existent and non-existent regulations relevant for RDCTs

4.1.1. Recruitment, enrolment and patient engagement

First, it was important to understand the current status on regulations of CTs, whether and how remote approaches are used to advertise CTs, to recruit and screen participants in CTs, to gather their informed consent. This information can be used to provide the CT participants with all the necessary information on the CT so that they could decide to join or not.

Remote recruitment

It has been shown that the remote recruitment of participants can facilitate recruitment in CTs and benefit people who were previously unable to join (e.g., those that live far from the investigational site). Recent years have seen an increasing interest in remote recruitment. Such capabilities can take the form of telemedicine, where investigators connect remotely but in real time with potential participants.

Remote screening

Home-based screening systems through a smartphone application designed especially for dedicated studies are being used in CTs. An automated transmission in real-time is realised through the study smartphone application to a secured cloud hosting and is then displayed on a web-based dashboard at the investigators' offices for review. When a diagnosis is made through the system, the patients are called back for a formal consultation to confirm the diagnosis before inclusion in the CT.

Remote consenting

The typical ICF is often a long document (more than 20 pages) with complicated information that must be understood by the participant. In this respect and in order to improve the understanding of the CTs for participants, sponsors are moving towards the use of remote consenting with videos to describe the relevant characteristics of the CT. While all involved stakeholders agree that the use of video facilitates the overall understanding of the content of the consent, opinions are still divided with regards to regulatory and legal compliance of electronic signatures. Electronic signatures should be accepted by ECs if they i) ensure that the signatory is able to be identified and ii) are linked to the signed data in such a way that any subsequent changes to the data can be detected.

136 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/804336/RQA_slides_for_MHRA_GCP_StEM.pdf

137 https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19#providing-investigational-medicinal-product-imp-to-trial-participants

Remote education

Education and awareness about CTs have been shown to improve the likelihood of participation[138] and compliance to CTs. In this respect, sponsors are embracing the remote education of CT participants in the knowledge of the importance of educational initiatives to improve CT participation.

Participant outreach

Digital advertising for CTs can help investigational sites to meet their targets. As expected, and in majority of cases, no specific regulations were found for remote recruitment, enrolment and patient engagement when the mapping was conducted. However specific regulations or proposals are available or under public consultation in some countries (see section 3.2.2.1). This is prompted primarily by the COVID-19 pandemic and the need to complete ongoing CTs while avoiding patients visiting hospitals to lower the risk of infection. No matter what local regulations on RDCTs are available, all remote activities for recruitment, enrolment and patient engagement must be reviewed and approved by ECs. Provided they are well justified and detailed, and in line with GCP and existing regulation, remote approaches for CTs should be approved by both ECs and NCAs.

4.1.2 Operations

Laboratories, imaging, patient reported outcome (ePRO), wearables and xxxomics (e.g., genomics, transcriptomics, proteomics and metabolomics).

Some of these technologies, such as ePRO and wearables, are relatively new and, as such, are not yet regulated at the national level. They are, however, being used increasingly more often in global studies. In any event, these newer technologies must all be fit for purpose and allow for the collection, storage processing and reporting of information and data applicable for use in clinical studies.

Home health interactions

This concept is also relatively new and is being practiced more regularly due to the current COVID-19 pandemic. Home health interactions should be adequately described in the consent form so that subjects are aware that this is an integral part of the study. This information should include procedures that will be undertaken by the home nurse (e.g., vital signs, drug administration, blood draws and sample collections).

Direct-to-patient interactions – telemedicine (e.g., video-call or phone call).

Video-calls are another relatively new technology. Data privacy and informed consent adherence are necessary in those countries where this can be adopted.

Direct-to-patient drug supplies and management.

Shipping of IMP directly to patients' homes is for instance not permissible in France but is allowed in Poland. Some of the considerations here include maintaining the stability of the IMP during transport, storage – especially for cold storage IMPs – and the reconciliation of drug or device supplies both during and at end of study.

