Remote Monitoring Technologies and Pandemic Preparedness - Regulatory Hurdles and Opportunities

Report

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Dutch summary

De COVID-19 pandemie heeft de noodzaak onderstreept om vanuit verschillende expertises en mogelijkheden te werken aan een versterkte pandemische paraatheid. De unieke eigenschappen van remote monitoring technologieën (zoals om op afstand en met precisie grote hoeveelheden data te verzamelen) bieden aanknopingspunten voor de inzet van RMTs tijdens toekomstige pandemieën. Voor de bredere inzetbaarheid van RMTs tijdens zowel non-pandemische als de pandemische periodes is regulatoire acceptatie langs de gehele RMT keten essentieel. Ondanks de potentie van RMTs is het huidige regulatoire RMT-landschap uitgebreid en op punten complex, wat een hindernis kan zijn om RMTs snel te implementeren. Inzicht in de knelpunten die de inzet vertragen of verhinderen, mogelijke oplossingen voor die knelpunten, en het delen van deze kennis met de juiste stakeholders dragen bij aan het ontwikkelen van een regulatoir systeem dat beter voorbereid is op een volgende pandemie.

In dit rapport hebben we onderzoek gedaan naar welke regulatoire en juridische knelpunten en kansen bestaan bij de toepassing van RMTs, met name voor het nemen van klinische beslissingen (clinical decision making) of regulatoire beslissingen (regulatory decision making). De *scope* van ons project is het Nederlandse veld, maar de internationale context is ook van belang vanwege Europese wet- en regelgeving en het internationale karakter van pandemieën. Dit hebben we gedaan door een mix van onderzoeksstrategieën toe te passen. We hebben onderzocht welke organisaties in Nederland, Europa en op globaal niveau belangrijke beslissingen nemen over de bestrijding van een pandemie. Ook hebben we onderzocht hoe de toelating van RMTs loopt, en welke organen een rol kunnen spelen bij versnelde toelating en gebruik van RMTs. Waar relevant hebben we andere aspecten die relevant zijn voor klinisch onderzoek (zoals ethiek en privacy) meegenomen. Daarnaast hebben we meerdere literatuurstudies uitgevoerd die ingaan op specifieke regulatoire aspecten van RMTs. Om specifiek meer inzicht te krijgen in de inzet van RMTs om regulatory decision making voor medicijnontwikkeling te ondersteunen hebben we de verschillende Qualification Advices, Qualification Opinions en Scientific Advices van de European Medicines Agency onderzocht. Om inzicht te krijgen in het inzetten van RMTs om klinische besluitvorming te ondersteunen hebben we een literatuurstudie uitgevoerd naar hoe RMTs ingezet zijn tijdens de COVID-19 pandemie. Ons onderzoek hebben we aangevuld met verschillende interviews met stakeholders uit het veld. De geinterviewde stakeholders omvatten verschillende regulators (CCMO, EMA), een expert op het gebied van beoordeling van medical devices, onderzoekers, een RMT ontwikkelaar en een groot farmaceutisch bedrijf. Tot slot hebben we een aantal overkoepelende bevindingen voorgelegd en bediscussieerd met een expert panel. De resultaten van het rapport hebben geleid tot een aantal aanbevelingen:

1) Bij het opstellen van pandemic preparedness en pandemic response plannen de relevante governance structuren mee te nemen in de strategie, en verantwoordelijkheden en mandaten van tevoren af te stemmen; 2) Een Ethics Advisory Board op te stellen dat in tijden van een pandemie de complexe besluitvorming kan ondersteunen, zowel nationaal als internationaal; 3) Verder te verkennen of er een platform kan worden opgezet (wellicht onder EUDAMED) om snel inzicht te kunnen geven in mogelijk beschikbare RMTs die vervolgens tijdens een pandemie ingezet kunnen worden; 4) de verschillende vrijstellingen die in dit rapport genoemd worden verder te onderzoeken voor hun toepaspaarheid tijdens een pandemie; 5) de activiteiten rondom het versnellen en verbeteren van klinische trials op de voet te volgen; 6) (specifiek voor innovators) om zo vroeg mogelijk tijdens de ontwikkeling van nieuwe technologiëen of therapieën de regulatoire paden mee te nemen, en een strategie daarvoor te ontwikkelen, en onderzoeksprotocollen te ontwikkelen die lijn zijn met latere regulatoire vereisten 7) verder te onderzoeken of er onder de CTR mogelijkheden zijn om relevante clinical trial applications te fast-tracken ten tijden van een gezondheidscrisis of pandemie; 8) verder uit te zoeken hoe verschillende medical devices en in vitro diagnostic devices (inclusief software) geëvalueerd worden onder de MDR en IVDR, waar de complexiteit van de nieuwe wetgeving voor problemen zorgt, en te onderzoeken of de wetgeving in sommige gevallen wat minder stringent kan; 9) verder uit te zoeken of RMTs die gevalideerd zijn voor een specifieke parameter voor een specifieke ziekte, ingezet kunnen worden om dezelfde parameter te meten in andere ziektes; 10) te investeren in educatie over regulatoire onderwerpen; 11) verder uit te werken of een platform, groep of systeem opgezet kan worden waar innovators in gesprek kunnen gaan met regulators, en specifieke feedback op hun technologieën kunnen krijgen, vergelijkbaar met de ITF, SA of QA procedures bij de EMA; 12) (specifiek voor RMT gebruik in medicijnontwikkeling) om op tijd met de EMA contact te zoeken via de passende procedures, en de relevante documentatie en geleerde lessen

beschreven in D3, D4, D5 en D7 mee te nemen; 13) (specifiek voor beleidsmakers) te onderzoeken hoe de aanwezigheid van de EMA verder benut kan worden om het regulatoire ecosysteem te versterken, en vroege engagement tijdens ontwikkeling gestimuleerd kan worden; 14) (specifiek voor RMT gebruik in medicijnontwikkeling) om zorg te dragen dat het gebruik van RMTs voldoende onderbouwd is en een data management plan beschikbaar is; 15) wanneer er klinische trials met gedecentraliseerde elementen opgezet worden (wat nuttig kan zijn voor of tijdens een pandemie) om van te voren goed de verschillende procedures, guidelines, en verantwoordelijkheden door te lopen en af te stemmen; 16) onderzoeken of verdere harmonisatie tussen EU lidstaten mogelijk is op het gebied van implementatie en uitvoering van wetgeving om klinische studies in verschillende landen makkelijker te maken; 17) te onderzoeken of er verdere harmonisatie mogelijk is tussen de verschillende "checkpoints" die relevant zijn voor medicijnontwikkeling met RMTs of RMT ontwikkeling op zichzelf 18) dat niet alleen de regulators, maar ook innovators (zoals farmaceutische bedrijven) streven naar dezelfde standaarden. Andere overwegingen die we in het rapport kort benoemen hebben te maken met ethische en privacy overwegingen, kostenoverwegingen, de druk op het zorgsysteem tijdens een pandemie, en inclusiviteit.

Dit rapport verschaft inzicht in de verschillende regulatoire knelpunten die inzet van RMTs belemmeren. Daarnaast dragen we een aantal opties aan om deze belemmeringen op te heffen of te verminderen. De aanbevelingen vormen een basis om verder te bouwen aan een regulatoir systeem wat bijdraagt aan een verbeterde pandemische paraatheid.

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1. INTRODUCTION

The past decade has been marked by significant technological developments in artificial intelligence, machine learning, sensors, processors, batteries, data storage and data infrastructures, and displays. This has resulted in various technologies that are easy to carry or wear, can collect data via various sensors, in a continuously and sensitive manner in different environments, store it for a prolonged amount of time, analyse these datasets and use machine learning to develop "smart" algorithms based on these data (Hee Lee & Yoon, 2021). These technologies have found their way into our daily lives via smartphones, wearables, and other consumer devices. Because of their interesting properties, these novel technologies are also increasingly being investigated for their potential to improve clinical trials (eg. trials set up to investigate the safety and efficacy of novel or repurposed medicinal products or therapies) and health care. One key property of these technologies is that they allow for "remote" collection and monitoring of data. In this report, the term Remote Monitoring Technology (RMT) is used here to refer to the combination of devices, including wearables or portable home health monitors, with information technology solutions (incl. software) that allow health data to be communicated to a healthcare provider or researcher without in-person contact (Majumder et al., 2017).

In the context of clinical trials and health care, these technologies greatly facilitate the collection of objective, sensitive, continuous measures of relevant symptoms, while patients are at home or during their day-to-day life, also referred to as "remote monitoring" (Clinical Trials Transformation Directive, 2017). These properties of relevance because hospital-based assessments can deviate considerably from daily living assessments (Warmerdam et al., 2020). In addition, during in-person visits to the hospital, it remains difficult to reliably ascertain complex fluctuating events (such as cardiac electrocardiographic events (Sana et al., 2020) Duncker et al., 2021)), rare events (such as falls in the context of Parkinson)(Silva de Lima 2020), events depending on patient recall (such as in depression) (Matcham, Barattieri Di San Pietro, et al., 2019)or gradually developing events (such as a slowly progressive decline in physical activities, or disease progression itself (Bloem et al., 2021).

Opportunities of remote monitoring technologies include developing more sensitive and meaningful outcomes, reducing patient- and carer burden during clinical trials, reducing costs, speeding up and improving clinical trials, facilitating inclusivity and recruitment, allowing for developments in areas of unmet medical need and for care to be provided in a different and more efficient way (Alboksmaty et al., 2022; de Jong et al., 2022; Muurling et al., 2021a; van Rijssel et al., 2022a). Because of their potential to transform clinical trials and clinical care, remote monitoring technologies are investigated and validated across a wide spectrum of diseases (Brem et al., 2023; European Medicines Agency, 2019; Viceconti et al., 2020).

Taking all these opportunities into consideration, it is not surprising that there is interest to explore the potential of RMTs to better prepare ourselves for a potential future pandemic. Even before COVID-19 emerged, it has been acknowledged that the world was not optimally prepared for a pandemic (Forman & Mossialos, 2021) Considerable efforts are undertaken in various research fields to better prepare for the next pandemic, ranging from understanding the epidemiology of COVID-19, to analysing pandemic response efforts, to investigating where the next potential pandemic pathogen will come from (Pollard et al., 2020) (Looi, 2023). Even though we can make educated guesses about the next pandemic threat, one can never be 100% sure about the next pandemic pathogen until it emerges and can be analysed, which in a way complicates our pandemic preparedness and responsiveness. Luckily, there is a lot that we *can* do to optimally prepare for a future pandemic. Innovative technologies can be leveraged and implemented, regulatory frameworks can be mapped out and improved, responsibilities can be aligned upon upfront, and we can build on lessons learned from our response to COVID-19.

Responses to pandemics are not only nationally but also internationally coordinated, contributing to complexity. The regulatory landscape around RMTs is complex and rather fragmented, causing hurdles for rapid acceptance, implementation, and use on large scale, as adoption and implementation of innovative technologies such as RMTs are – with good reason - highly dependent on the regulatory acceptance of these technologies (Contardi, 2019; de Jong et al., 2022; Dekker et al., 2021a). This hinders RMT application during normal, non-pandemic situations, and rapid implementation during potential future pandemics. The next pandemic will most likely be caused by a currently unknown pathogen. Understanding the regulatory

framework around RMTs, and gaining insight into the hurdles that slow down or prevent the implementation, can help to identify solutions to overcome these hurdles. In addition, insight into exemptions that could accelerate the use of RMTs that are adequate for the next pandemic could help to identify solutions to shorten the regular timelines for research and assessment of new technologies and devices, and potential supply shortages. Evaluating the lessons learned from COVID-19 can also help to identify potential solutions that can help implement RMTs to improve our pandemic preparedness. Sharing this knowledge with the relevant stakeholders also helps to facilitate the implementation of RMTs. Overall, this should contribute to the development of a regulatory system that is better prepared to implement novel technologies, particularly in a future pandemic.

1.1. Aim and scope

In this report, we summarize the findings of our research project, that investigated the regulatory hurdles, solutions, exemptions and opportunities for RMTs to support regulatory decision making, and monitoring diseases in a clinical setting to inform clinical decision making, particularly in the context of a pandemic.

As this is a very broad topic that can be approached from different angles and with different levels of detail, it is important to mention the scope of our work:

1) We focus on the Dutch ecosystem. However, due to increasing legal and regulatory harmonisation across EU member states, EU centers and structures for pandemic preparedness, the role and tasks of the WHO and the global impact of pandemics, and the international nature of clinical research and innovation, international laws and regulations are also of relevance and discussed where applicable.
2) We have focussed on the potential of RMTs in the context of regulatory decision making and clinical decision making. Monitoring using RMTs with the primary and only intention to monitor spread of a pandemic pathogen ("surveillance") or more general health monitoring is outside of the scope of our work (figure 1).
3) We use the term pre-pandemic as the phase in which no pandemic pathogen is affecting global health. The term pandemic is used to describe an epidemic occurring on a scale that crosses international boundaries, usually affecting people on a worldwide scale. This is quite close to the WHO definition of a Public Health Emergency of International Concern ("an extraordinary event which is determined to constitute a public health risk to other States through the international spread of disease and to potentially require a coordinated international response") (*WHO Webpage: Emergencies: International Health Regulations and Emergency Committees*, 2019) and is aligned with the structure and definitions of the infectious disease classifications in the Wet Publieke Gezondheidszorg. The transition between a pre-pandemic phase and the pandemic phase can be marked by an epidemic phase, in which a pathogen is spreading locally, but not (yet) affecting global health (World Health Organization., 2018)
4) We use the term regulatory to describe the processes, organisations, bodies and institutions that are tasked with checking and controlling whether others adhere to applicable rules, regulations and laws. We focus on the most essential processes, organisations and bodies.
5) We focus on pandemic pathogens in humans.

For the sake of clarity and as is customary in legal reports, refences in the legal parts of this document are added in footnotes. As is customary in scientific publications in the biomedical field, references in those sections are added in the [name, year] format and listed in a bibliography at the end of this report.

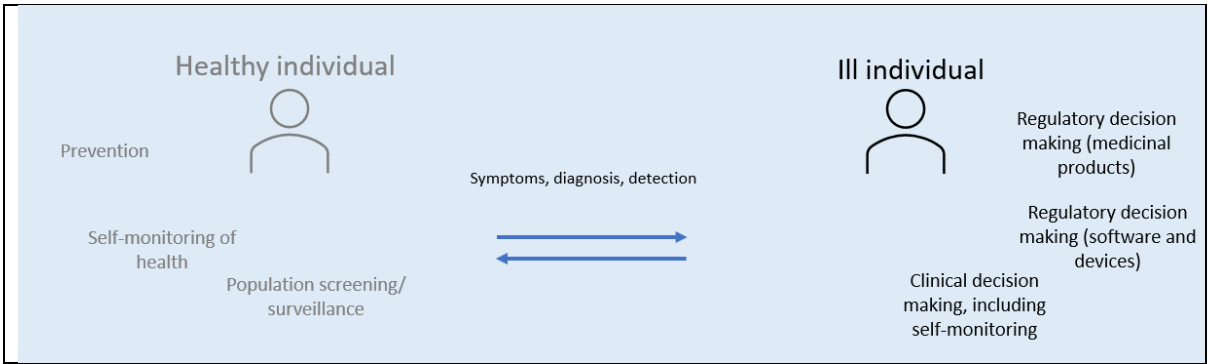

Figure 1: "Monitoring" is a very broad term that can be used to describe different activities. The intended use and context of use of a remote monitoring technology determine the regulatory topics that are of relevance. In our report, we focus on use of RMTs to measure symptoms, to perform diagnoses or to detect pathogens and on regulatory and clinical decision making facilitated by or needed for RMTs.

1.2. Materials, Methods and deliverables

To come to a useful overview of hurdles and opportunities for the regulatory framework surrounding RMTs, to draw lessons learned from the COVID-19 pandemic, and to come to suggestions that can be of use in a future pandemic, we combined a number of approaches:

1) In D1/2, we mapped out the legislative framework that is relevant for the organisation and decision making in a pandemic, and for the evaluation of remote monitoring technologies, and, where applicable, reflected on the COVID-19 pandemic. To this end we analysed the governance- and legislative structures applicable to the (pre)pandemic phase on national, European and international level, legislation and standards related to RMTs in general, guidelines and differences between traditional trials and decentralized trials, and privacy and ethical aspects of RMT.
2) In D3, we report on 4 interviews that we executed with different stakeholders in the field of RMTs and drug development/clinical research: One with a large innovator in the pharmaceutical field, one with a small/medium-sized enterprise (SME) that develops digital biomarkers, one with a consultant with extensive hands-on experience with the Medical Device Regulation (MDR) and In Vitro Diagnostic Regulation (IVDR), and one interview with the European Medicines Agency (EMA), the regulatory body that evaluates and monitors medicinal products within the European Union (EU) and the European Economic Area (EEA).
3) In D4, we evaluated the publications from the Trials@Home project, which investigates hurdles and opportunities (including regulatory ones) of decentralised clinical trials, which have a strong RMT component and applicability in potential future pandemics.
4) In D5, we evaluated the publications and deliverable reports from the RADAR-AD project. This project focusses on RMTs in the context of novel outcome measures, and contained a multi-centre, multi-country clinical trial using RMTs.
5) To further substantiate our literature studies from D4 and D5, in D6 we performed interviews with investigators involved in Trials@Home and RADAR-AD. Since review and approval of clinical study protocols make up such an important milestone in research and involve a regulatory step as well, we supplemented our interviews with and interview with The Central Committee on Research involving Human Subjects (CCMO), the Dutch governmental organization that assesses if a clinical trial is law abiding.
6) In D7, we specifically evaluated the Scientific Advices (SAs), Qualification Opinions (QOs), and Qualification Advices (QAs) issued by the Committee of Human Medicinal Products (CHMP) from the EMA. This gives insight in the types of questions that are asked by applicants of these procedures, insight on technologies, diseases and endpoints of frequent interest, and insight in the current position of the EMA in RMTs to support regulatory decision making.
7) In D8 we searched the clinicaltrials.gov website to get a better understanding of whether and how RMTs are being implemented to gather extra data during phase 4 studies in the EU.
8) In D9 we report on an expert meeting, in which we discussed our key findings with experts from the field.
9) D10 has been assimilated into D1/2
10) In D11 we investigated how Remote Monitoring has been used to for at home patient monitoring to inform clinical decision making during COVID-19, and whether any regulatory hurdles and opportunities have been mentioned in those studies.

Sometimes, deliverable reports contain cross-references to other reports, as the topics and findings intersect. In the next chapters, we will describe the key findings from these reports, place them in a larger context and work towards a general set of hurdles and opportunities.