In those countries where specific regulations do not exist or where it is not clear whether the remote process is allowed, reference can be made, in theory, to any applicable EU guidelines (if they exist). Finally, it may be required to engage with the specific MS on this topic prior to any CTA submission, especially if there is any prior precedence that the MS has not accepted that specific remote element. One potential good practice is to consider mentioning those trial activities that are remote or new in the covering letter to the regulators and ECs. Furthermore, for transparency, the protocol and other related documents should provide sufficient detail about these remote elements to all relevant study

[138] Kenneth Getz, Impact of In-Pharmacy Education on Patients' Knowledge and Attitudes About Clinical Trials, March 14, 2013, Drug Information Journal

personnel (e.g., study staff, investigators and nurses). Information should be appropriately presented and worded; there is a need to avoid excessively lengthy protocol for NCA and EC review.

4.1.3 Data acquisition, processing, archiving, data quality, close out and reporting

There is regulatory concern over whether the systems of electronic data capture meet the requisites of a certified copy that is not under the exclusive control of the sponsor. This requirement arises from the EMA eSource reflection paper: EMA/INS/GCP/454280/2010, "Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials". Notably, the eSource direct data capture (DDC), which was deemed as qualified[139] by the EMA in July 2019, is a platform for the digital capture of CT source data, thus combining source documentation and case report forms into one application. Regulations state that the archiving of eCRF data is the responsibility of the investigator. The current practice of archiving is to make a PDF copy of the data on digital optic discs, such as DVDs or Blu-rays, and then post the disc to the site.

Remote source data verification that provides the sponsor with copies of medical records or remote access to electronic medical records violates trial participants' rights and is not allowed. In addition, requiring the site staff to redact all medical charts would most likely put too much burden on the sites, nor does it enable sufficient verification by monitors. Therefore, this process should not be recommended.

However, there have been some exceptions. For instance, during the COVID-19 pandemic, the Danish government allowed remote source data verification (rSDV) under certain conditions, such as ensuring that the rights of the trial participants are protected and avoiding unnecessary burden on site staff. Furthermore, the remote access to the source data could only take place from a location within the EU/EEA and under secure conditions. The principal investigator and the institution's data officer were also required to assess the necessity for monitors to sign a written confidentiality agreement. The agreement must contain the commitment to securely destroy any documents, whether paper or electronic, as soon as they have been used for SDV. It must also contain the commitment not to make any additional copies of any non-pseudonymised document.

The European Commission supported by EMA also published in March 2020 a guidance (version 3; 28 of April 2020) to allow rSDV to conclude a trial that could facilitate the marketing authorization of COVID-19 and life-saving medicines under the COVID-19 pandemic. The recent EMA guidance on CT management during the pandemic (version 4; 4 February 2021) increased the permission of rSDV to CTs for life-threatening diseases, CTs where the absence of SDV could pose risks to participants' safety or data integrity and CTs with vulnerable participants and pivotal CTs. Additionally, this EMA guidance permits rSDV conducted outside the EEA if the data protection is equivalent to the EU.[140] However, it would be important to establish a permanent guidance on rSDV as the task will be paramount for RDCTs.

4.2 Legal considerations relevant to RDCTs

Overall, and unsurprisingly, the mapping shows that legal rules for CTs are set mainly at the European level. On occasion, national laws and regulations specify or add additional requirements, such as for digital consent to participate in a trial.

Of particular relevance is where CTs intersect with the regulations concerning healthcare. Those relate especially to the following:

[139] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/qualification-opinion-esource-direct-data-capture-ddc_en.pdf
[140] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

- Remote prescription of pharmaceutical products;
- Remote consultation of patients by the physician;
- Home devices and wearables to monitor the patient.

In some countries, these affairs are explicitly regulated; in others, much is left to professional standards. The latter tend to be more flexible, but none explicitly take the situation of CTs into account. Therefore, much is left to interpretation, and there are two schools of thought that are relevant for such interpretation. One considers that anything that is not explicitly regulated is therefore not allowed. The other assumes the opposite, namely that if something is not explicitly regulated, it may be allowed. This latter school of thought is more in line with regulations in a liberal society but clearly provides less certainty and requires a justification of the actors involved in this interpretation. This can only be achieved on a case-by-case basis with inside knowledge of this particular legal system.

Further exploration of legal considerations and challenges to RDCTs should therefore focus more specifically on the EU legal framework and the guidelines and guidance that it incorporates (e.g., ICH-GCP and the EMA). It should explore whether the concepts and rules contained therein still accurately "track" RDCTs. Although this mapping exercise demonstrates that the legal framework still is applicable, certain conceptual definitions and rules may become problematic. These problems can pertain to the conduct of RDCTs themselves but also to the underlying assumptions of these laws and regulations. From a broader perspective, the essence of the regulations regarding CTs seems to be as follows:

- control of the CT in order to get valid, unchallengeable answers to the questions (or endpoints) of the protocol, and
- participant protection.

Some examples of this are listed below:

Recital 44 of the CTR

"The conduct of a clinical trial should be adequately monitored by the sponsor in order to ensure the reliability and robustness of the results. Monitoring may also contribute to subject safety, taking into account the characteristics of the clinical trial and respect for fundamental rights of subjects. When establishing the extent of monitoring, the characteristics of the clinical trial should be taken into account."

Though this amounts to a certain amount of flexibility given the characteristics of the trial, home monitoring must be set in place while at the same time respecting the privacy of the participant.

Clinical trial site

This term is not defined in the CTR but in the ICH-GCP, where it is determined as "the location(s) where trial-related are actually conducted" (1.58). However, this definition certainly seems to encompass the place where the IMP is being administered. Many clauses in both regulations refer to the "site" but are at odds with RDCTs. One example of this is the definition of a multicentre trial in 1.40 ICH-GCP:

> "A clinical trial conducted according to a single protocol but at more than one site, and *therefore* [italics added], carried out by more than one investigator."

In the case of an RDCT, there can be may "sites", meaning homes, but only one PI (in the sense of the CTR). There are many instances where "site" means the place where all trial-related activities are actually conducted. The addition of a site is a substantial modification according to the CTR (Article 15). However, the addition of new participant and hence their home where some of trial

activities will take place cannot be seen as such, nor if a participant were to move homes during the conduct of the trial. Though the original ICH-GCP implied that all sites should be monitored, the addendum to E6 R2 provides more flexibility. A different definition of "site" in the context of RDCTs would be welcome, such as "where trial-related activities are actually coordinated".

Signed informed consent

In both the CTR and ICH-GCP, the consent should be signed. The person who conducts the informed consent discussion should sign as well (ICH-GCP 4.8.8 and article 29.1 CTR). This presupposes both persons being at the same location at the same time. Though this process could also be achieved by tele-discussions and electronic discussions, there is no clear guidance on this. Moreover, not all MSs currently accept an electronic signature in the context of a CT (e.g., see the hesitative change in the law in the Netherlands in section 3.2.2.1).

These and other issues will be investigated further in conjunction with ethical and regulatory requirements in EAGLE (in the context of future tasks and deliverables of WP4).

4.3 Ethical regulations relevant to RDCTs

The mapping of ethical regulations revealed no specific dominant framework for RDCTs. The most important ethical guidance documents for CTs are also applicable in the remote setting. The guidance generally consists of relatively open norms. For example, with regard to informed consent, the Declaration of Helsinki requires that each potential subject should be adequately informed of relevant aspects of the study and that special attention should be given to the specific information needs of individual potential subjects. In site-based trials, these requirements can be met in a face-to-face conversation with the potential subjects. There is, however, neither consensus nor specific guidance available as to how this should be ensured in the context of a RDCT. Therefore, the norms applicable to clinical research generally require greater specification in order to guide ethical practice in RDCTs.

The increased use of (remote) technology and intensified data and sample collection are ethically relevant aspects of RDCTs. With these aspects comes the need for additional guidance of research. In this mapping effort, we found that ethical guidelines have been issued for collections of data and samples and that several recommendations have been made to achieve a harmonised governance framework for the use of big data and digital technologies. In addition, there is a growing body of literature on the ethical governance of digital technologies in health care and research. An analysis of this literature falls outside the scope of this mapping exercise. Overall, it appears that at an aggregate level, a number of themes can be identified. Nonetheless, an abundance of principles and norms are proposed to fulfil the requirements for ethical research in a digital context.[141] These range from the need to adapt current evidence-based standards, to issues of privacy, oversight, accountability and public trust, as well as national and international data governance and management.[142] These themes are also core elements of the ethical regulation of CTs, despite that their place in regulatory documents is not always straightforward.[143] There is, however, a substantial basis on which to explicate and operationalise an ethical framework for RDCTs in the current widely accepted ethical guidance documents for clinical and big data research.