2. RESULTS

2.1. Results of Deliverable 1 and Deliverable 2: Analysis of the legal frameworks supporting pandemic preparedness and remote monitoring technology evaluation

Key players involved in responses to pandemics

A coordinated response to a pandemic is complex. Different key players have different tasks, responsibilities and mandates. The COVID-19 pandemic has revealed weaknesses in policies and strategies concerning responses to pandemics, which – amongst other factors- caused the EU to struggle to adequately respond to the pandemic (Forman & Mossialos, 2021). To gain insight into the governmental interplay involved in pandemic responses, we mapped out the key players and their roles involved in a national pandemic response, which is shown in figure 2. In the Netherlands, the chairmen of the safety regions and the National Institute for Public Health and Environment (RIVM), on behalf of the Ministry of Health, Welfare and Sport (Ministry of VWS) are part of the governance structure on a national level. A cluster of so-called reference laboratories in the Netherlands forms a diagnostic network that plays an important role in the identification of pathogens and novel strains, scientific advice, collaboration and research, surveillance and outbreak management. On an EU level, in response to COVID-19, a new authority has been established to help strengthen the EU's ability to prevent, detect, and rapidly respond to cross-border health emergencies, called HERA (the Health Emergency Preparedness and Response Authority). The role of the EMA in potential future health crises has been strengthened, with the aim to fortify the EU's pandemic preparedness. [1] The European Centre for Disease Prevention and Control (ECDC) is a key player as well. In a global context, the World Health Organisation is an important player. Article 49 of the International Health Regulations (IHR) establishes the procedure for determining whether a situation is a public health emergency of international concern.

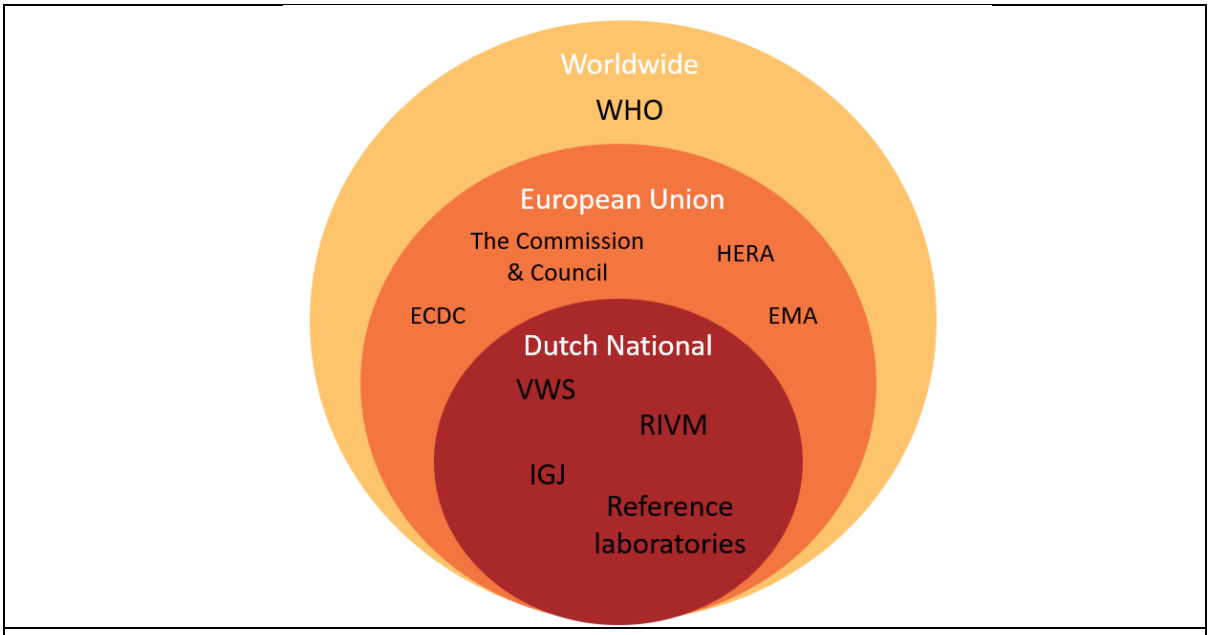

Figure 2: Different key players are involved in responses to pandemics

The legal framework around RMTs

The regulatory framework around RMTs is fragmented and takes place across multiple levels, adding to its complexity. Depending on its exact application, products may circle around borderline criteria for consumer

[1] Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices.

products, medicinal products, medical devices and in vitro diagnostics. The regulatory pathways for putting these different products on the market differ significantly, adding to complexity.

In some cases (studies investigating medicinal products), studies with RMTs will have to follow the Clinical Trial Regulation (CTR). On 31 January 2022, the Regulation repealed the Clinical Trials Directive (EC) No. 2001/20/EC and national implementing legislation in the EU Member States, which regulated clinical trials in the EU until the Regulation's entry into application. In the operational execution of the Regulation, significant differences have been implemented with the goal to improve harmonisation in the execution of clinical trials across the EU. One of these is the introduction of the Clinical Trials Information System (CTIS). Clinical trial sponsors can use CTIS to apply for authorisation to run a clinical trial in up to 30 EEA countries via a single online application. Studies testing MDs that falling in a high-risk category will have to be tested in a clinical study, but currently do not have to follow the CTR.

As explained in more detail in D1/2, an RMT often consists of a combination of the elements software and device. Depending on the purpose and context in which this RMT is used, the different elements of the RMT will have to follow the Medical Device Regulation (MDR), In Vitro Diagnostic Regulation (IVDR), or the or the General Product Safety Regulation. The MDR[2] came into force on May 26, 2021, and the IVDR[3] on May 26, 2022. It should be noted hence that the legislation regulating medical devices during COVID-19 differs significantly from the legislation that is applicable now. The MDR and IVDR are the successors of the Medical Device Directive (MDD) and In Vitro Diagnostics Directive (IVDD), and were introduced with the aim to fill gaps that emerged due to novel innovations (such as RMTs), harmonise interpretation across Member States, and simplify the regulatory framework (Contardi, 2019). The revisions of the Directives and their transition to Regulations have resulted in thorough changes in the regulatory framework around RMTs. This sometimes poses a problem to innovators. On the other hand, the MDR and IVDR contain exemptions for public health crises, which can be useful in the case of a pandemic. Exploring the full implications of the transition from MDD to MDR and from IVDD to IVDR is beyond the scope of this project. The essential elements in the context of this report of the MDR and the IVDR are explained into more detail in D1/D2.

The requirements for devices before they may be put on the market or into service with the required CE mark depend on their risk class. Classification of MDs and IVDs happens happens according to a risk-based system, taking into account the vulnerability of the human body and the potential risks associated with the devices. The classification is being determined on a set of criteria (MDCG 2021-24).

For a MD the risk classes are:
Class I: Low risk – self-assessment
Class IIa: low to moderate risk – Notified body assessment required
Class IIb: moderate to high risk – Notified body assessment required
Class III.[4] High risk – Notified body assessment required

The general classification for IVD are:[5]
Class A: low individual and low public health risk
Class B: moderate individual and/or low public health risk
Class C: high individual and/or moderate public health risk

[2] 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.

[3] Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU.

[4] Classification is to be carried out in accordance with Annex VIII to the MDR. In addition, and according to Article 52(7)(a), (b) and (c), Class I devices can be further subdivided into Is – sterile condition, Im – measuring function and Ir – reusable surgical.

[5] For IVDR the corresponding references are Article 47 and Annex VIII.

Class D: high individual and high public health risk.

RMTs will most likely be classified as IIa and IIb (for an MD) and/or class C and D (for an IVD) during a pandemic, depending on the infectious disease[6].

All devices must, for putting on the market or into service, comply with all relevant obligations, such as:
- meet the general safety and performance requirements, including the requirements regarding the information to be supplied by the manufacturer.
- be subject to the reporting requirements under the medical device vigilance system;
- be CE marked (except custom-made devices and devices intended for clinical investigation);
- be assigned a Unique Device Identifier (UDI) number and be registered in the electronic system.

To support the implementation of both the MDR and the IVDR, facilitate adherence to all rules and regulations, and improve transparency and coordination of information regarding medical devices available on the EU market, EUDAMED, a special European IT system was developed. This is a multipurpose system, and aimed to function as a registration system, a collaboration system, and a dissemination system (partially open to the public). EUDAMED is instituted to improve transparency and coordination of information regarding medical devices available on the EU market. It consists of six modules: actor registration, unique device identification (UDI) and device registration, notified bodies and certificates, clinical investigations and performance studies, vigilance and market.[7] EUDAMED will be released in the fourth quarter of 2024.[8]

Although EUDAMED is not fully operational yet, it will be used as a central data base, providing information on:

1) available devices on the EU market, their intended use, economic actors involved
2) important post market surveillance data

In terms of regulatory processes around RMTs before they are placed on the market, each EU Member State has its own Competent Authority (IGJ in the Netherlands) which acts to ensure that the requirements of the medical device regulations are adequately implemented into national law of that member state. They also appoint and supervise the notified bodies (NBs). NB assess, at the request of a manufacturer, whether the manufacturers claim that the device meets the general safety and performance requirements is correct. The positive outcome of this assessment forms the basis of the CE marking. NBs are private organisations, however their authority and associated tasks are based on the respective regulations (Contardi, 2019). An up-to-date list with NBs can be found in the NANDO Information System (*NANDO Information System*, n.d.).

Procurement of RMTs for future pandemics and during a pandemic
The application of RMTs on a larger scale leads to the question on the status of the purchaser of these devices. Procurement of test-related services and safety materials has been a tremendous challenge during the COVID-19 pandemic (Hartendorp et al., 2021). A similar situation could occur if RMTs are broadly applied to monitor patients during a pandemic, and the RMT supply chain is being led through a national public body, which might be the only option in a tense market during a pandemic. Procurement of RMTs in advance, before the next pandemic hits, is tricky, as the characteristics and quantities needed will differ depending on the situation and pandemic pathogen. HERA, WHO and/or EMA might play a role in purchasing products needed in the

[6] Annex VIII: 2.4. Rule 4
Devices intended for self-testing are classified as class C, except for devices for the detection of pregnancy, for fertility testing and for determining cholesterol level, and devices for the detection of glucose, erythrocytes, leucocytes and bacteria in urine, which are classified as class B.
(b) Devices intended for near-patient testing are classified in their own right.
[7] The obligations to register can be found in Articles 29 and Article 31. Article 31 requires economic operators (Manufacturers, Authorised Representatives and Importers) to register to obtain a Single Registration Number or "SRN". Article 29 requires manufacturers to upload information about each device, including its UDI information.
[8] md_eudamed_timeline_en.pdf (europa.eu)

pandemic phase. Furthermore, some parts of the RMT chain might be already used by a significant part of the population (consumer products such as watches, apps etc). When connected with medical software (including apps), which will be classified as software as a medical device, these devices might be an interesting element of the RMT dataflow. The question is whether these devices when used for monitoring in the context of a trial would be acceptable for MRECs . When data is collected to support regulatory decision making, it is essential to engage with the EMA early on to check if they would accept the collected data to support decision on market authorisation applications (MAAs).

Potential tools for rapid access to suitable RMTs on a national scale, EU scale, and limited scale
It is important to stress that all pre-market and post market authorisation procedures and obligations are meant to constantly monitor the benefit/risk performance of a MD and an IVD.

On a national level, it is possible for IGJ to facilitate an exemption for the affixation of a CE-mark for a specific term.[9] This approach could be further investigated for its applicability a future pandemic.

On an EU level, there are exemption rules in the MDR and IVDR. Both the MDR and IVDR explicitly foresee in an exemption related to the conformity assessment procedures if the use of the product is in the interest of public health or patient safety or health.[10]

Any deviation in the form of an exemption as regulated under the MDR and IVDR could have an impact on the quality of the product and potentially on the health of the user, which should be thoroughly considered and if possible, outweighed against the benefit for governance and pandemic policy in terms of public interest and individual risk. This process has to be monitored, as any stage of the pandemic might result in a different outcome. An Ethics Advisory Board ("EAB") on both national and international level would support adequate consideration in this complex decision making, where different interests will have to be balanced.

Moreover, a competent authority (e.g. IGJ) may, by way of derogation,[11] authorise placing on the market or putting into service of a specific device for which the procedures referred to in the relevant articles of the MDR and IVDR have not been carried out, but of which the use is in the interest of public health or patient safety or health.[12] Although NBs does not have the authority to initiate or authorize exemptions of the premarket obligations (including affixing of CE marking), they may be important stakeholders in the exemption decision making.

Another "exemption" is the confirmation of a non-compliance status of a device at the request of a manufacturer.[13] This decision can have an interaction on European level as the Commission may, following this notification in exceptional cases relating to public health or patient safety or health, extend for a limited period of time the validity of an authorisation granted by a Member State into the territory of the Union and set the conditions under which the device may be placed on the market or put into service.[14]

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[9] 'Geen uitzondering meer voor levering professionele mondkapjes en handschoenen aan de zorg zonder CE-markering' 30 September 2021 <https://www.igj.nl/actueel/nieuws/2021/09/30/geen-uitzondering-meer-voor-levering-professionele-mondkapjes-en-handschoenen-aan-de-zorg-zonder-ce-markering>; 'Medische hulpmiddelen vanaf 1 september weer alleen met CE-markering toegestaan' 21 October 2020 <https://www.igj.nl/actueel/nieuws/2020/08/11/medische-hulpmiddelen-vanaf-1-september-weer-alleen-met-ce-markering-toegestaan>

[10] art. 59 MDR, art. 54 IVDR.

[11] From Article 52 MDR

[12] art. 59 MDR and. 54 IVDR

[13] This procedure might be relevant in the context of required exemptions as where a Competent Authority has applied this procedure [Article 97 MDR] with the effect that the device may be placed on the market despite its non-compliance, no additional derogation pursuant to Article 59 MDR, an exemption requested by the manufacturer is necessary. MDCG 2022-18

[14] Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 107(3)). However on duly justified imperative grounds of urgency relating to the health and safety of humans, the Commission shall adopt immediately applicable implementing acts (in accordance with the procedure referred to in Article 107(4)).

Several possible options may be created for exemptions on a limited scale as needed, as for example small national clinical trials.

In-house/custom-made devices: This exemption is general and might be relevant for the use of RMTs during a pandemic. MDs can be manufactured and used within EU health institutions, on a non-industrial scale, to address the specific needs of target patient groups which cannot be met or cannot be met at the appropriate level of performance, by an equivalent CE-marked device available on the market. In-house medical devices are exempted from most of the provisions of the MD and IVD Regulations,[15] provided the health institution adheres to certain conditions to ensure the highest level of health protection [16] . A European MDCG Guidance on in-house devices in the interest of public health or a public health crisis would significantly support a rapid development of RMT, especially in the early phases of a pandemic for either DCTs and/or monitoring symptoms of the infectious disease.[17]

"Off-label" use of MD and IVD: Off-label is a well-known term and option in the field of medicinal products. It entails that a medicinal product is prescribed for a different purpose than what the EMA or FDA approved it for. Off-label use is only possible when protocols and legislation are strictly followed.[18] A similar context of "off-label" use of MD and IVD might be an option for use in the event of shortages or absence of adequate devices during a pandemic period. This would entail that a device is used outside of its approved instructions for use, including indications. Off-label use of medical devices could form the solution during a pandemic when no adequate equivalent devices are on the market. It is recommended to prepare guidelines to ensure balanced application of this non-regulated option.

Research only: This exemption seems to only apply to the MD and IVD for which the trial has been set up to investigate the safety and performance of that specific device.[19]

Compassionate use: Member States may facilitate compassionate use of a medicinal product under specific conditions.[20] A similar mechanism exists in the USA, where the FDA has expanded access programmes for medical devices. In the EU, there is no related mechanism for medical devices. However, medical device compassionate use programs may be coordinated and implemented by EU Member States according to national rules and legislation. It is recommended to develop guidelines for compassionate use and expanded access during a pandemic.

[15] 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; Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU.

[16] Laid out in Article 5(5) of the relevant Regulation and: zie Paper over wanneer dat mag (in house devices)

[17] 'custom-made device' means any device specifically made in accordance with a written prescription of any person authorised by national law by virtue of that person's professional qualifications which gives, under that person's responsibility, specific design characteristics, and is intended for the sole use of a particular patient exclusively to meet their individual conditions and needs, Art. 2(3) MDR.

[18] Art. 68 Geneesmiddelenwet; see also for the respective professional standards:
'Off-label voorschrijven' (Statement, 13 January 2018) <https://www.igj.nl/publicaties/standpunten/2018/01/13/off-label-voorschrijven>; 'Off-label voorschrijven' (Dossier, 10 June 2020) <https://www.knmg.nl/advies-richtlijnen/dossiers/off-label-voorschrijven>

[19] Investigational device is defined under art. 1(46) MDR as "a device that is assessed in a clinical investigation." investigational devices are exempted from the obligations to bear the CE marking of conformity (art. 20(1) MDR). Art. 52(3) MDR holds more exemptions for specific classes of devices and exemptions for investigational devices.

[20] Art. 83 Regulation 726/2004: 1. By way of exemption from Article 6 of Directive 2001/83/EC Member States may make a medicinal product for human use belonging to the categories referred to in Article 3(1) and (2) of this Regulation available for compassionate use. Art. 3(1) verwijst naar Annex 1.]

Named patient: Named patient has not been regulated in the MDR or IVDR. In view of the limited scale and restrictive conditions, and the particular tailoring of the named patient procedures to medicinal products, it is not likely that this use will be an suitable option for RMT during a pandemic. [21]

Regulations and guidelines for clinical trials: From traditional clinical trials to decentralised clinical trials
Over the past years, there has been a considerable interest in decentralising clinical trials, and moving elements of clinical trials from the hospital setting to an at home or "real world" setting (*IDEA-FAST Website*, 2023; *Trials@Home Website*, 2023). Decentralised clinical trials rely heavily on RMTs which is further explored in other deliverables in this report (D3-6).

A key principle of clinical trial execution is that they may only be conducted if the rights, safety, dignity and well-being of participants are protected and prevail over all other interests, and if the trial is designed to generate reliable and robust data.[22] Both when clinical trials contain decentralised elements right from the start, as well as when a traditional trial is converted to a decentralised one, these principles will have to be adequately met. This can pose issues, especially when a traditional trial is mid-way changed to a decentralised one. Before medical scientific research can be executed, it will have to be evaluated and approved by a relevant authority, which in the Netherlands is the CCMO (Central Committee on Research Involving Human Subjects) and/or Medical Research Ethics Committee (MREC).

For international DCTs, an important obstacle is that regulations, professional qualifications and guidelines might differ per participating research institute and country. This lack of harmonisation is especially a barrier to the organisation of multinational trials and requires coordination between different authorities, even more so during a pandemic. The element of fragmentation also relates to data protection: some legislative elements of data protection, particularly for health data, are divergently arranged at the EU member state level.

From 31 January 2023, all primary/initial submissions for research with a medicinal product are subject to the CTR and must be submitted in the Clinical Trials Information System (**CTIS**).[23] [24] By 31 January 2025, any ongoing trials approved under the Clinical Trials Directive will fall under the Clinical Trials Regulation.[25] At this moment there is not a specific legal framework for fast-track approval in case of a healthcare crisis or transfer of a TCT to a DCT.[26]

Privacy and ethical aspects
Setting up DCTs, or preparing for switches from a TCT to a DCT requires thorough consideration, preparations of guidelines, risk analysis, standardized forms for informed consent, Dat Privacy Impact Assessment (DPIA) and Data Management Plans (DMP), clear division and allocation of responsibilities of all healthcare providers. In case of a pandemic, instructions to procure balanced decisions balancing the interest and safety of the individual (patient) against the public health crisis affecting the whole population would be of value. These considerations and documentation should be evaluated and reconsidered preferably before a possible future pandemic situation occurs. Ethical aspects of these decisions could be considered during the non-pandemic phase and the pandemic phase. The applicable regulation puts the position and rights of the individual central in the trial, while the pandemic phase requires weighing of interests of individuals on different levels. As this aspect must be weighed continuously leading to different outcomes in the different phases of a pandemic, the

[21] Art. 83 Medicinal Product Regulation.
[22] Art. 3 Clinical Trials Regulation;
[23] 'Entry into application of the Clinical Trials Regulation' <https://health.ec.europa.eu/medicinal-products/clinical-trials/entry-application-clinical-trials-regulation_en>
[24] 'Clinical trials in the European Union' <https://euclinicaltrials.eu/>; 'Clinical Trials Regulation (EU) No 536/2014: Questions and Answers' (February 2023, v6.4) <https://health.ec.europa.eu/system/files/2023-04/regulation5362014_qa_en.pdf>, Question 1.2.
[25] 'Clinical trials in the European Union' <https://euclinicaltrials.eu/>
[26] Was possible during COVID (national): 'Versnelde procedure (fast track) beoordeling onderzoeksdossiers coronavirus' (News, 27 March 2020) <https://www.ccmo.nl/actueel/nieuws/2020/03/13/versnelde-procedure-fast-track-beoordeling-onderzoeksdossiers-coronavirus>

instalment of a national pandemic Ethical and Legal Advisory Board is recommended. RMT will create more privacy questions that need to be considered as an element of pandemic preparedness.

Overall recommendations and conclusions from the analysis of the legal framework
Analysing regulatory and legal bottlenecks and opportunities of RMTs related to efficacy and safety of interventions during a pre-pandemic and pandemic phase requires an integral approach. Many elements have been changed significantly since the last phase of the COVID-19 pandemic. Several changes related to governance on national, EU and international level, are essential to the national pandemic preparedness policy. The legislative structure in the Netherlands during the years 2019 up to and including 2022 led to a fragmented approach strongly based on cooperation. The recent amendments to this framework are likely to streamline the governance structure, while also facilitating flexibility. The role of the reference laboratories remain relevant in the national and international legislative context.

The most important governance changes on EU level are the strengthened roles for HERA and EMA. The strengthened roles help could help bridge shortages in a tense market. However, at present one may assume that HERA and EMA will perform tasks at an EU level rather than at the request or needs of an individual Member State. This element may require an alignment of the national (pre) pandemic policy and measures based thereon with the policy, tasks and conditions of HERA and EMA in the pandemic phase during which a rapid response is essential.

During the COVID-19 pandemic, important lessons were learned related to the centralized procurement of essential pandemic tests and equipment through a public body of an individual Member State. Procurement procedures by public bodies will most likely pose a challenge, as the exact characteristics of the infectious disease might be difficult to define to the extent needed by the procurement regulation. Even specific social and health procedures and exemptions in the field of innovative products might not be the right answer to the situation arisen. Moreover, any procedure or exemption chosen might provoke legal procedures of competitors which will put the rapid response needed at risk.

Depending on the exact use, these risks may be mitigated by putting a consumer product already used on a large scale as a point of departure for the RMT data flow. The data flow of RMT entails the use of other instruments and software as well. These instruments might be on the market with the required intended use and CE mark. This assumption cannot be qualified as a starting point for RMT applied for trials involving healthcare products needed to cure, suppress or monitor the (symptoms of) the infectious disease. As shown during the COVID-19 pandemic, software, instruments and in vitro diagnostics shall have to be developed or adapted. Depending on the legal qualification of these instruments, consumer product, medical device and/or medical software, applicable regulations will facilitate a limited or more extensive development line and production possibilities in the likely event that adequate devices for a specific pandemic are not on the market.

The regulations for MDs and IVDs changed recently with the transition from the MDR and IVDR to the MDD and IVDD. This means that lessons learned during COVID-19 relating to the assessment of MDs and IVDs cannot automatically be extrapolated to a future pandemic. The transition from the CTD to the CTR (unintentionally) also took place over the pandemic. All these changes were introduced with the aim to harmonise legislations across the EU, and to make the legal framework better suitable for the challenges of today.

The MDR and IVDR are more stringent than their predecessors, which could cause issues during a future pandemic if suitable devices are not on the market. However, several clauses of the MDR and IVDR foresee in adapted procedures where a health crisis occurs. These may be initiated by several actors on national and international level.[193] These possibilities and options for exemptions could be the basis of solid preparational measures for a possible pandemic phase. Nonetheless, the ideal set up for a RMT during a pandemic phase should be further explored.

Setting up DCTs, or preparing for switches from a TCT to a DCT requires thorough consideration, and

preparation of various procedures, guidelines, and alignment on responsibilities upfront. An Ethical Advisory Board can help to balance different interests (eg. those of patients, healthcare provides, and the general population) and advise on decisions to be taken.

2.2. Results of Deliverable 3: Interviews with innovators, a consultant, and the EMA

In D3, we report on 4 interviews that we executed with different stakeholders in the field of RMTs and drug development/clinical research. It is important to note that these interviews reflect experiences and personal standpoints. All interview reports were approved by the interviewees.

Industry perspective: Interview with a small/medium-sized enterprise (SME) that develops digital biomarkers and tools for clinical decision making

A lot of innovation in the field of medical devices and software comes from small to medium-sized enterprises. The EU defines SMEs as enterprises employing less than 250 persons, and having an annual turnover of up to 50 million euros.

Hurdles mentioned by the interviewed SME include the following:

1) Complexity of the newly implemented MDR. This dramatically slows down the development due a lack of knowledge regarding the requirements of the MDR, increased costs, longer waiting times at notified bodies, and difficulty providing necessary data. Furthermore, the requirements to prove the validity of the proposed clinical endpoint are not very clear.
2) The safety and efficacy requirements for approval are very stringent for software intended for clinical decision making. Once an application has been submitted, the product may no longer be altered as it needs to be evaluated "as is". For traditional medicinal products (such as small molecules) or certain medical devices (such as implants) this process makes sense. However, in the case of software products being used in the healthcare environment (such as to support clinical decision making), this might be too stringent, and could prevent innovation to benefit patients.
3) The current timelines for review of a technology by a NB are considerable (currently running up to 85 weeks). At the time of writing, there were 37 NBs that are accredited to assess the technology according to the MDR.
4) Smaller innovators such as start-ups and scale-ups do not always have the regulatory knowledge and ability to assimilate all the necessary information. In those cases, the legislation and the way that it is enforced can lead to innovations being shelved until resources become available.
5) NBs only approve or reject applications, and do not offer scientific advice. Coupled with a cost of ~20,000-35,000 euros per review request, this represents a significant expense to developing novel digital therapies, and is not always a constructive interaction.
6) People working on digital tools (eg. software engineers) are usually intrinsically driven by and educated on technical opportunities, and not always aware of the regulatory requirements they are expected to comply with when their innovations are to be implemented in the clinical environment.
7) Once a digital biomarker is technically and clinically validated for a specific disease, the digital biomarker needs to be clinically validated for each new disease. For general parameters such as fatigue, this requirement might be too stringent.
8) Funding to provide real-world evidence is difficult to achieve.

As for potential solutions, the following where mentioned:

1) It would help to get more clarity on the requirements for different types of software solutions. One way would be to have a body that does not only approve or deny applications, but also gives scientific advice, similar to how the EMA operates.
2) A practical piece of advice is to work with consultants that have expert knowledge on the MDR and IVDR. Exchanging knowledge with other SMEs and other organisations with regulatory expertise is also deemed valuable.
3) In certain cases, it should be re-evaluated whether the requirements for software products need to be as tight as they currently are.

4) The capacity of the NBs is currently a huge issue. Expanding the capacity of the NBs with relevant specialists could help.
5) Taking regulatory requirements up into the curriculum of future software developers helps with bringing this topic on their radar.
6) Easier access to funds that would allow to power studies focussed on gathering real-world evidence, leading to acceptance by health technology assessment bodies and insurers would help to overcome another hurdle.

Industry perspective: Interview with a large innovator in the pharmaceutical field

Innovators in the pharmaceutical field have showed considerable interest in the past years in the many opportunities that RMTs can provide. Interests includes for example investiting whether digital health technologies can be employed to better characterize disease states and stratify patient populations. At the same time digital health technology can be used to quantitatively measure patient functionality, which is often subjective and difficult to measure by clinicians. This may give doctors an extra tool in their arsenal, in addition to existing ones, to make informed medical decisions. Pharaceutical innovators are usually very large, internationally operating organisations.

Hurdles discussed by the interviewed pharmaceutical innovator include:

1) Lack of harmonisation across the ecosystem. It is noted that regulators are usually no the bottleneck in the adoption of digital health technologies in clinical trials. The regulator's expectations are clear to sponsors, but regulators are not able to facilitate harmonization across the ecosystem (eg. different companies working in the same disease area).
2) Technology firms developing RMTs are often SMEs that lack the resources to successfully scale up production and make it available in multiple countries. This has generally made sponsors reluctant to perform large scale clinical trials with technology startups, preferentially working together with larger more established technologies companies.
3) Technology has been shown to be useful in exploratory and proof-of-concept studies. Upscaling of the product is often an issue, as well as the lack of MDR CE marking. The use of real-world data from consumer grade devices is not well managed, often has missing data, poor signal to noise ratio and the expectations of regulators are less clear.
4) Sponsors would like to discuss as early as possible with regulators if a novel biomarker would be accepted, often without being able yet to demonstrate that its works. To which the regulators request proof that the technology works as expected, which leads to a catch-22. Additionally, the logistics and associated costs around validating a technology can be an issue.

Possible solutions include:

1) First and foremost: Harmonisation. The entire ecosystem of pharmaceutical players would need to strive to develop the same standards. Large public-private partnerships such as IDEA-FAST and Mobilize-D aim to harmonize standards of digital health technologies. Currently, the EMA and EFPIA have been aiming to achieve this through various programs to standardize the digital health space in clinical trials.
2) Many sponsors are currently learning from each other, for example via working groups in EFPIA's digital endpoint sub-group on how to implement technology whilst keeping it cost effective, as well as harmonization and standardization of clinical endpoints. TUFTS university is conducting research to determine the net present value of digital measures which will be published later this year.
3) The development of clearly defined standards to RMT development would much help. This should include for example what and how the technology is measuring, as well as a description of the technology and the evidence gathered through clinical validation, like an ISO standard. Second, an open library or repository should be created with all the possible measurements and technologies that have been validated and that are reproducible. This would avoid fragmentation with many sponsors developing their own digital biomarker and create a specialized service ecosystem which would be cheaper, more efficient and of higher quality. The adoption of these validated biomarkers would be faster and more widely accepted.

The specific use of RMTs in pandemic preparedness was also discussed. Application of RMTs during a pandemic was deemed difficult, and not only due to regulatory bottlenecks. If RMTs were to be applied to screen the population for disease symptoms, the costs are expected to be very high, as population screening in general is a costly activity. A cost-benefit analysis would need to be done to identify which high risk population groups would benefit most from screening or monitoring. Another factor to consider is who would ultimately bear the costs of monitoring. This is more a political issue than a technical or a regulatory one. Finally, it might be easier to have a pandemic response plan in place rather than a pandemic preparedness plan.

Consultancy perspective: Interview with a consultant with hands-on experience
Many organizations find the complex legislation difficult to work with. Consultants can offer support with the writing of product technical documentation for regulatory approval, the set-up of quality management systems, and support for related product or process validation studies. Furthermore, they train organizations on the job.

Hurdles discussed include:

1) Difficulty defining clear claims and related functionality and mode of action of their product in order to assess what Regulation is applicable. Related to that, difficulties with building technical documentation with the evidence supporting the claims, and ensuring a quality management system is in place to guarantee the quality of related processes is also often observed.
2) With the introduction of the MDR and IVDR it can also be difficult to interpret if the product in question is considered a medical device or not.
3) It can be difficult for developers to understand why the rules are so stringent and the regulatory approval rates are so slow. Some software products and RMTs can be seen as innovations with a low risk to the user by the innovator, but still require the same approval process as devices falling into a higher MDR risk category.
4) During a pandemic, many technologies were needed “yesterday” so the question arises how we can speed up the review process of technologies.
5) During a pandemic the healthcare system is under enormous pressure with healthcare professionals not having time to spend on additional clinical trials for medical devices.
6) Currently there are long waiting times at the NBs
7) In the recent past, harmonisation across EU member states has been an issue. This is expected to improve with the transition from the MDD and IVDD to the MDR and IVDR

Opportunities discussed include:

1) Clearly defining claims needs to be planned early on in the development process to avoid frustrations, issues with timelines, complications with investors, and quality issues
2) Consultancies can assist with the detailing the product claims and help understanding how the definitions or requirement of MDR/IVDR apply. They can also assist in the setup of a quality management system.
3) To help improve the knowledge gap and understanding of regulatory procedures, a suggestion would be to include regulatory topics in the university curriculums of relevant studies.
4) Platform technologies have been suggested where once the technology works for one disease area, the technology can be implemented for another disease area with defined but relative limited effort.
5) Expanding the capacity of the notified bodies would help reduce the timelines. As a first start, Recently an amendment to the MDR/IVDR has been published (REGULATION (EU) 2023/607) allowing longer transfer periods for certain devices under certain conditions, slightly relieving the pressure on NBs.
6) The implementation of the MDR/IVDR is a good step forward to European harmonisation of processes
7) Notified bodies currently do not offer sparring/review on the study plan upfront. It would be beneficial if there would be more opportunity for notified bodies to provide this service, especially in a pandemic

The regulator perspective: Interview with the European Medicines Agency
The EMA provided several useful explanations, resources and tips that can be followed by innovators. Existing guidance and recommendations often incorporate experiences and examples seen by regulators.

It was explained that endpoints measured by RMTs need to be clinically relevant (either in themselves or as a surrogate to a clinically significant endpoint), in order to be accepted for regulatory purposes. However, the RMT may be measuring an endpoint that would require regulatory qualification before it can be accepted. In these cases, the assessment of the clinical performance of the RMT by a NB may be complicated by the need for regulatory qualification of the novel endpoint measured by the RMT first, but given that such qualification may take time, the endpoint should only be used as exploratory (i.e. not with the intent to guide clinical decisions) until it is considered qualified. There is no platform, during either medicine development or evaluation/authorisation where notified bodies and the EMA discuss the evaluation of RMTs, but the evaluation of a MD or IVD cannot and should not require the acceptability of the RMT for regulatory purposes.

Study design of clinical trials depend on the relationship of the RMT with acceptable clinical endpoints. It is recommended to apply for scientific advice or qualification advice in advance of the clinical trial start to confirm validity of the measure and sound implementation in protocol. Consideration should be given to key guidance documents, as follows:

- CTCG recommendations on decentralised elements in clinical trials,
- NfG on computerized systems and electronic data in CTs, ICH-E6 as well as to the
- Qualification opinion on eSource Direct Data Capture (DDC) (EMA/CHMP/SAWP/483349/2019).

Scientific advice can be requested at any point during development, and ideally the interaction should commence early. Submissions can follow the formal pathway following registration of the sponsor with EMA and acquisition of a Research Product Identifier (RPI) for the product under development (see Requesting scientific advice or protocol assistance from EMA), but initial contact may be sought directly with the EMA scientific advice (scientificadvice@ema.europa.eu). Medicine developers are well aware of the option for EMA/CHMP/SAWP/centralised scientific advice and Qualification of Novel Methodologies. On the other hand, academic developers, MedTech and small companies (pharma or medtech) may be less familiar with the existence or the mode of interaction with the EMA.

Other useful guidelines and tips include the following:

- Guideline on computerized systems and electronic data in clinical trials: https://www.ema.europa.eu/documents/regulatory-procedural-guideline/guideline-computerised-systems-electronic-data-clinical-trials_en.pdf
- Recommendation paper on decentralized elements in clinical trials: https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en
- Concept paper for ICH E6 (R3) Guideline for Good Clinical Practice Annex-2: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Annex2_ConceptPaper_2023_0405.pdf
- MDCG 2022-10 Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR) https://health.ec.europa.eu/system/files/2022-05/mdcg_2022-10_en.pdf
- The methodology used to identify critical medical devices is published on the EMA website (https://www.ema.europa.eu/en/documents/other/methodology-establishment-public-health-emergency-critical-medical-devices-list_en.pdf)
- Draft Reflection Paper on the use of AI in medicinal product lifecycle https://www.ema.europa.eu/documents/scientific-guideline/draft-reflection-paper-use-artificial-intelligence-ai-medicinal-product-lifecycle_en.pdf

Conceptually, the development of the digital biomarkers does not differ much from other biomarkers. There is however a grey area concerning the remit of EMA versus other actors (e.g. NBs), including the appropriateness and capability to exchange confidential information if needed.

It was also mentioned that there is also a lack of expertise in the network to evaluate the impact of certain technologies and methodologies on the areas pertaining to the remit of the different bodies.

2.3. Results from Deliverable 4: Literature study on decentralised clinical trials

The landscape of clinical trials has undergone a notable transformation, shifting from traditional in-clinic setups to embrace decentralized elements, including RMTs. This transition, enabled by digital innovations, has prompted the Trials@Home consortium to explore the regulatory implications of using RMTs into European clinical trials. In terms of opportunities for RMTs, it is described in the Trials@Home literature that regulatory bodies have demonstrated a willingness to accept telemedicine, particularly evident during the COVID-19 pandemic, where telemedicine was adopted to ensure trial continuity and lower infection risk (de Jong et al., 2021, 2022). Decentralized trial methods, including telemedicine visits and direct-to-patient drug supply, have gained traction (Suman et al., 2022). Regulatory bodies like the EMA, the FD and National Competent Authorities (NCAs) have provided guidance, facilitating the incorporation of RMTs in DCT pilots. Initiatives such as the EMA's Innovation Task force (ITF) or Clinical Trials Transformation Initiative (CTTI) underline a concerted effort to foster collaboration between regulators and sponsors (DCT Project Team, 2022; Rogers et al., 2022).