[141] Kalkman S, Mostert M, Gerlinger C, van Delden JJM, van Thiel GJMW. Responsible data sharing in international health research: a systematic review of principles and norms. BMC Medical Ethics 2019;20:21
[142] Vayena E, T Haeusermann, Afua A, Blasimme A. Digital Health: meeting the ethical and policy challenges. : Swiss Med Wkly. 2018;148:w14571
[143] Bernabe RDLC, van Thiel GJMW, Gispen CC, Breekveldt NS, van Delden JJM. The ambivalent place of ethics in European regulatory documents. Drug Discovery Today 2018; 23(2):205-207

4.4 Insights into other initiatives

Some initiatives that are assessing the use of innovative study designs and technologies have been formed. In the United States, the Clinical Trials Transformation Initiative[144] (CTTI), a public-private partnership co-founded by Duke University and the US Food and Drug Administration (FDA) in 2007, includes more than 80 members from across the CT ecosystem. The CTTI's mission is to "develop and drive adoption of practices that will increase the quality and efficiency of clinical trials". They have released some recommendations of interest, namely those pertaining to RDCTs[145] in 2018 and to optimising mobile CTs by engaging patients and sites[146] in 2019. The CTTI is already planning to revisit[147] their initial recommendations on RDCTs based on lessons learnt from the COVID-19 pandemic wherein there has been the need to adapt and move forward with CTs.

Another initiative of interest is TransCelerate,[148] a non-profit organisation that was launched in 2012 to "identify, prioritise, design and facilitate implementation of solutions designed to drive the efficient, effective and high-quality delivery of new medicines". TransCelerate currently includes more than 19 biopharmaceutical organisations. They have not yet issued any specific recommendations on RDCTs.

The clinical research and technology companies of the Association of Clinical Research Organizations (ACRO) have published a white paper with information on designing and conducting DCTs and in 2019 has established a new committee composed of ACRO member company experts, to examine the benefits and challenges of DCTs.[149]

4.5 Recommendations for the conduct of the pan-EU pilot study

Extra considerations: timing and feasibility

Since the Trials@Home pan-EU pilot study is planned to start when the CT directive still applies (i.e., in 2021), some options must be assessed to identify and evaluate the best approach to design and perform the study. For instance, the VHP might still be an option for submission depending on the planned starting date of the pan-EU pilot study and the confirmation of the full functionality of the CTIS. As stated in section 3.1, starting 60 days before the new regulation's effective date, initial clinical trial applications and substantial modifications applications via VHP will no longer be accepted and processed by the VHP administrator.

During the COVID-19 pandemic, Health Authorities have allowed sponsors to use alternative approaches to ensure the continuation of clinical studies that might catalyse the change of regulatory requirements for RDCTs in the long term. The mapping conducted for this Deliverable showed that, at times, regulations at the national level add requirements for specific trial activities.

A wide range of considerations has to be taken into account for country selection. The selection of EU MSs for the pan-EU pilot study will likely be influenced not only by the findings of the mapping of regulations described in this Deliverable but also in terms of CT feasibility related to the trial population, participants' safety and preferences, logistics and available resources for participant support as described in Deliverable 1.2 from WP1 BEST (Best practices in RDCTs).[150]

[144] https://www.ctti-clinicaltrials.org/
[145] https://ctti-clinicaltrials.org/wp-content/uploads/2021/06/CTTI_DCT_Recs.pdf
[146] https://ctti-clinicaltrials.org/wp-content/uploads/2021/06/CTTI_DHT_Engaging_Patients_and_Sites_Recs.pdf
[147] https://ctti-clinicaltrials.org/type/news/ctti-updates-dct-recommendations-in-response-to-covid-19/
[148] https://transceleratebiopharmainc.com/
[149] https://www.acrohealth.org/wp-content/uploads/2020/08/ACRO-White-Paper-FINAL-for-WEBSITE-UPLOAD.pdf
[150] https://trialsathome.com/wp-content/uploads/2020/09/Trials@Home-D1.2-Criteria-for-selection-of-appropriate-trials.pdf

Early interaction with regulators

There is an increasing awareness that regulators need to work more closely with payers in providing joint scientific advice to the innovative pharmaceutical industry.[151,152] The expectation is that improved interactions will benefit society with faster market access to new medicines. From a pharmaceutical industry perspective, there are clear benefits for early-stage consultation with regulators and payers. As regulators want to bring new effective medicines to patients faster, they will probably have no major concerns with increased early-stage interactions with the industry and payers.