Conversely, many hurdles have been noted related to RMT adoption in clinical trials. Sponsors are hesitant to employ DCTs as they are currently no standardized or well-established implementation pathways (Coert et al., 2021; Gelis et al., 2023a; van Rijssel et al., 2022b). Sponsors experience a lack of clarity in validation requirements of using RMTs in a clinical trial to achieve a market authorization for a medicinal product as well as uncertainty about the acceptability of novel digital endpoints. Regulators only accept RMT-based clinical endpoints to support regulatory decision making in a trial when a RMT used is sufficiently validated. Without proper validation, RMTs can be used for measuring exploratory endpoints in a clinical trial. Using a non-CE marked device as an exploratory endpoint or during the early phase in drug development can also be accepted by regulators. However, in general it is recommended to use a CE-marked device in its intended use to collect data to support regulatory decision making (Gelis et al., 2023). For a sponsor to use a non-CE marked digital device as a primary or secondary endpoint in a clinical trial a possible separate application may be requested by the regulators. This dramatically increases the regulatory burden for sponsors as they would have to submit two applications in parallel, one for the medicinal product and one for the medical device (Gelis et al., 2023).

The sharing and protection of participants' personal data, the ownership of data generated by RMTs, and compliance with the General Data Protection Regulation (GDPR) all contribute to the complexity of DCTs. With the introduction of Artificial Intelligence (AI) to analyse data, the complex interplay between the hardware, sensors, and algorithm makes evaluation by regulators even more difficult (Coravos et al., 2019). In addition, the generation of “Big Data” datasets can make it challenging to interpret the data, and difficult to extract meaning (de Jong et al., 2022; Gelis et al., 2023).

It is recommended to consult a data protection officer during the setup of a clinical trial (Lalova-Spinks et al., 2022). Both the participants and trial staff face new burdens with the introduction of RMTs. While RMTs can offer convenient data collection, it can potentially overwhelm participants, particularly those with limited digital literacy. Participants in DCT gain a certain responsibility towards certain aspects of data collection. Site staff have to be trained to use devices and handle technological issues. Striking a balance between innovation and regulatory compliance is crucial to realizing the full potential of RMTs in advancing clinical research.

In summary, we have identified some contradictory but not mutually exclusive findings in the literature, in which it is noted that regulators show openness to RMTs whilst simultaneously expressing concerns about safety, privacy, and validity. It is currently unknown if the concerns are due to regulator hesitancy, or due to innovations not meeting the required standards. The absence of standardized or well-established implementation pathways seem to be a significant hurdle (Coert et al., 2021; Gelis et al., 2023a; van Rijssel et al., 2022b).

2.4. Results from Deliverable 5: Studying EU-wide, multi-centre clinical trials on RMTs using the learnings from RADAR-AD

The IMI funded RADAR-AD project investigated the potential of RMTs in Alzheimer's Disease. Many findings coming from this project are disease-agnostic, and can hence be considered for the use of RMTs in the context of future pandemics. Due to the design and overall strategy of the project, the project gives important insight in:

- How medical ethical committees in different Member States interpret EU legislation and evaluate clinical trial applications with remote monitoring technologies (Muurling et al., 2021b, 2023).
- Feedback received from the ITF of the EMA on remote monitoring technologies (Stolk, 2020)
- Technologies and endpoints that innovators are asking opinions and advice for via Qualification Advices (QAs), Scientific Advices (SAs) and Qualification Opinions (QOs), and insight in the opinions and advice provided by the EMA (Dekker et al., 2021a)

Evaluation of clinical trials applications by MRECs in different EU Member States

Following the declaration of Helsinki and the CTR, medical research is only allowed when the research protocol has been reviewed by an independent committee (Carlson et al., 2004) (European Parliament, 2022). This task is executed by Medical Research Ethics Committees (MRECs). In RADAR-AD, 10 different MRECs in 9 different countries evaluated the clinical trial protocol. It was found that the MREC feedback on the research protocol differed considerably on issues raised, evaluation run times, and the level of scrutiny. Multi-site/multi-country studies executed in the EU would greatly benefit from a harmonization in research ethics governance processes. The change from CTD to CTR was partly fuelled by the widely recognised problems arising from the lack of harmonisation under the CTD (Petrini, 2014). However, as it only entered into application by 31st January 2022, it remains to be determined to what extent harmonisation and a swifter review of multi-centre clinical trials working with RMTs will be achieved under the new legislative framework of the CTR.

Upon analysis, 4 key themes emerged on which the MRECs raised questions. These are data management, participant's wellbeing, methodological issues, and issues pertaining to the regulatory category of RMTs (Muurling et al., 2023). Our review showed that the regulatory status of a device was not considered in the selection of devices for the project. If one plans to apply for a market authorisation application for a therapeutical product and information gathered via apps or devices is used to support the application, the relevant regulatory and legal will have to be met. Innovators and investigators are advised to consider the regulatory status of devices early on, so that informed decisions can be taken (Stavropoulos, 2020).

Recommendations from the authors to improve the review process leading to a sound research protocol included engaging an institutional data protection officer, performing a patient advisory board review of the protocol, stimulating a strategy for ethical reflections during the study, and working on a mutual understanding with the MRECs on the definition of a medical device (Muurling et al., 2023).

Lessons learned from engaging with the EMA ITF

The EMA offers the opportunity to engage with their ITF, in order to foster an early dialogue with applicants on innovative aspects in medicines development (European Medicines Agency, 2023b). The ITF meeting is reported on in D3.10 (Stolk, 2020) and contains valuable insights into regulatory considerations when developing RMTs and RMT-based endpoints. The feedback is summarised below in a detailed way.

Table 1: summary of feedback points per topic

Topic	*Advice*
Collecting data from multiple sources	- Focus on one aspect with the most promising evidence - Noting that the validation of novel endpoints and biomarkers is a resource- and time intensive task - Convincing evidence from prospective studies in the context of use (CoU) is needed

	- For the introduction of a new endpoint, validation should be in comparison to the existing accepted (gold) standard, and claims should be specific and unambiguous - Further guidance could be provided by the EMA using the qualification advice process
Stratification of patients based on RMTs and RMT-based endpoints	- Currently, patient reported outcome (PRO) data is not sufficient for MAA in the CNS domain except for headache - PRO can only complement objective, primary outcomes. The PRO as secondary outcome should be validated in studies, where it is important to assure sufficient adherence and address missing data and the timing of data collection
Regulatory acceptance of data coming from consumer-grade (non-medical grade) devices for the measurement of clinical outcomes	- Regulators would like to have assurance of the quality of the data generated. Algorithms using data of non-validated devices will be challenged. The use of devices CE-marked for medical use is hence recommended.
Acceptability of aggregated data coming from consumer grade (non-medical grade) devices	- In the meantime, a guideline on computerised systems and electronic data in clinical trials has been published, which touches on topics related to data and devices (European Medicines Agency, 2023a) - Main issues are the traceability to the individual person, and the quality and integrity of data. Within the International Conference on Harmonization (ICH) a revision of the E6 guideline (Good Clinical Practice) is addressing the issue of utilisation and verification of other sources of data.
Regulatory requirements for open-source based platforms for data collection	- An open-source platform is likely acceptable as long as the system complies with a number of aspects that could be reviewed by the EMA Scientific Advice Working Party, including the principles of Good Clinical Practice. Attention should be paid to the requirements of the General Data Protection Regulation (GDPR). - Within the European Commission, initiatives are considered for setting standards with the aim of ultimately seeking international harmonisation, for example via the ICH.

Topics of attention mentioned during the RADAR-AD ITF meeting have also been addressed in a publication on insights coming from the qualification of the SV95C in Duchenne muscular dystrophy (Servais et al., 2022). The first wearable-derived digital clinical outcome assessment qualified by the EMA was the qualification for the use of stride velocity 95th centile (SV95C) measured by a suitable device for use as a secondary endpoint in trials for Duchenne muscular dystrophy (European Medicines Agency, 2019). Topics of attention include the importance of thorough validation of the data collection devices, issues pertaining to privacy, selecting the most promising evidence, and comparing it to the gold standard (Servais et al., 2022). These points are essential to take into consideration when developing digital biomarkers to support market authorisation applications for medicinal products. Manufacturers, investigators or sponsors working on RMTs in the context of infectious diseases are advised to reflect on these topics early on, and engage with regulators as early as possible. In addition, sufficient resources will have to be made available to support such a qualification process. It was also recommended to address certain topics again at a qualification advice meeting, which is a more formal and in-depth process compared to a meeting with the ITF. Engaging with regulators early on in the development process is imperative to the success of developing novel tools and technologies, which has been mentioned elsewhere as well (Izmailova et al., 2021). Both the ITF and the qualification advice procedure are good pathways to engage with the EMA in the early stages of development (Gelis et al., 2023b).

Evaluation of QOs, QAs and SAs – EMA's Committee for Medicinal Products for Human Use perspective
The publication by Dekker et al., 2021 reports on evaluating qualification opinions (QOs) and qualification advices (QAs) as well as scientific advices (SAs) of the Committee for Medicinal Products for Human Use (CHMP). This study was performed to gain insight in the types of devices that are intended to be used in clinical trials for supporting/submitting application for obtaining marketing authorization (registration trials) and the main recommendations of the CHMP. In the SAs, accelerometers to measure activity and/or sleep parameters were the most frequently used devices, followed by mobile applications and glucose monitoring devices. Usually, these measures were proposed as secondary or exploratory endpoints. The main recommendations of the CHMP were related to relevance of the (novel) outcome measure; validation, precision, accuracy, sensitivity, and specificity; compliance; sampling interval; and data handling and privacy. Despite a trend in increased use over time, the use of RMTs in registration trials is still relatively rare. Insights in the main recommendations of the CHMP may stimulate the use of novel RMTs in a regulatory context (Dekker et al., 2021a). An update of this analysis is provided in deliverable 7 of this report.

2.5. Results from D6: Interviews with researchers working on RMTs and DCTs, and interview with members of the Central Committee on Research involving Human Subjects (CCMO)

In D6, we report on 3 interviews that we executed with investigators involved in Trials@Home and RADAR-AD. Since review and approval of clinical study protocols make up such an important milestone in research and involve a regulatory step as well, we supplemented our interviews with and interview with The Central Committee on Research involving Human Subjects (CCMO), the Dutch governmental organization that assesses if a clinical trial is law abiding. It is important to note that these interviews reflect personal experiences and standpoints. All interview reports were approved by the interviewees.

Investigator perspective: Investigating DCTs

Decentralized clinical trials can be especially useful in targeting patients that are hard to find, such as for example orphan disease patients. The use of DCTs may also enhance the retention and adherence of participants, as the technology enables a more seamless integration in the patient's life without the need for frequent clinic visits. Hybrid trials will probably be the dominant future form. Both DCTs as well as hybrid types will almost certainly require application of RMTs. The COVID-19 pandemic catalyzed the adoption of more flexible trial design elements, such as direct-to-patient shipments and the use of remote monitoring tools.

The Trials@Home consortium had many discussions with regulators. They had discussions with the EMA's ITF where they discussed various aspects of the trial, such as e-consent, safety monitoring, data privacy & quality, as well direct-to-patient shipment. Regulators also had concerns about data quality and how to ensure that adverse events were being recorded by the patient.

In terms of regulatory hurdles, it was mentioned that the recent adoption of the CTR will help make clinical trial applications simpler. Nonetheless, it was observed that this process is not flawless yet. For example, there can still be differences in interpretations of laws between different regulators and competent authorities. At the time of writing, not all countries have adopted the CTR in their respective national laws yet, which might change over the next couple of months.

As the approval has shifted from a national level to a centralized EU level, the ability to contact the regulators directly through CTIS has been difficult. Lastly, the new regulatory framework needs to work for all items, and needs to be interpreted in a consistent way. However, the "human factor" in decision making is not always transparent or comprehensible, which can lead to inconsistencies.

In terms of opportunities to remove regulatory barriers, the following items were discussed:

- We are on the right path to changing the regulatory dialogue, and improving harmonisation across EU Member States. The EMA has set out a workplan to accelerate Clinical trials in the EU (ACT-EU). Over time, with more data becoming available from DCTs, trust is developed.
- DCTs' data collection standards are very strict, as is also the case for a conventional trial. These strict standards might provide hurdles, and affect the benefit/risk balance. It would be good to have an open discussion on this topic with the regulators, and take context into consideration.
- Devices used in DCTs need the EU's medical device CE marking to be used for clinical endpoints. However, the Trials@Home trial is using CE marked devices as a proof of concept of what is possible in remote trials, and less so in developing novel digital clinical endpoints.

In addition, as advice for designing DCTs with RMTs (such as for example during a pandemic), the following points were mentioned: First, the study may attract a more diverse patient population which should be taken into account. It is crucial to incorporate a patient expert panel in the study design. The panel will be able to think along in the design of the trial regarding patient preferences, the materials used in the trial and the data that will be collected. Secondly, researchers need to be able to clearly explain the added value of the remote aspects. A data management plan needs to be available to demonstrate knowledge of the various data streams and privacy concerns. Thirdly, many pharmaceutical companies use external vendors for their remote monitoring technologies. This has led to concerns with the regulators regarding privacy and accountability for

the data, as often different apps or platforms need to work together. Accountability and responsibility for data quality have to be absolutely clear from the start of the study. The same goes for how software updates are handled and affect data collection, and for fragmentation of the collected data.

In the future, more trials will be hybrid trials, meaning that part of the trial will be executed remotely. The COVID-19 pandemic showed that decentralized aspects of trials were essential for the continuity of many trials. Unfortunately, many trials without remote aspects were halted, to the detriment of the patients. The pandemic catalysed the adoption of RMTs in clinical trials. This adoption can be further leveraged for pandemic preparedness.

Investigator perspective: Developing new endpoints based on RMTs
In the RADAR-AD project, a multi-country, multicentre trial was executed to investigate the possibilities of RMTs. This means that the research protocol had to be approved in various countries. This was a big regulatory hurdle, and sometimes required adaptations of the protocol to fit with local regulations. For example, the approval for camera usage in different countries in RADAR-AD was often a point of contention by different MRECs as the GDPR was interpreted differently. In the future, it would be good to have a clear harmonization between the local MRECs whereby definitions are aligned, and cultural differences are considered.

In the Netherlands, the Dutch law on medical research involving human subjects act (*Wet medisch-wetenschappelijk onderzoek met mensen;* WMO) and GDPR standards for data privacy and security are very clear, so that was not a real issue.

One important challenge at the start of the project was knowing how "good" the new digital endpoint had to be. It was difficult to match the digital endpoint with the clinical gold standard. However, the EMA was pragmatically positive about the study, noting that it was an important exploratory trial with a lot of potential.

Another challenge pertained to software updates negatively impacting the study. Ideally, you want to collect data the same way for all the research participants. However, with a software update the layout, instructions, or even the algorithm used to analyze the raw data can change. Alignment between the device and software provider and the investigator upfront is essential to avoid these types of issues. Ultimately, when it is unclear what the software updates mean for the validity of the digital endpoint, this will be a huge limitation of the study, and often these results will not be accepted by a regulator.

To measure an endpoint and have it accepted by the EMA, the devices will have to comply with relevant regulations, often meaning that they should be CE marked medical devices. Although it is understandable that this is the current standard of the EMA, a bit more leniency could eventually also bring value to patients. Relevant data regarding a disease can be generated even if the device is not CE marked as a medical device but shall be considered an exploratory endpoint.

In potential future pandemics, RMTs could be used to measure symptoms, behavior, cognition or even act as reminders for participants to take their medication from afar. Moreover, RMTs could act as a surrogate for in-person measured endpoints. Another advantage, such as telemedicine, enables contact with research participants without requiring them to physically visit the clinic. RADAR-AD has successfully demonstrated that the trial was able to start during the COVID-19 pandemic as well as ensuring proper contact with patients, clinical trial sites and overall study continuation.

Regulator perspective: CCMO
Following the Dutch WMO, the CCMO assesses whether a clinical study is law abiding. Moreover, the CCMO assesses whether the pre-clinical studies give enough ground to safely start a clinical trial. The Central Review of Medical Research Involving Human Subjects Decree (*Besluit centrale beoordeling medisch-wetenschappelijk onderzoek met mensen*; BCB) stipulates which types of research have to be reviewed by the CCMO. In the

Netherlands there are also 14 accredited MRECs. These are involved in the evaluation of all the other clinical trials.

The CCMO is involved in creating policies, supervision of MRECs and gives guidance on certain topics. Furthermore, the CCMO also acts as a liaison between the European competent authorities (involved in assessing clinical trials) and the Dutch MRECs. CCMO is involved in implementing the European regulations (CTR, MDR, IVDR) and supporting the MRECs with any questions they might have. If the Netherlands is chosen to be the lead country of the assessment of the clinical trial, the CCMO is responsible for the evaluation of the protocol under the CTR.

The CCMO assesses the feasibility of studies on medical ethical questions. Its mandate does not cover acceptance of endpoints in the context of drug development. Therefore, it is possible that the study design is sound, but the CBG or EMA would not accept the clinical endpoints to allow for a market authorization of a medicinal product. The CCMO assesses whether a clinical endpoint is relevant for the study itself, which is a different point of view than the market authorization point of view.

It was mentioned that the CTR brings clear benefits and is an important step forward in harmonisation. Downsides are that under the CTR sponsors have to handle very short timelines, and that the system still experiences some teething problems. In addition, the EU Member States have a different approach to how they assess clinical trials. National laws and guidances can be slightly different, and the interpretation by national committees of certain topics can differ. For international studies, consensus on these topics has to be reached. However, this will take time.

For designing clinical trials with decentralised elements using RMTs, also CCMO referred to the EMA's recommendation paper on this topic: (European Medicines Agency, 2022b) .

The safety and performance of software when used as a medical device are of paramount importance. The software needs to correctly and accurately convey data especially if it is used in a medical decision. Upcoming software techniques offer exciting possibilities but also come with new types of risks that need to be evaluated. Harmonization and lawmaking will take time.

It is probably not feasible to have enough infrastructure ready during the beginning of a pandemic to be able to fully remotely monitor patients. A cost-benefit analysis could be done to see if the government should invest in the remote aspect. The COVID-19 pandemic has accelerated the adoption of RMTs and proven that the technology can be successfully incorporated in clinical trials.

2.6. Results from Deliverable 7: The use of remote monitoring technologies: A review of recent regulatory scientific advices, qualification opinions and qualification advices issued by the European Medicines Agency between 2020 and 2022

Chapter under embargo, pending publication
For more information, please contact vera.nies@lygature.org

2.7. Results from Deliverable 8: RMT use in phase 4 studies

Clinical trials are vital in the development of new medicines and medical devices. Phase 4 clinical trials can be conducted to collect additional safety and real-world efficacy data after market authorization of a drug (Suvarna, 2010). Due to their properties that allow them to sensitively and objectively collect data over prolonged timepoints and in a real-world environment, RMTs may be used to collect additional data to get additional insights on the safety and efficacy profile of a medicinal product in a real-world environment (Clinical Trials Transformation Directive, 2017). This can be done both during non-pandemic as well as pandemic situations.

To get better insight into the use of RMTs in phase 4 trials in the EU, we used the database clinicaltrials.gov to search for studies between 2013 and 2022 that used RMTs in clinical trials that were classified as a phase 4 clinical trial in the EU. Twelve clinical trials met our inclusion criteria. Of those 12 studies, 8 studies (66%) used a RMT to measure patients' adherence to medication, and 4 studies (33%) used RMTs to measure a physiological parameter such as sleep or blood glucose levels. Looking at the total number studies labelled phase 4 in the EU (1.515), only a fraction of those studies uses RMTs. It is to be noted that we might have missed studies, as not all phase 4 studies are labelled as such in the database.

The relatively low adoption of RMTs in the identified phase 4 trials could be due to several factors. It could partly be due to a methodological limitation of our study. A study similar to ours investigating the use of "connected digital products" ran into a similar issue, noting that many studies in the database are not labelled with the study phase (Marra et al., 2020). Another explanation is that regulatory expectations are not always clear, which could lead to sponsor hesitancy in developing novel digital biomarkers. Another observation is that the majority of phase 4 studies using RMTs are executed in the USA. A potential explanation for this is that the regulatory landscape for RMTs in the USA is less scattered compared to the EU.

Further research is recommended to better understand the factors influencing sponsors' decisions to use (or not use) RMTs in their clinical trials, particularly in phase 4 studies. This could for example be done via in-depth interviews with sponsors.

2.8. Results from Deliverable 9: Expert meeting

As an integrated part of this assignment and to discuss a subset of our findings with experts from the field, the RSNN organised an expert meeting on the 16th of October 2023, to discuss the topic "Remote Monitoring Technologies for Regulatory Decision Making: From technology push to clinical endpoint." Various national experts from academia, industry and governmental bodies were invited to share their current knowledge and personal views under the Chatham House Rules. The experts were briefed ahead of the meeting on the topics that were discussed during the expert meeting.

The table below provides a summary of the identified hurdles and potential solutions to those hurdles.

Table 2: summary of identified hurdles and potential solutions, as identified in the project, and as discussed with the experts

Hurdle	Solution
1 Lack of precedence, limited and fragmented regulatory guidance, and absence of standards and established approaches to validation and implementation	
1.1 Changed legislation: From MDD and IVDD to MDR and IVDR, and from CTD to CTR	Evaluate impact of changes in a structured way; pre-empt potential hurdles
1.2 Fragmentated feedback and assessment of each step of the development process; high costs, resource (knowledge and funding) heavy process	"one-stop-shop" for integrated feedback and advice, potentially building on already available knowledge and infrastructures
1.3 Lack of knowledge of innovators on regulatory routes and regulations	Take the topic of regulatory affairs up in the curriculum of relevant studies; Netherlands well-positioned to become a knowledge hub; Engage consultants;
2 Lack of appropriate resources (knowledge and funding) to manage product validation and handle regulatory burden	
2.1 Lack of appropriate resources (knowledge and funding) to manage product validation and handle regulatory burden.	Increase interaction between regulators and innovators to explore and validate RMTs and develop digital endpoints in a precompetitive space, for example via projects funded by the Innovative Medicines Initiative,
2.2 Assessment of software and devices under the MDR and IVDR takes a long time due to shortages at the notified bodies. Requirements are not always clear and processes to ask for feedback are not present at the NBs	Exemptions could be applied during a pandemic. Invest in education and training of assessors at NBs. Set up a feedback system for feedback on devices, similar to QA and SA at the European Medical Agency (EMA)
3 Not knowing the next pandemic pathogen complicates the process of validating devices in the correct context of use and in a timely manner	
3.1 Lack of time and information to assess the safety and validity of a RMT in the pandemic context	Pandemic-specific exemptions: - Allow for the use of validated RMTs to be used outside of their context of use (different disease context) - Allow for the use of validated RMTs to be used outside of their context of use (from hospital- to home-setting) - Fast-tracking of RMT review - Align upfront (before a pandemic) on regional, national and international mandates, tasks and responsibilities
4. Increased use of decentralised clinical trial elements facilitated by RMTs is highly complex.	
4.1 Complexity of switching from traditional to decentralised clinical trial	Prepare protocols, lines of responsibility, guidelines upfront; discuss regulatory acceptability of collected data

All experts present during the meeting were in agreement with the identified hurdles underlying RMT utilization for regulatory decision making, deriving from the ZonMw Regulatory Pandemic Preparedness program. All experts present during the meeting agreed with the proposed solutions for each of the hurdles (see table 2). All experts provided valuable feedback that helped to further detail the proposed solutions.

Key items and conclusions of the discussions are described below.

- All experts present during the meeting were in agreement with the identified hurdles underlying RMT utilization for regulatory decision making, deriving from the ZonMw Regulatory Pandemic Preparedness program (see table 1 for a summary).
- All experts present during the meeting agreed with the proposed solutions for each of the hurdles (see table 1 for a summary). All experts provided valuable feedback that helped to further detail the proposed solutions.
- The transitions from MDD and IVDD to MDR and IVDR, as well as the from CTD to CTR, was set forth to harmonize across EU member states which is a welcomed development better suited for novel technologies, including RMTs. However, knowledge regarding the changed legislation, regulatory requirements, and the roles and responsibilities need to be further improved and communicated amongst all stakeholders. Furthermore, the changed legislation has resulted in a significant delay of RMT assessment which is expected by some experts to be solved on relatively short notice. However, other experts still experience delays at the notified bodies.
- Early, and low threshold interaction between regulators and RMT developers should be improved to facilitate tailored regulatory advice. Various initiatives and pilots exist to explore the possibilities for interaction. Successful outcomes of these initiatives and pilots will also help to raise regulatory awareness and aids with education of MDR, IVDR and the CTR.
- A precompetitive space is crucial to bring together the various stakeholders with each their own expertise and knowledge to achieve digitalization of endpoints by RMT utilization, through the development of novel endpoints or via digitalization of existing endpoints.
- Improved pandemic preparedness is crucial since scientific, regulatory, and clinical ecosystems are under severe strain during a pandemic. The non-pandemic, “cold phase” needs to be utilized to increase the pandemic preparedness by:
    - Taking the lessons learned from the Netherland’s response to the COVID-19 pandemic but also learning how other countries responded.
    - Increasing understanding of the existing regulatory routes and requirements amongst all stakeholders that could potentially play a role during the next pandemic. This can be achieved by preparing (pandemic-specific) protocols and guidelines, as well as increased transparency of the regulatory authorities and the lines of responsibility.
    - Steps should be taken to ensure early interactions with citizens to inform them about data collection methods and data protection laws. During a pandemic, with the citizen’s trust in data collection already fostered, could make the adoption of RMTs easier.
    - By planning RMT utilization for different pandemic scenarios based on the characteristics of the pandemic pathogen. Amongst others, a RMT “toolbox” providing an international overview of RMTs that have received certification and/or have been validated for use in a specific context of use could help to quickly respond to a novel pandemic by testing and validating RMTs previously validated in a different context.
    - Allow for pandemic-specific exemptions that facilitate the needed regulatory adaptation while safeguarding the risk for the general population. For example, flexible fast-track approval processes and repurposing processes for RMTs, including feedback rounds at notified bodies and other relevant regulatory authorities, could be considered to facilitate RMT utilization.

2.9. Results from Deliverable 11: Review on the Use of Remote Monitoring Technologies to Measure Physiological Parameters and PROs in COVID-19 Patients for Clinical Decision Making

Chapter under embargo, pending publication
For more information, please contact vera.nies@lygature.org

3. OVERALL CONCLUSIONS AND RECOMMENDATIONS

Key players in pandemic responses

A coordinated response to a pandemic is complex. Different authorities have different tasks, responsibilities and mandates. In the Netherlands, the chairmen of the safety regions and the RIVM (on behalf of the Ministry of VWS) are part of the governance structure on a national level. A network of reference laboratories plays an important role in the identification of pathogens and novel strains, advice based on scientific knowledge and expertise, collaboration and research, surveillance and outbreak management. On an EU level, it has also become clear that a new authority was needed to help strengthen the EU's ability to prevent, detect, and rapidly respond to cross-border health emergencies. Hence, HERA (the Health Emergency Preparedness and Response Authority) was established. The role of the EMA in potential future health crises has been strengthened as well. In a global context, the World Health Organisation is an important player. Our first recommendation is that when considering pandemic preparedness and response plans, all these governance structures will have to be taken into account. An important part of pandemic preparedness is that their responsibilities and mandates will have to be aligned upon before the next pandemic hits.

Rapid identification and procurement of suitable RMTs

One of the topics that would benefit from alignment is the topic of procurement, which has been a tremendous problem during the COVID-19 pandemic (Hartendorp et al., 2021). A similar situation could occur if RMTs are broadly applied during a pandemic. HERA, WHO and/or EMA might play a role in purchasing products needed in the pandemic phase. Procurement of RMTs in advance is tricky, as the characteristics and quantities needed will differ depending on the situation and pandemic pathogen. Some parts of the RMT chain might be already used by a significant part of the population (consumer products such as watches, apps etc). When connected with medical software (including apps), these devices might be an interesting element of the RMT dataflow. The question is whether these devices, when used for monitoring either in the context of clinical decision making or regulatory decision making, are safe and sufficiently validated, and hence accepted by the different regulators. It is important to stress that all pre- and post-market authorisation procedures and obligations are meant to monitor the benefit/risk performance of a MD and/or IVD. Any deviation of those procedures could have an impact on the quality of the product and potentially on the health of the user, which should be outweighed against the benefit for governance and pandemic policy in terms of public interest and individual risk. Our second recommendation is to establish an Ethics Advisory Board that can support complex decision making throughout the different phases of a pandemic, where different interests will have to be balanced. Our third recommendation is to explore whether a platform can be set up (such as for example by using EUDAMED) to provide insight into available RMTs that can be swiftly put to use during a pandemic.

Tools for rapid availability of RMTs: Exemptions

We looked into exemptions that could facilitate rapid access to RMTs for patients. Also here it should be noted that regulatory requirements are in place to evaluate and monitor the benefits, risks, quality and validity of a product, so if exemptions are to be used, one should balance the added value of using the exemption against potential risks. On a national level, it is possible for IGJ to facilitate an exemption for the affixation of a CE-mark for a specific term.[1] Moreover, a competent authority (e.g. IGJ) may authorise placing on the market or putting into service of a device for which the procedures referred to in the relevant articles of the MDR and IVDR have not been carried out, but of which the use is in the interest of public health or patient safety or health.[2] Another "exemption" is the confirmation of a non-compliance status of a device at the request of a manufacturer.[1] As for exemptions for limited scale use, the option of in-house devices is most likely the best suitable option. To our knowledge, compassionate use programs or "off-label use" programs for MDs and IVDs, in analogy of exemptions for medicinal products, do currently not exist in the Netherlands. On an EU level, there are exemption rules in the MDR and IVDR. Both the MDR and IVDR explicitly foresee in an exemption related to the conformity assessment procedures if the use of the product is in the interest of public health or patient safety or health.[1] Our fourth recommendation is to further investigate the applicability of these exemptions, rank them according to their suitability or sort them for different scenarios during a future pandemic to help fortify the pandemic response on a national level.

Regulatory pathways for RMTs

Next to looking into key governmental structures involved in pandemic responses, we analysed which regulatory pathways RMTs have to follow in order to be able to reach the patient. We evaluated different "checkpoints" that RMTs will encounter during their pathway towards patients, either for 1) clinical decision making (figure 6) or for 2) regulatory decision making (figure 7). For both pathways, parts of the relevant legislation have recently changed to update the legal framework. The MDR and IVDR are the successors of the MDD and IVDD, and were introduced with the aim to fill gaps that emerged due to novel innovations (such as RMTs), harmonise interpretation across Member States, and simplify the regulatory framework (Contardi, 2019). The change from CTD to CTR was also at least partly fuelled by the widely recognised problems arising from the lack of harmonisation under the CTD (Petrini, 2014). It should be noted that the legislation regulating medical devices during COVID-19 differs from the legislation that is applicable now.

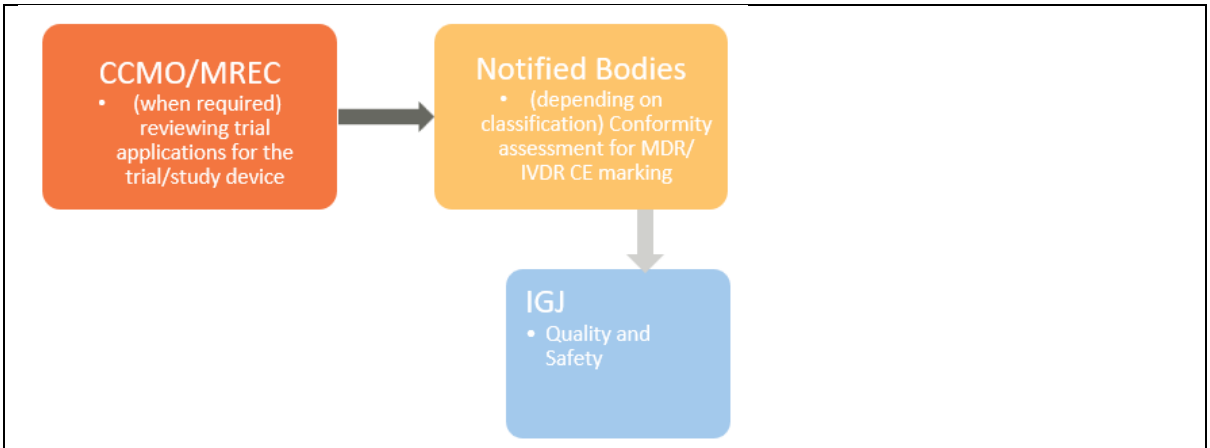

Figure 6: *Regulatory pathway for RMTs used to support clinical decision making*

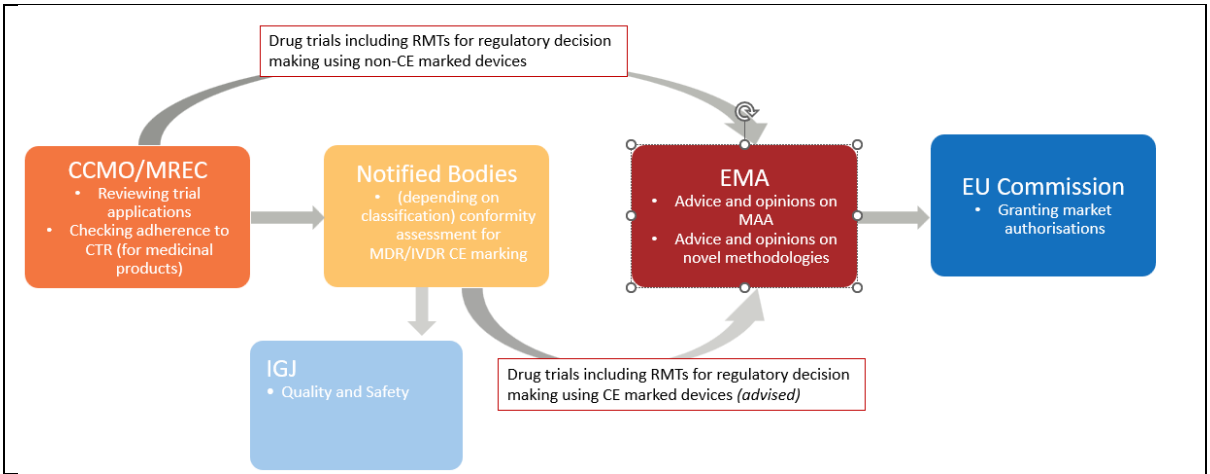

Figure 7: *Regulatory pathway for RMTs used to support regulatory decision making for MAAs*

The first checkpoint: CCMO/METC

The evaluation of the clinical trial protocol by the CCMO or an METC can be considered as the first "checkpoint" in the regulatory pathway. As discussed, the recent adoption of the CTR aims to facilitate harmonisation and to help make clinical trial applications simpler. Nonetheless, it was observed that this process is not flawless yet. For example, there can still be differences in interpretations of laws between different regulators and competent authorities. At the time of writing, not all countries have adopted the CTR in their respective national laws yet, which might change over the next couple of months. As the approval has shifted from a national level to a centralized EU level, the ability to contact the regulators directly through CTIS has been difficult. The new regulatory framework needs to work for all items, and needs to be interpreted in a consistent way. However, the "human factor" in decision making is not always transparent or comprehensible,

which can lead to inconsistencies. As an opportunity to remove any barriers, it was mentioned that we are on the right path to changing the regulatory dialogue, and improving harmonisation across EU Member States. The EMA has set out a workplan to accelerate Clinical trials in the EU (ACT-EU), so more is expected to follow soon. Our fifth recommendation is to keep following the discussions around the workplan to accelerate clinical trials closely. For innovators, our specific sixth recommendation is to think about the regulatory pathway and develop a strategy to navigate it as early as possible, and develop clinical research protocols in line with regulatory requirements that might become of relevance in later stages. Detailed topics of attention can be found in Deliverable report 5. Our seventh recommendation is to explore whether fast-tracking of trial applications during health crises can be incorporated into the CTR.