The development of new methodologies to run clinical research and development requires all stakeholders' involvement, including the pharmaceutical industry, clinical centres and regulators. The EMA has published scientific articles addressing early interaction aspects to improve the generation of evidence and accelerate the approval process. The Agency has also released an updated version of the Q&A document "Qualification of digital technology-based methodologies to support approval of medicinal products".[153]

New technologies play a crucial role in generating real-world-data and the continuous monitoring of physiological parameters. The support of development of reliable digital devices provides an adequate data quality level to meet regulatory needs. These devices can be classified under the regulatory point of view as medical devices or medicinal products depending on their primary mode of action (alone or in combination with a medicine).

It is expected that the pan-EU pilot study of the Trials@Home consortium will start at the beginning of 2022. Therefore, the consortium is working on the interaction with the EMA's Innovation Task Force (ITF). The ITF is a multidisciplinary group with scientific, regulatory and legal competences.[154] The ITF was set up to ensure coordination across the Agency and provide a forum for early dialogue with applicants on innovative medicine development aspects. The interaction between the consortium and the ITF aims to explore the regulatory expectations of data collected in different settings and review the planned design for the pan-EU pilot study.

5. Conclusion

Remote decentralized clinical trials allow the monitoring of participants' directly from their home during each CT stage. Technology (apps and monitoring devices) and web-based platforms are the cornerstones of these CTs. They improve participant recruitment, the convenience of participants and adherence to CTs. Despite these advantages, they suffer various challenges: i) data privacy with the transfer of extensive sensitive data via internet ii) data integrity, accuracy and reliability iii) regulatory acceptance.

The COVID-19 pandemic has forced the clinical research community to re-evaluate how to manage CTs. During this period, Health Authorities have allowed sponsors to use alternative methods to ensure the continuation of clinical studies.[155] This flexibility paved the way for decentralized clinical

[151] Frønsdal KB, Pichler F, Mardhani-Bayne L, et al. Interaction initiatives between regulatory, health technology assessment and coverage bodies, and industry. Int J Technol Assess Health Care 2012;28(4):374-814)

[152] Wonder M. What can be gained from increased early-stage interaction between regulators, payers and the pharmaceutical industry? Expert Rev Pharmacoecon Outcomes Res. 2014 Aug;14(4):465-7. doi: 10.1586/14737167.2014.917966. Epub 2014 May 12. PMID: 24820934.

[153] https://www.ema.europa.eu/en/documents/other/questions-answers-qualification-digital-technology-based-methodologies-support-approval-medicinal_en.pdf

[154] https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines#ema's-innovation-task-force-(itf)-section

[155] de Jong A.J.; Santa-Ana-Tellez Y.; van Thiel G.J.M.W.; Zuidgeest M. G.P.; Siiskonen S.J.; Mistry D.; de Boer A.; Gardarsdottir H.

trial methods such as remote consent, direct to patient, direct to patient IMP supply, and home health visits and started defining the "new normal" in the CT area. Although some remote activities have been used in regular healthcare, such as telemedicine and home health visits in the absence of regulatory guidance surrounding decentralized trials, concerns remain around the use of remote technology in CTs.

Regulators should consider these risks and benefits to improve the content of guidance for the conduct of CTs and RDCTs.

In the EU mapping, we found regulations at the national level for some remote trial activities in few countries. This type of regulation or guidance might already exist in the form of SOPs, policies or codes of conduct. Whilst compulsory to adhere to, these rules are much harder to monitor and enforce and might have high variability from site to site and country to country. We recommend minimal requirements to be incorporated in the regulations to ensure participants' safety and robustness of CT results. Some of the essential requirements that should be considered include the participants' consent for the provision of remote trial activities paired with a requirement to provide an overview of what the participant can foresee from CT conducted remotely. It is crucial to ensure that any trial activity is appropriate for participants' safety and that sufficient information on the participant's medical record is available, which protects data confidentiality and guaranteeing security during the exchange of information.

Even though decentralized clinical trial activities have been commonly conducted in some countries included in the EU mapping, the relevant regulations are still evolving.

6. Repository for primary data

The source information, an Excel-file containing detailed information on the mapping, is available upon request or in the following link: Mapping of regulations

COVID-19 and the Emerging Regulatory Guidance for Ongoing Clinical Trials in the European Union. Clin. Pharmacol. Ther. Epub 2021 February