The second checkpoint: Notified bodies

The evaluation of RMTs by NBs can be considered a second "checkpoint" in the pathway. We came across several hurdles related to this checkpoint. These include the (perceived) complexity of the newly implemented regulations, the long waiting times at NBs, the very stringent requirements for software leaving little room for software modifications, unclear requirements to prove the validity of proposed clinical endpoints, the necessity to validate RMTs for each specific disease (even though the have been technically an clinically validated for a different disease), and the absence of the possibility to engage with NBs for scientific advice. A knowledge gap was also mentioned: RMT developers and clinicians often lack awareness and knowledge about regulatory relevance and requirements, whereas regulators (eg. at the EMA or at NBs) often struggle to comprehend aspects of RMTs, such as data flow or machine learning. Recently an amendment to the MDR/IVDR has been published (REGULATION (EU) 2023/607) allowing longer transfer periods for certain devices under certain conditions, slightly relieving the pressure on NBs. We have several recommendations to tackle some of these hurdles. Our eighth recommendation is to investigate how different MDs and IVDs (including software) are being evaluated under the new MDR and IVDR, where the complexity causes problems, and whether these can be resolved by either loosening the requirements or explaining why the requirements should remain stringent. Ultimately, when it is unclear what the software updates mean for the validity of the digital endpoint, this will be a huge limitation of the study, and often these results will (with good reason) not be accepted by a regulator (eg. the EMA in case of data supporting MAAs). Along similar lines, our nineth recommendation is to investigate in which cases RMTs validated for a specific parameter in a specific disease (a specific context of use) can use the same parameter for other diseases or in other settings. The latter (using devices approved for in-hospital settings in a home setting) would be in line with the reported relaxed regulations of the FDA during the COVID-19 pandemic, allowing RMTs which were previously approved for use in an in-hospital setting, to be used in a home environment without additional submissions, as described in D11 (U.S. Food and Drug Administration, 2020). It is important to note that these regulatory adaptations in the US are perhaps more feasible because the FDA assesses both medical devices and medicines, while the EMA evaluates mainly medicinal products, and conformity with requirements for CE marking is evaluated by NBs. Moreover, composing and maintaining an (inter)national overview of validated and approved RMTs and their context of use will help to identify technologies that can measure physiological parameters remotely relevant in the disease progression of future pandemics. The pandemic-specific regulatory adaptations may thereby play a crucial role in allowing RMTs validated in a non-pandemic situation to form an accelerated solution in a future pandemic. Our tenth recommendation is to invest in education on regulatory topics, to help (future) developers, implementors and users of RMTs as well as to ensure sufficient capacity of evaluators at NBs. Our eleventh recommendation is to investigate whether a platform, group or system can be set up where innovators can engage in discussions with regulators, get specific feedback on RMTs and other technologies, similar to the ITF or SA or QA procedures at the EMA. Pilots have been initiated in which these panels of medical experts are being consulted for clinical evaluation of high-risk devices (EMA Pilots Scientific Advice for Certain High-Risk Medical Devices | European Medicines Agency, n.d.). Similarly, a focus group has been established with involvement of the NBs, European Commission, and the EMA as 'one-stop shop'-pilot to provide scientific advice on drug and medicine combinations. This pilot has been terminated for unknown reasons. Publishing the lessons learned from this pilot may aid similar future initiatives.

The third checkpoint: EMA (in the context of drug development)

The evaluation of RMT collected data to support MAA's at the EMA can be considered a third "checkpoint". This is where the legislation around medicinal products intersects with legislation on MDs and IVDs, and has become a very hot topic over the past few years. During the writing of this report, several publications came out which explored similar questions like our report. The paper by Gelis and colleagues provides a comprehensive description and comparison of relevant pathways for this step at the EMA and the FDA (Gelis et al., 2023b). A paper by Colloud and colleagues presents four case studies that provide insight in regulatory approaches, which illustrate the complexity of the topic and underline the need for increased collaborations between stakeholders (Colloud et al., 2023). Our analysis on the QOs, QAs and SAs, which builds on an earlier publication (Dekker et al., 2021) provides relevant insights into topics of interest for innovators, and how these are perceived and evaluated by the CHMP. Detailed topics of attention, which are of relevance both to developers as well as to regulators, can be found in D7. Overall, despite a trend in increased use over time, the use of RMTs in registration trials is still relatively rare. Of note, no QOs, QAs or SAs were issued in the field of infectious diseases. Our analysis on the application of RMTs in phase 4 studies also provides an indication that RMTs are not widely used yet. In our interview with the EMA in D3, the EMA provided us with a comprehensive list of references to useful documents that can be used by innovators to help develop a suitable regulatory strategy. As mentioned across different deliverables and publications, engaging with regulators early on in the development process is imperative to the success of developing novel tools and technologies. Both the ITF and the QA and SA procedures are good pathways to engage with the EMA in the early stages of development, to confirm validity of the measure and sound implementation in the research protocol. Our twelfth recommendation for developers and innovators is hence to engage with the EMA via the suitable procedures, and take the relevant documentation and lessons learned from D3, D4, D5 and D7 into consideration. Of note, endpoints measured by RMTs need to be clinically relevant in order to be accepted for regulatory purposes. However, the RMT may be measuring an endpoint that would require regulatory qualification before it can be accepted. Novel endpoints can be filed together with MAAs. To reduce the risk of endpoints not being accepted, it is however advised to apply fpr for scientific advice and qualification advice at the EMA. Conceptually, the development of digital biomarkers does not differ much from other biomarkers. There is however a grey area concerning the remit of EMA versus other actors (e.g. NBs), including the appropriateness and capability to exchange confidential information if needed. Researchers need to be able to clearly explain the added value of the RMT. As pharmaceutical companies use external vendors for their remote monitoring technologies, concerns have arisen on privacy and accountability for the data, as often different apps or platforms need to work together. Accountability and responsibility for data quality as well as adherence to the GDPR have to be absolutely clear from the start of the study. The same goes for how software updates are handled and affect data collection, and for fragmentation of the collected data. Our thirteenth recommendation is for policy makers, to investigate how the presence of the EMA in the Netherlands can be further leveraged to strengthen the regulatory ecosystem. The presence of the EMA should make it relatively easy for innovators to engage with the EMA, and go for early advice. It is advised to investigate how early engagement can be promoted or facilitated. Our fourteenth recommendation is for innovators, to ensure that when planning on using RMTs in studies, that the use is sufficiently justified, and to ensure that a data management plan is available to demonstrate knowledge of the various data streams and privacy concerns.

Decentralised clinical trials (DCTs)

Particular attention has been paid to DCTs in this report. Trials that incorporate decentralised elements such as RMTs right from the start have a good chance of being able to continue during pandemics. A key principle of clinical trial execution is that trials may only be conducted if the rights, safety, dignity and well-being of participants are protected and prevail over all other interests, and if the trial is designed to generate reliable and robust data.[1]Both when clinical trials contain decentralised elements right from the start, as well as when a traditional trial is converted to a decentralised one, these principles will have to be adequately met. Switching from a TCT to a DCT was not deemed a very favourable option, as this would greatly affect the way that data is collected, which might compromise data integrity. Our fifteenth recommendation is that when DCTs are being set up, thorough evaluation and preparation of various procedures, guidelines, and alignment on responsibilities upfront should take place. DCTs' data collection standards are very strict, as is also the case for a conventional trial. These strict standards might provide hurdles, and affect the benefit/risk balance. It

would be good to have an open discussion on this topic with the regulators (eg. CCMO/METC, EMA, NBs, IGJ), and take context into consideration. Of note, devices used in DCTs need the EU's medical device CE marking to be used for clinical endpoints. Before medical scientific research can be executed, it will have to be evaluated and approved by a relevant body (CCMO or METC in the Netherlands). For multi-country DCTs, an important obstacle in the review and approval of the research protocol is that regulations and guidelines might differ per participating research institute and country. Professional qualifications and certifications are not harmonized. This lack of harmonisation is especially a barrier to the organisation of multinational trials and requires coordination between different authorities, regulators, and research institutions, even more so during a pandemic. Our sixteenth recommendation is to further explore whether harmonisation of the implementation of regulations across EU Member States can take place to facilitate multi-country DCTs. Our seventeenth recommendation is to explore whether harmonisation across the different "checkpoints" can be facilitated, and allow for a "one-stop-shop" platform for integrated, aligned feedback and advice.

Harmonisation in the ecosystem

Next to harmonisation in legislation and in regulatory handling, one of our interviewees pointed out that the innovators themselves can also contribute to harmonisation and to removing redundancies. It was noted that regulators are usually not the bottleneck in the adoption of RMTs in clinical trials. The regulator's expectations (especially those from the EMA) are clear to sponsors, but regulators are not able to facilitate harmonization across the full ecosystem: that is something that should be picked up by different stakeholders in the ecosystem itself. Hurdles mentioned included that RMT developers are often SMEs that lack the resources to successfully scale up production and make it available in multiple countries. This has generally made sponsors reluctant to perform large scale clinical trials with technology startups, and prefer to work with larger more established companies. Technology has often been shown to be useful in exploratory and proof-of-concept studies. Upscaling of the product is often an issue, as well as the lack of MDR CE marking. The use of real-world data from consumer grade devices is not well managed, often has missing data, poor signal to noise ratio and the expectations of regulators (in this case, NBs) are less clear. Sponsors would like to discuss as early as possible with regulators if a novel biomarker would be accepted, often without being able yet to demonstrate that its works (especially in the case of start-ups). To which the regulators request proof that the technology works as expected, which leads to a catch-22. Additionally, the logistics and associated costs around validating a technology can be an issue. The following recommendations can help to tackle these issues. Our eighteenth recommendation is for the entire ecosystem of pharmaceutical players to strive to develop the same standards. Steps have been made in public-private partnerships funded by the IHI, such as IDEA-FAST, RADAR-AD and Mobilize-D. The EMA and EFPIA aim to contribute to this topic through various programs to standardize the digital health space in clinical trials. Many sponsors are currently learning from each other, for example via working groups in EFPIA's digital endpoint sub-group. In addition, the development of clearly defined standards to RMT development would much help. Second, an open library or repository with all the possible measurements and technologies that have been validated and that are reproducible would help as well to adopt and develop RMTs and digital biomarkers.

Other considerations

Next to regulatory hurdles and opportunities, other topics that could facilitate a suitable regulatory ecosystem for RMTs and an improved pandemic preparedness emerged in this project. An often-mentioned bottleneck included the costs associated with the wide application of RMTs, the cost-benefit balance, and the responsibility of covering these costs. Another bottleneck is that during a pandemic the healthcare system is under enormous pressure with healthcare professionals not having time to spend on additional clinical trials for innovative technologies. The topic of inclusivity was also touched upon: Many RMTs require a certain level of digital proficiency, which means that you might lose people that are less "tech-savvy". Incorporating a patient expert panel during the study design might help. During the expert meeting, the relevance of informing and involving the general public on these topics was also deemed of paramount importance to help create a decent base of support, and to understand concerns of the general public. Our nineteenth recommendation is to take these considerations into account as well, both in the development of a pandemic preparedness strategy as well as in the overall pathway for RMT development.

With this report, and our recommendations, we hope to have provided a comprehensive overview of the various regulatory hurdles surrounding RMTs, and how these can be tackled to improve our pandemic preparedness for a future pandemic.

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ABBREVIATIONS

ACT-EU	Accelerating Clinical Trials in the EU
AI	Artificial Intelligence
CBG	Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen, Netherlands)
CCMO	Central Committee on Research involving Human Subjects
CE	Conformité Européene (European Conformity)
CHMP	Committee of Human Medicinal Products (EMA)
CoU	Context of Use
CTD	Clinical Trials Directive
CTIS	Clinical Trials Information System
CTR	Clinical Trials Regulation
CTTI	Clinical Trials Transformation Initiative
DCT	Decentralized clinical trial
DMP	Data Management Plan
DPIA	Data Privacy Impact Assessment
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
ELAB	Ethics and legal advisory board
EMA	European Medicines Agency
EU	European Union
EUDAMED	European database on medical devices
FDA	Food and Drug Administration
GDPR	General Data Protection Regulation
HERA	Health Emergency Preparedness and Response Authority
IGJ	Health and Youth Care Inspectorate
IHI	Innovative Health Initative
IHR	International Health Regulations
IMU	Inertial measurement units
ITF	Innovation Task Force (EMA)
IVD	In-Vitro Diagnostic Device
IVDD	In-Vitro Diagnostic Directive
IVDR	In-Vitro Diagnostic Regulation
MAA	Market authorization application
MD	Medical device
MDCG	Medical Device Coordination Group (EMA)
MDD	Medical Device Directive
MDR	Medical Device Regulation
MREC	Medical Research Ethics Committee
NB	Notified Body
NCA	National Competent Authority
PRO	Patient reported outcome
QA	Qualification Advices
QO	Qualification Opinions

RADAR-AD	Remote Assessment of Disease and Relapse – Alzheimer's Disease
RIVM	National Institute for Public Health and Environment
RMT	Remote Monitoring Technology
SA	Scientific Advices
SME	Small medium enterprise
SmPC	Summary of Product Characteristics
TCT	Traditional Clinical Trial
UDI	Unique Device Identifier
VWS	National Ministry of Health, Welfare and Sport
WHO	World Health Organization
WMO	Wet medisch-wetenschappelijk onderzoek met mensen (Dutch law on medical research involving human subjects)

Deliverable 1 and Deliverable 2:
Analysis of the legal frameworks supporting pandemic preparedness remote monitoring technology evaluation

Abstract

In this deliverable, the organisation, responsibilities and actors involved in a national pandemic response are discussed. The national context includes the National Institute for Public Health and Environment, the Ministry of Health, Welfare and Sport and the Municipal Health Services. The main legal framework is the Dutch Public Health Act. The key players in the EU context are the European Centre for Disease Prevention and Control, the Health Emergency Preparedness Response Authority, the European Medicines Agency, the European Commission and the European Council. The different competencies of these institutions are discussed in this deliverable. In the international context, the World Health Organisation is the main player.

A complex bottleneck discussed in this deliverable is the purchasing of RMTs in the pandemic situation, which could be an issue both at the national and European level. Additionally, an important factor regarding the speed at which RMTs can be purchased is the assessment and evaluation of the technology by the relevant bodies. This should also be prepared as much as possible. The RMT could be a medical device (MD) under the Medical Device Regulation, an in vitro diagnostic (IVD) under the In Vitro Diagnostics Regulation, and if the RMT contains Artificial Intelligence, it will also fall under the proposed Artificial Intelligence Regulation.

If the RMT is a MD or IVD, it will be assessed and classified in a certain risk class. In general, the RMT will have to meet safety and performance requirements, be subject to a vigilance system, be CE-marked and be assigned a Unique Device Identifier. For IVD, an important task is assigned to the EU reference laboratories, which will verify the performance claimed by the manufacturer.

A number of tools for rapid access to RMTs on national and European scale are discussed, such as exemptions under the MDR and IVDR. Additionally, exemptions for limited scale and defined users, such as in-house devices, off-label use, the research only exemption, compassionate use and named patient exemption, are explained. EUDAMED is defined as a central database that can provide information during a pandemic period on available devices on the EU market and post market surveillance data. Regarding data access, new regulations are in the making and are briefly discussed, such as the proposed Data Act.

A related topic is the regulation of clinical trials and the transfer from traditional clinical trials to decentralized clinical trials. In this context, it is explained how the rules of the Clinical Trials Regulation and related Dutch rules (WMO) would apply to and influence the way in which these trials can be amended. Important topics are the responsibility and control of the researcher, the suitability of the facility, informed consent, and the robustness of the trials, and hence of the study results.

One chapter is dedicated to data protection, privacy and ethical aspects, specifically in the situation that RMTs are used in DCTs. Besides the GDPR, the MDR and IVDR also set rules regarding data protection and the processing of personal data. Issues revolving around informed consent are tackled and the need for a DPIA or DMP is discussed. Third country transfer and data protection in the metaverse are briefly touched upon. This chapter is concluded with a paragraph on ethical aspects and the necessity of establishing an Ethical Advisory Board.

The deliverable is concluded with lessons learned and recommendations.

List with abbreviations

AI	Artificial Intelligence
CCMO	Dutch Central Committee on Research Involving Human Subjects
CIOMS	Council for International Organizations of Medical Sciences
Commission	The Commission of the European Union
CS	Common specifications
CTIS	Clinical Trials Information System
CTD	Clinical Trials Directive
CTR	Clinical Trials Regulation
DCT	Decentralized Clinical Trials
DGA	Data Governance Act
DMP	Data Management Plan
DPIA	Data Protection Impact Assessment
DTx	Digital therapies
ECDC	European Centre for Disease Prevention and Control
EDPB	European Data Protection Board
CE marking	European Conformity marking
EHDS	European Health Data Space
EHR	Electronic health record
EAB	Ethical Advisory Board
EMA	European Medicines Agency
EU	European Union
EUDAMED	European Database on Medical Devices
FSCA	Field Safety Corrective Actions
GCP	Good clinical practice
GDPR	General Data Protection Regulation
GDPS	General Product Safety Directive
GGD	Municipal Health Service
GPP	Good pharmacovigilance practice
HERA	European Health Emergency Preparedness Response Authority
HCP	Healthcare Provider
IGJ	Health and Youth Care Inspectorate of the Netherlands
IHR	International Health Regulations
IVD	In Vitro Diagnostic
IVDD	In Vitro Diagnostic Directive
IVDR	In Vitro Diagnostic Regulation
INB	Intergovernmental negotiating body
MAA	Market Authority Application
MD	Medical device
MDCG	Medical Device Coordination Group
MDD	Medical Device Directive
MDR	Medical Device Regulation
MDSW	Medical Device Software
MEB	Medicines Evaluation Board
Ministry of VWS	Ministry of Health, Welfare and Sport
Mir	Manufacturer incident report
MPD	Medicinal Product Directive
MREC	Medical Research Ethics Committee
POC	Point of Care
RIVM	National Institute for Public Health and Environment
RMT	Remote monitoring technology
SAMD	Software as a Medical Device
SWOT	Strength, Weaknesses, Opportunities and Threats
TCT	Traditional Clinical Trials
TFEU	Treaty on the Functioning of the European Union

UAVG	Uitvoeringswet Algemene Verordening Gegevensbescherming (Dutch GDPR Implementation Act)
UDI	Unique Device Identifier
VOG	Verklaring Omtrent het Gedrag (Certificate of Conduct)
Wbo	Wet op het bevolkingsonderzoek (Population Screening Act)
WGBO	Wet op de Geneeskundige Behandelingsovereenkomst
WHO	World Health Organization
WHA	World Health Assembly
WMA	World Medical Association
WMO	Wet medisch-wetenschappelijk onderzoek met mensen (Medical Research Involving Human Subjects Act)
Wpg	Wet publieke gezondheid (Public Health Act)

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Contents

1. Introduction

The purpose of this deliverable report (D1&D2) is to analyse the legislative framework related to pandemic responses and the application of Remote Monitoring Technologies (RMT). To this end we will first analyse the governance and legislative structure applicable to the (pre)pandemic phase on national, European and international level (Chapter 2), the definition, structure, devices and software related to Remote Monitoring in general and applicable legislation and standards (Chapter 3), guidelines and differences between traditional trials (including clinical trials (medicinal products), performance evaluation (In- Vitro Diagnostics (IVD)) as well as clinical investigations and evaluation studies (medical devices (MD)) and decentralized trials (including the same evaluations and investigation) (Chapter 4), Privacy and ethical aspects of RMT (Chapter 5) and lessons learned, recommendations (Chapter 6). These recommendations are based on the central topic of this report: Speaking from a legal perspective, what can be done to improve our pandemic preparedness by using RMTs?

During the (pre)pandemic phase, RMTs may be used to:
(a) carry out clinical trials for the development and introduction of medicinal products (including vaccines);
(b) carry out clinical trials/studies/investigations/performance evaluations for the development and qualification of devices and diagnostic products to be used during the pandemic to detect or monitor symptoms of the pandemic related infection;[1]
(c) carry out other clinical trials other than described under (a) and (b) in another setting than the traditional hospital environment to limit risks of infection with the pandemic pathogen and possibly relieve hospital staff where indicated;
(d) monitoring the pandemic infectious disease or, in the prepandemic period the symptoms of a (suspected) pandemic disease (either or not in combination with (a), (b) or (c) in a clinical trial setting.

These options may be carried out:

1) in a clinical setting at a hospital;
2) at home; or
3) in a Point of Care other than a hospital and or;
4) in a hybrid form combining 1) and 2), 2) and 3) or 1) and 3).

The option under 1) shall be referred to as Traditional Clinical Trials (TCT). The other options (2,3, and 4) shall in the context of this report be referred to as Decentralized Clinical Trials (DCT).

The regulatory framework will not include standards such as NEN and RIVM test standards as they might undergo important changes when a possible pandemic might arise. Where relevant in the respective context, we use MDCG guidelines.

During a (pre)pandemic phase, there is interplay between national and international regulations and cooperations. Hence, the relevant regulatory framework is categorized in national and international (mostly EU and occasionally worldwide) regulatory instruments where indicated. These may be more or less important dependent on the nature, phase and development of a pandemic and the challenges that the pandemic may create for the governmental bodies in charge if (the signs of) a pandemic manifest itself. This report also incorporates some of the lessons learned from the COVID-19 pandemic. However, the relevant regulatory framework for most RMTs has been changed significantly. Changes include, but are not limited to, the transition from the MDD to the MDR and IVDR, and the transition from CTD to CTR. Furthermore, the context of the key players underwent or shall undergo changes, as detailed in chapter 2.1. Another relevant development is that as the number of DCTs is growing, change is expected in adapted guidelines and legislation.

[1] See also Deliverable report 11 “Review on the Use of Remote Monitoring Technologies to Measure Physiological Parameters and PROs in COVID-19 Patients for Clinical Decision Making”.

2. The organisation, responsibilities and actors involved in a pandemic response

2.1: National key players

The governance for pandemic preparedness in the Netherlands is mostly regulated in the Public Health Act[2] (hereafter: **Wpg**). This act is an umbrella regulation regulating a variety of topics of public healthcare, for example child welfare services, care for the elderly, accidents and disasters, suppression of vectors, vaccination programmes and the monitoring and controlling of communicable diseases. A communicable disease (''infectieziekte") is not defined in Dutch legislation as such. However, the Wpg does list which diseases fall under group A1, A2, B1, B2 and C. The Wpg defines COVID-19 as an infectious disease in group A2.[3] Irrespective the abovementioned, the terms “contamination” (besmetting) and “infection” (infectie) are defined. These definitions correspond with the definitions given in the International Health Regulations (IHR) of the World Health Organization (**WHO**).[4] Depending on, amongst others, the severity of the consequences of a circulating pathogen amongst the population (for example with regards to communicable diseases), different actors, such as the chairmen of the safety regions and the National Institute for Public Health and Environment **(RIVM**), on behalf of the Ministry of Health, Welfare and Sport (**Ministry of VWS**) are part of the governance structure on national level. The controlling of a communicable disease belonging to group A1 or A2, as well as the controlling of new subtype humane influenzavirus, in case of a serious danger to the public health, is the responsibility of the chairmen of the safety regions.[5]

An important role is given to the reference laboratories, according to RIVM.[6] The European Centre for Disease Prevention and Control (**ECDC**), as further outlined in 2.2, defines reference laboratories as follows: "*The reference laboratory has state-of-the-art validated laboratory methods in operation and the ability to deliver accurate confirmation of diagnostic results within its field of expertise*". This may include the analysis of samples in a variety of areas, such as the verification of results (e.g., detection or confirmation) reported by external laboratories, the detection of specific microbial markers and the investigation of atypical samples.[7] This definition has also been used by the RIVM and is included in the Wpg.[8] The reference laboratories can give early warning in case of unusual occurrences of certain pathogens (surveillance function) and can provide surge capacity as part of a national preparedness plan. The goal of a reference laboratory is to have state-of-the-art knowledge and diagnostic abilities on a certain micro-organism. This knowledge is a shared with other laboratories, but also with the ministry of VWS and Municipal Health Services (**GGDs**).[9] One of the core tasks of

[2] Wet van 9 oktober 2008, houdende bepalingen over de zorg voor de publieke gezondheid (Wet publieke gezondheid)

[3] Art. 1 Regeling 2019-nCoV; there is, however, a proposed amendment to change this, so COVID-19 is then no longer classified into a certain group: Wijziging van de Wet publieke gezondheid in verband met het afschalen van de A-status van covid-19 | Tweede Kamer der Staten-Generaal (Wijziging van de Wet publieke gezondheid om te voorzien in een directe sturingsbevoegdheid van de Minister van Volksgezondheid, Welzijn en Sport op de directeur publieke gezondheid van de gemeentelijke gezondheidsdienst en in een grondslag voor het stellen van regels over de uitvoering van de algemene infectieziektebestrijding door de gemeentelijke gezondheidsdienst (Tweede tranche wijziging Wet publieke gezondheid))

[4] International Health Regulations (2005), WHO, 3rd edition (2016).

[5] Art. 6(4) Wet publieke gezondheid.

[6] H.A. Bijlmer, ‘Rapport “Structuur Referentielaboratoria in Nederland”’ (RIVM briefrapport 230481001/2012) <https://www.rivm.nl/bibliotheek/rapporten/230481001.pdf>.

[7] ECDC, ‘Core functions of microbiology reference laboratories for communicable diseases’, June 2010. <https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/1006_TER_Core_functions_of_reference_labs.pdf>.

[8] H.A. Bijlmer, ‘Rapport “Structuur Referentielaboratoria in Nederland”’ (RIVM briefrapport 230481001/2012) <https://www.rivm.nl/bibliotheek/rapporten/230481001.pdf>; art. 1, sub ac, Wpg.

[9] H.A. Bijlmer, ‘Rapport “Structuur Referentielaboratoria in Nederland”’ (RIVM briefrapport 230481001/2012) <https://www.rivm.nl/bibliotheek/rapporten/230481001.pdf>.

the reference laboratories is surveillance, early detection and outbreak management.[10] The reference laboratories are supported financially by RIVM.[11]A national reference laboratory is a laboratory that bundles all core functions. There are also laboratories that only execute a few of the functions; these are called Expertise Centers.[12]

In the IVDR, (see also chapter 3) the term reference laboratories is related to a central role in verifying the performance claimed by the manufacturer and the compliance of the device with the applicable common specifications (**CS**).[13] According to art. 100 of the IVDR, EU reference laboratories can be designated by the Commission for specific devices, or a category or group of devices, or for specific hazards related to a category or group of devices. These reference laboratories must conclude a contract with a notified body before verifying the performance of a device and its compliance with applicable common specifications. The reference laboratory then provides its opinion to the notified body, which ultimately takes the decision on whether the in vitro diagnostic device is compliant with the relevant regulations.[14] Therefore, this is a different type of reference laboratory than the reference laboratory mentioned in the Wpg. Though not formulated specifically in the Wpg, one may assume that the reference laboratories in the Netherlands will play an important role in the prepandemic period and possibly, during the pandemic period (as further outlined in chapter 4).

2.2 EU key players

On EU level several key players will perform tasks related to the pandemic as well.[15]

ECDC

The European Centre for Disease Prevention and Control (ECDC) is an agency of the European Union, governed by the Regulation of the European Parliament and of the Council of April 2004.[16] The mission of the centre is to identify and assess current and emerging threats to human health from communicable diseases and related special health issues, to report thereon and, where appropriate, to ensure that information thereon is presented in an accessible and comprehensive way. This centre shall act in collaboration with competent bodies of the Member States or on its own initiative. In providing recommendations to the Union and national levels it shall, where necessary, cooperate with Member States considering existing national crisis management plans and the respective circumstances of each Member State.

In case the outbreaks of diseases of unknown origin may spread within or to the Union, the Centre shall act on its own initiative until the source of the outbreak is known,[17] respecting the responsibilities of the Members States of the European Union, the Commission of the European Union (**the Commission)** and the responsibilities of third countries and organizations active within the field of public health, in particular the WHO, in order to ensure that there shall be comprehensiveness, coherence and complementarity of action and that actions are coordinated. In more concrete terms, the ECDC shall make, at the request of the Health Security Committee of the European Medicines Agency (**EMA**), the Member States or on its own initiative,

[10] Advies commissie Verburgh: Een netwerk van medisch-microbiologische referentielaboratoria in Nederland (11 september 2017), p. 6.
[11] H.A. Bijlmer, 'Rapport "Structuur Referentielaboratoria in Nederland"' (RIVM briefrapport 230481001/2012) <https://www.rivm.nl/bibliotheek/rapporten/230481001.pdf>.
[12] H.A. Bijlmer, 'Rapport "Structuur Referentielaboratoria in Nederland"' (RIVM briefrapport 230481001/2012) <https://www.rivm.nl/bibliotheek/rapporten/230481001.pdf>.
[13] Art. 48(5) IVDR; Laboratory tests performed by an EU reference laboratory shall in particular focus on analytical and diagnostic sensitivity using the best available reference materials.
[14] Art 11-12 Commission Implementing Regulation (EU) 2022/944 of 17 June 2022 laying down rules for the application of Regulation (EU) 2017/746 of the European Parliament and of the Council as regards the tasks of and criteria for European Union reference laboratories in the field of in vitro diagnostic medical devices.
[15] The role of the notified bodies is discussed in Chapter 3
[16] Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 April 2004 establishing a European centre for disease prevention and control.
[17] Art. 3 Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 April 2004 establishing a European centre for disease prevention and control.

epidemiological forecasts and provide data and easily accessible relevant analyses of available information.[18] ECDC has a well-established specific mandate in case of communicable disease threats.[19]

HERA

In the European context, the European Health Emergency Preparedness Response Authority (**HERA**) has been established as a Commission service.[20] HERA is set up to strengthen Europe's ability to prevent, detect, and rapidly respond to cross-border health emergencies, by ensuring the development, manufacturing, procurement, and equitable distribution of key medical countermeasures.[21] HERA is built on two pillars: the Commission Decision establishing HERA, and secondly the Regulation on the Joint Procurement of Medical Countermeasures in the Event of a Public Health Emergency, which is in force.[22]

HERA's mission is amongst others to strengthen health security coordination within the Union during preparedness and crisis response times, and bringing together Member States, the industry and the relevant stakeholders in a collaborative, shared effort.[23]

During the first part of the COVID-19 pandemic, HERA played an important role in the stockpiling capacity and distribution of vaccines. However, for tasks such as swift procurement and distribution of medical countermeasures, HERA relied mostly on the policy and actions of the Member States. This federated approach created a competition between Member States, resulting in shortages in several Member States like the Netherlands, while the essence for controlling an infectious disease is more likely to be a cross border response in Europe. This is probably why a second pillar was needed to support HERA, namely, the Council Regulation (EU) 2022/2372 of 24 October 2022 on a framework of measures for ensuring the supply of crisis-relevant medical countermeasures in the event of a public health emergency at Union level.[24]

HERA will have different modes of operation during preparedness and crisis times. In the "preparedness phase", it will steer investments and actions in strengthening prevention, preparedness and readiness for new public health emergencies. In the "crisis phase", HERA will be able to draw on stronger powers for swift decision-making and implementation of emergency measures. Its actions in both phases will be aimed at ensuring swift access to safe and effective medical countermeasures and at the scale needed, for, as we

[18] Art. 11.4 Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 April 2004 establishing a European centre for disease prevention and control.

[19] COM(2021) 576 final, Introducing HERA, the European Health Emergency preparedness and Response Authority, the next step towards completing the European Health Union, p. 3.

[20] Commission Decision of 16.9.2021 establishing the Health Emergency Preparedness and Response Authority, art. 1.

[21] COM(2021) 576 final, Introducing HERA, the European Health Emergency preparedness and Response Authority, the next step towards completing the European Health Union, p. 1.

[22] Council Regulation (EU) 2022/2372 of 24 October 2022 on a framework of measures for ensuring the supply of crisis-relevant medical countermeasures in the event of a public health emergency at Union level.

[23] Commission Decision of 16.9.2021 establishing the Health Emergency Preparedness and Response Authority, art. 2(1): see annex I.

[24] Given that this Regulation aims to ensure the supply and the timely availability and accessibility of crisis-relevant medical countermeasures addressing the economic impacts caused by public health emergencies, it is based on Article 122(1) of the Treaty on the Functioning of the European Union (TFEU). The Council may act pursuant to Article 122(1) TFEU to adopt measures that are appropriate to address the economic situation, in particular if severe difficulties arise in the supply of certain products in view of art. 1(2) of Council Regulation (EU) 2022/2372 of 24 October 2022; The framework is defined in art 1 of Council Regulation (EU) 2022/2372 of 24 October 2022 on a framework of measures for ensuring the supply of crisis-relevant medical countermeasures in the event of a public health emergency at Union level.

assume, all Member States. In both phases, HERA will integrate its operations with existing crisis management mechanisms.[25]

As European clinical trial networks for vaccines and therapeutics, as well as platforms, are the pan-European backbone to accelerate trials and connect all development stakeholders for designing and conducting trials, these platforms should be easily adjustable to respond to a broad range of potential threats and reduce current lead times. A first basis for cooperation is VACCELERATE– the first EU-wide network for COVID-19 vaccine trials, launched as part of the HERA Incubator. The objective of ensuring the provision of medical countermeasures shall be tailored in the field of stockpiling and EU procurement.At this stage one may take into consideration that HERA shall take adequate measures to procure the timely distribution of RMTs when needed by several Member States for controlling a pandemic more specifically related to essential clinical trials, monitoring the infectious disease or a policy for releasing the burden of hospital institutions.

EMA:
The European Medicines Agency (**EMA)** is the regulatory body responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU.[26] Throughout the crisis, EMA's regulatory capacity to evaluate and monitor the safety and efficacy of vaccines, therapeutics, and diagnostics has been constantly demonstrated. However, it has no mandate in the area of medical countermeasures other than medicinal products, and does not carry out procurement, stockpiling and distribution of capacities in the EU.[27]

The role of EMA in crisis preparedness has been strengthened in 2022 by Regulation (EU) 2022/123 of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices.[28]

This regulation provides a framework including preparing for, preventing, coordinating and managing the impact of public health emergencies on medicinal products and on medical devices and the impact of major events on medicinal products and on medical devices at Union level and for monitoring, preventing, and reporting on shortages of medicinal products and on shortages of medical devices.[29] However, it is not quite clear to which products the medical devices relate and if these products are meant to cover RMTs for a DCT as well.[30]

European Commission and European Council:
There is no specific legal ground for buying medical devices or medicinal products for the EU and/or its member states. However, art. 28 EC Treaty does state that the Commission shall take all necessary action within the limits of the powers conferred on the Commission, with a view to mitigating actual or potential shortages of medical devices included on the public health emergency critical devices list, including, where necessary, granting temporary exemptions at Union level pursuant to Article 59(3) of Regulation (EU) 2017/745 or Article 54(3) of Regulation (EU) 2017/746, while respecting the conditions set out in those Articles and seeking to ensure both patient and product safety. On 3 March 2022, the European Council adopted a decision

[25] COM(2021) 576 final, Introducing HERA, the European Health Emergency preparedness and Response Authority, the next step towards completing the European Health Union, p. 2.
[26] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
[27] COM(2021) 576 final, Introducing HERA, the European Health Emergency preparedness and Response Authority, the next step towards completing the European Health Union, p. 3.
[28] Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices.
[29] Art. 1 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
[30] COM(2021) 576 final, Introducing HERA, the European Health Emergency preparedness and Response Authority, the next step towards completing the European Health Union, p. 3.

to authorise the opening of negotiations for an international agreement on pandemic prevention, preparedness and response.

2.3 Worldwide key players

The World Health Organisation (**WHO**) is the United Nations agency that connects nations, partners and people to promote health, keep the world safe and serve the vulnerable – so everyone, everywhere can attain the highest level of health. The International Health Regulations (2005) (IHR) provide an overarching legal framework that defines countries' rights and obligations in handling public health events and emergencies that have the potential to cross borders. The purpose and scope of the IHR (2005) are "to prevent, protect against, control and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade." Article 49 IHR establishes the procedure for determining whether a situation is a public health emergency of international concern. The WHO can give recommendations to the States Parties when facing a public health emergency. However, this mostly concerns trade and travel restrictions or measures.[31] Art. 49 IHR establishes the procedure for determining whether a situation is a public health emergency of international concern. In December 2021, the World Health Assembly (**WHA**) established an intergovernmental negotiating body (**INB**) to draft and negotiate a convention, agreement or other international instrument under the Constitution of the World Health Organization to strengthen pandemic prevention, preparedness and response. Negotiations on the draft will continue until May 2024 according to a timetable laid out by the World Health Assembly.[32] More specifically, such an instrument can enhance international cooperation in a number of priority areas, such as surveillance, alerts and response, but also in general trust in the international health system.[33] WHO procures and supplies on a yearly basis a significant amount of goods and services to enable its important public health mandate. On 3 March 2022, the European Council adopted a decision to authorise the opening of negotiations for an international agreement on pandemic prevention, preparedness and response.[34]

Figure 1 describes the key players in pandemic responses.

[31] Based on art. 12(1) IHR, the Director-General shall determine, based on the information received, whether an event constitutes a public health emergency of international concern in accordance with the criteria and the procedure set out in these IHR. If the Director-General considers, based on an assessment under these Regulations, that a public health emergency of international concern is occurring, the Director-General shall consult with the State Party in whose territory the event arises regarding this preliminary determination. If the Director-General and the State Party are in agreement regarding this determination, the Director-General shall, in accordance with the procedure set forth in Article 49, seek the views of the Committee established under Article 48 (hereinafter the "Emergency Committee") on appropriate temporary recommendations.

[32] 'Timeline and deliverables', WHO (First meeting of the intergovernmental negotiating body to draft and negotiate a WHO Convention, Agreement or other international instrument on pandemic prevention, preparedness and response), 22 March 2022 <https://apps.who.int/gb/inb/pdf_files/inb1/A_INB1_6Rev1-en.pdf>: An international convention, agreement or other international instrument on pandemics would support and focus on: early detection and prevention of pandemics; resilience to future pandemics; response to any future pandemics, in particular by ensuring universal and equitable access to medical solutions, such as vaccines, medicines and diagnostics; a stronger international health framework with the WHO as the coordinating authority on global health matters; the "One Health" approach, connecting the health of humans, animals and our planet).

[33] 'An international agreement on pandemic prevention and preparedness' <www.consilium.europa.eu/en/policies/coronavirus/pandemic-treaty/>.

[34] 'Council gives green light to start negotiations on international pandemic treaty' (press release, 3 March 2022) <www.consilium.europa.eu/en/press/press-releases/2022/03/03/council-gives-green-light-to-start-negotiations-on-international-pandemic-treaty/>.

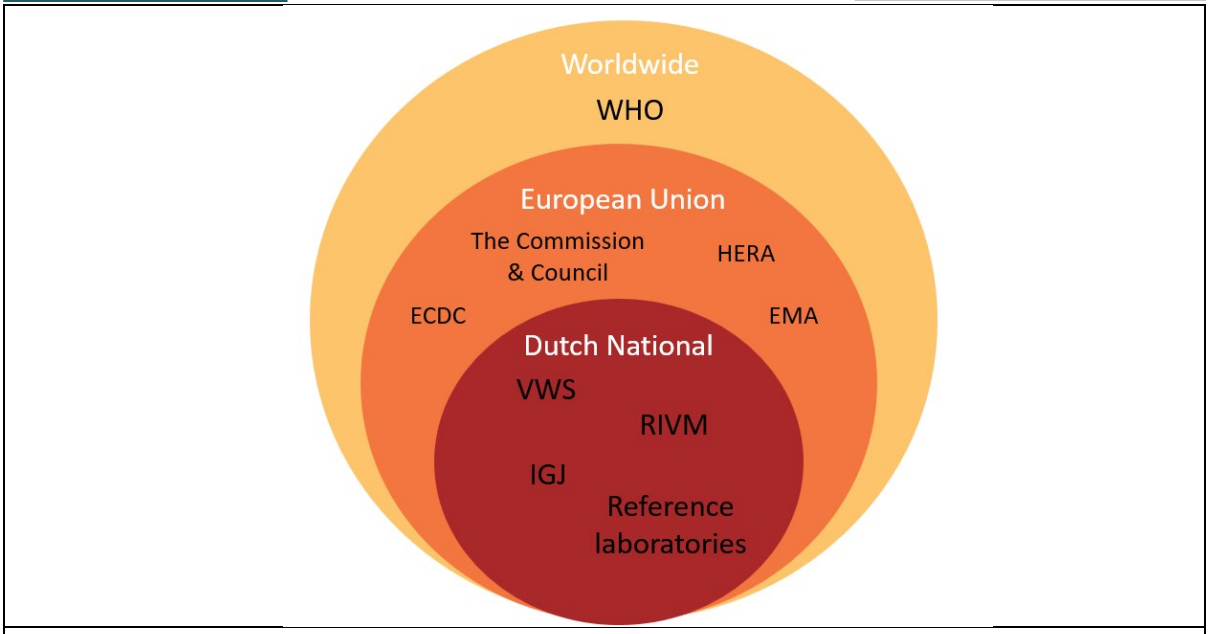

Figure 1: Different key players are involved in responses to pandemics

3. Remote monitoring technologies

3.1 General

Remote Monitoring means, in the context of this deliverable report, the monitoring of an individual in his or her home environment or at a point of care by means of a technological system for the purposes defined under Chapter 1 a), b), c) and d) only. Remote Monitoring entails a data flow driven by software and devices. This device can be an apparatus (laptop, I-pad, medical instrument or a wearable sensor). A wearable covers a broad range of items and technologies. A wearable can be a watch, headset or any apparatus that can be attached to the body of a person. RMTs can, to a certain extent, be applied by a lay person at home or by a healthcare provider ("**HCP**") visiting the patient at home or a Point of Care (**POC**). Wearables can communicate either directly through embedded wireless connectivity or through another device (e.g., a smartphone). Smart wearables may have control, communication, storage and actuation capabilities.[35] A wearable may be a consumer or lifestyle product (a watch, mobile phone or tablet) to measure heart rate during a workout and not for medical necessity. Possible software connected to a consumer product wearable can be a consumer product or a medical device. A wearable may also be a medical device. The purpose of a wearable or device is essential for the applicable regulations and market requirements as further outlined in Chapter 3.3 and 3.4.

The essence of RMTs applied in (pre)pandemic situation for either one or all tasks defined under Chapter 1 a), b), c), and d) entails the same data flow as in other situations. However, the elements constituting the flow may differ in terms of the purpose of the respective elements, the purpose and context of the dataflow and applicable regulation. The ideal configuration is dependent on multiple factors such as urgent need, international context, the trial and investigational product.

The following chapter explains the regulatory aspects of the products, the specific barriers and challenges that may arise during a (pre)pandemic period as a basis for further research into concrete preparations for the ideal set-up for a (pre)pandemic application.

3.2 Procurement of RMTs during crisis situations

It is difficult to establish a definitive purchasing framework for RMTs, as the characteristics and quantities needed will differ depending on the situation and pandemic pathogen. Definitive answers in advance of a pandemic are difficult to find for all parts of the RMT dataflow, as the exact criteria or properties thereof might be still under investigation/research during the early stage of the pandemic.

The exact criteria or properties of essential parts of the monitoring of the (symptoms) of the infectious disease remains an uncertainty. Action needed in view of not only regulatory requirements, but also relevant information sources, exemptions (national and international level) can be taken at hand as preparations. However, it is anticipated that large quantities of wearables and/or devices will be needed during a pandemic. The Netherlands, a relatively small country with a limited demand in comparison with other European countries or the worldwide spectrum, shall most likely not be the most prioritized purchaser. This also occurred during the COVID- 19 pandemic.[36] As explained in Chapter 1, HERA, WHO and/or EMA might play a role in purchasing products needed in the pandemic phase, most likely where an international demand is at play.

This situation can be prepared adequately if Member States align their policies for using RMT and possibly even for a preferred option for the data flow as well. If this situation is not feasible, the products for the RMT dataflow could be procured by the Sponsor of a trial, Minister of Health, the hospital conducting the trial, (reference) laboratories and citizens. It is not likely that the sponsor of the trial would be in a stronger market position if the remote monitoring is related to the Netherlands only. Furthermore, transparency rules, financial considerations of the manufacturer and informed consent documents might complicate this option. A similar

[35] European Commission, 'Smart Wearables Reflection and Orientation Paper Including Feedback from Stakeholders', December 2017, p. 4

[36] *Special report on EU COVID-19 vaccine procurement: Sufficient doses secured after initial challenges, but performance of the process not sufficiently assessed* (European Court of Auditors, 2022).

challenge will arise when a traditional trial is transformed to a decentralized option during a pandemic.[37] It is questionable whether a "one size fits for all" RMT system can be set up by the sponsor in an international trial. Furthermore, this option does not foresee in a RMT dataflow whereby the trial is combined with purpose d) the monitoring of possible symptoms of the suspected infectious disease ((pre)pandemic) or the infectious disease (pandemic) which might be essential when RMT is being applied during a pandemic.

More in general, the award of public contracts (by the State through the Minister of Health or public hospitals) must comply with the principles of the Treaty on the Functioning of the European Union (TFEU) and, in the context of this report, Directive 2014/24/EU on public procurement [38] and the Aanbestedingswet 2012.[39] Important challenges to consider during especially a prepandemic phase is that the exact criteria for elements of the RMT to be acquired, might be difficult to find and formulate as indicated in these regulations.[40] Moreover, legal proceedings of competitors in a competition where large volumes are involved, might put the most urgent timelines and public need at risk.[41] The possible exemptions, situations of extreme urgency (dwingende spoed)[42] and for innovative products may offer alternatives however under strict conditions.

Some parts of the RMT chain might be already used by a significant part of the population (watches, apps etc). When connected with medical software (including apps), these devices might be an interesting element of the RMT dataflow. The question is whether these devices when used for monitoring in the context of a trial would be acceptable for METCs. When data is collected to support regulatory decision making, it is essential to engage with the EMA early on to check if they would accept the collected data to support decision on market authorisation applications. When data is collected to support clinical decision making, the notified bodies will have to assess whether the devices and software collecting these data are sufficiently validated.

Non-public hospitals and laboratories are not under the scope of regulations on public contracts and might have a stronger position in the market of RMTs for the four options (a), (b), (c) and (d) mentioned in Chapter 1.

3.3 Regulatory and risk classifications of products used for remote monitoring

As remote monitoring entails a flow of several possible combinations of the elements software, devices and/or wearables, there might be several options for forming the most adequate (pre) pandemic set up depending on the regulatory status of each element.

For DCT the following processes and sequences in the data flow may be applied:

Patient/citizen (RMT = consumer product) Wearable is a consumer product, including iPad, iPhone, etc.	Software (e.g. app) most likely as a medical device	Data collection (hospital/laboratory) (including software as an accessory to a medical device)

Telecommunication (phone, iPad)	Verbal communication	Data collection inserted in server.

[37] See chapter 4.
[38] Directive 2014/24/EU of the European Parliament and of the Council of 26 February 2014 on public procurement and repealing Directive 2004/18/EC; Wet van 1 november 2012, houdende nieuwe regels omtrent aanbestedingen (Aanbestedingswet 2012).
[39] Aanbestedingswet 2012.
[40] Art. 2.31a e.v. Aanbestedingswet 2012.
[41] See e.g procurement Rechtbank Den Haag 14 February 2023, ECLI:NL:RBDHA:2023:1820, C/09/639789 / KG ZA 22-1106.
[42] Art. 2.32 lid 1, onderdeel c, Aanbestedingswet 2012.

Patient/citizen (RMT = MD/IVD)	Software accessory (supports	Data collection (hospital/laboratory) (possibly

Figure 2: data flows in different situations.

Although these diagrams may vary depending on the POC and/or the at home situation and products used, the continuous factor shall be the element of software connecting devices, independent of its regulatory status.

Furthermore, the starting point for the data flow is either a hospital institution, a laboratory or a GGD. The endpoint shall be the patient at home or a POC. For suitable products already available on the market, the timelines needed for regulatory adjustments (eg. a rapid transfer of an existing clinical trial or starting a clinical trial for new products, which involves setting up or amending protocols, quality and safety and/or privacy assessments, complete and sign forms, facilitate (renewed) informed consent, prepare explanation and testing of the products individually and in the required chain) may align with the short lines required for pandemic situations if prepared adequately.

However, full preparedness for certified devices, software and in vitro diagnostics with the intended use as required for any possible infectious disease or pandemic, for any possible trial, for any possible medicinal product in any situation a pandemic might evoke, in sufficient but large quantities, is currently unrealistic.

Adequate preparedness might be supported by an analysis of the adequate RMT dataflow. An adequate dataflow is a dataflow bearing minimum risks while offering the most flexibility, availability of estimated quantities. However, even in that ideal situation, elements of the RMT dataflow most likely will have to be adapted or developed.

Almost any product manufactured in the EU has to be in conformity with applicable rules. However, the regulatory path for the general CE of consumer products differs considerably from the path for development and market admission of medical devices or in vitro diagnostics (including software). The timelines for development, assessment, studies, evaluation and processing by the relevant bodies and other regulatory procedures are mostly influenced by the scope and risk classification and possibly and partly by the end-user (patient or healthcare professional) as explained and outlined in the following paragraphs.[43] An important factor for the classification of a medical device is the purpose of the device, as provided by the manufacturer. As far as medicinal products are concerned, the presentation and description of use of the manufacturer is an important element for establishing the borderline between a medical device and a medicinal product as well. Dependent on its use (either as an accessory of a medical device or not), the software to be used in the device and/or RMT datraflow shall be classified as a medical device or an accessory supporting a medical device.

3.4 Product classification: Medical Devices, in vitro Diagnostic Devices or consumer products?

The borderlines of these products are mostly influenced by their purpose and consequently their role in the RMT dataflow that could be formed by both consumer products and medical devices and/or in-vitro diagnostics. Borderlines categorize medical devices on the one hand and medicinal products on the other as well. An example is the use of digital therapies (**DTx**), which provide patients with evidence-based therapeutic interventions that are driven by software programs to prevent, manage, alleviate or treat a medical disorder or disease. They can be used independently or in combination with medications, devices or other therapies to optimize patient care and achieve positive clinical outcomes. Though the DTx are not borderline products (they are medical devices), in practice this type of device can lead to regulatory questions and uncertainties.

Borderlines are mostly marked by the definitions in the applicable regulations.

A Medical Device means:

[43] Art. 71 Medicinal Product Directive; as far as MDR/IVDR are concerned, for medicinal products other aspects as likeliness to present a danger even when used correctly or likely to be used incorrectly are relevant.

"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:

— diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
— diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
— investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
— 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."[44]

The last sentence marks an important element for the borderline between a medical device on the one hand and a medicinal product on the other.

Medical devices can simultaneously be machinery according to art. 1(12) MDR.[45]

An accessory for a medical device means:

"an article which, whilst not being itself a medical device, is intended by its manufacturer to be used together with one or several particular medical device(s) to specifically enable the medical device(s) to be used in accordance with its/their intended purpose(s) or to specifically and directly assist the medical functionality of the medical device(s) in terms of its/their intended purpose(s);"[46]

A RMT dataflow may consequently be formed by (consumer) products, medical devices (either software or not), an accessory, in vitro diagnostics, medicinal products or a combination thereof. The software may be driving or influencing the use of a medical device.[47] However, medical device software intended by the manufacturer, to be used, alone or in combination for a purpose as described in the definition of medical device in the MDR/ IVDR is general referred to as Medical Device Software (**MDSW**), regardless of whether the software is independent or driving or influencing the use of a device.[48]In other words: a MDSW must have a medical purpose on its own, such as providing immediate decision-triggering information or support for healthcare professionals. It should be noted that the intended purpose as described by the manufacturer of the software is relevant for the qualification and classification of any device. Software which is intended to process, analyse, create or modify medical information, may be qualified as a medical device software if the creation or modification of that information is governed by a medical intended purpose. However, altering the representation of data for embellishment/cosmetic or compatibility purposes does not readily qualify the software as medical device software.[49]

An In-Vitro Device means:

"any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the

[44] Art. 2(1) MDR.
[45] Machinery is defined in the Regulation on machinery as an assembly of parts or components, which are (intended to be) fitted with a driving system or intended for lifting loads (art. 3(1)).
[46] Art. 2(2) MDR.
[47] MDCG 2019-11 Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR, p. 3.
[48] MDCG 2019-11 Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR, p. 6-7.
[49] MDCG 2019-11 Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR, p. 6.

manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:
(a) concerning a physiological or pathological process or state;
(b) concerning congenital physical or mental impairments;
(c) concerning the predisposition to a medical condition or a disease;
(d) to determine the safety and compatibility with potential recipients;
(e) to predict treatment response or reactions;
(f) to define or monitoring therapeutic measures. Specimen receptacles shall also be deemed to be in vitro diagnostic medical devices;"[50]

A medicinal product is defined, in the Directive (Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use), hereinafter "**Medicines Directive**" as:

"(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis." [51]

The aforementioned definitions establish the demarcation between the MDR and Medicinal Product Directive ("**MPD**") and IVDR and MPD.

Pursuant to the definition of a medicinal product as set out above in the Medicines Directive, two criteria are essential: in Article 1 under 2A, the 'presentation criterium' and in Article 1 under 2B, the 'intended or actual function criterium'.

The scope of the General Products Safety Directive (**GPSD)**[52] is limited as a result of the borderline rules. The GPSD only applies to products in so far as there are no specific provisions with the same objective in rules of Community law governing the safety of the products concerned.[53]

Art. 2, sub a, of the GPSD defines a product as:

"any product — including in the context of providing a service — which is intended for consumers or likely, under reasonably foreseeable conditions, to be used by consumers even if not intended for them, and is supplied or made available, whether for consideration or not, in the course of a commercial activity, and whether new, used or reconditioned."

The general safety requirement of the GPSD is stated in art. 3, which obliges producers to place safe products on the market.

The distinction between medical devices and *in vitro* diagnostic medical devices is marked by the purpose of the device.

The Manual on borderline and classification[54] describes in concrete the legislative status of several products. This Manual, however, should be read in conjunction with other documents providing guidance on borderline,

[50] Art. 2(2) IVDR.
[51] Art. 1(2) Medicinal Product Directive.
[52] Directive 2001/95/EC of the European Parliament and of the Council of 3 December 2001 on general product safety.
[53] Art. 1(1) GPSD.
[54] Manual on borderline and classification for medical devices under Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746 on in vitro diagnostic medical devices Version 3 – September 2023.

such as with regard to software.[55] Some examples of borderline are included in the Annex on borderline.

The borderline between medical device and medicinal product is made clear by the exclusion in art. 1 MDR: "*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.*"

A medical device shall be qualified as a medicinal product if it achieves its principal intended action by pharmacological, immunological or metabolic means, in or on the human body. Borderline cases concern medical devices that are supported by, for example, a medicinal product.

The proposed Artificial Intelligence **(AI)** regulation[56] (hereinafter also: AI Act) is not relevant for marking borderlines. The regulation divides AI systems into three categories: unacceptable-risk AI systems, high-risk AI systems, and limited- and minimal-risk AI systems. Art. 6(1) jo. Annex II, number 11 and 12, AI Act realises an interaction with the MDR and IVDR. This leads to the conclusion that MDR and IVDR products functioning on the basis of AI will have to comply with the rules set by the AI Act as well as the MDR or IVDR. In other words: these regulations do not collide, but rather integrate realising probably extra steps for development.

Though AI development is relevant for pandemic preparedness, this subject does not fall within the scope of this report.
It is recommended to address the AI developments in the context of DCT and pandemic preparedness more precisely in a possible following report since this Act will cumulate the definitions, borderline guidelines, and transition rules for any element in the RMT dataflow.

3.5 Medical Devices and In Vitro Diagnostics: the pathway to the market

The dataflow in RMT may, when considering the borderlines as explained in 3.4, be formed by the following products:

A: The product used by the patient is a MD or an IVD and the software for this instrument is an accessory and not a MD or IVD itself;
B: The product used by the patient is a consumer/lifestyle product and the software linking the outcome data and processing these data to the clinical site qualifies as MD or IVD;
C: The product functions as telemonitoring that could qualify as MD ;
D: The product functions as teleconferencing that would most probably not qualify as a MD.
As explained below:[57]

		Regulatory status			
		Medical device	In-vitro diagnostic device	Accessory	Consumer product

[55] Such as MDCG 2022-5 Guidance on borderline between medical devices and medicinal products under Regulation (EU) 2017/745 on medical devices and MDCG 2019-11 Qualification and classification of software - Regulation (EU) 2017/745 and Regulation (EU) 2017/746.
[56] Proposal for a Regulation of the European Parliament and of the Council laying down harmonised rules on Artificial Intelligence (Artificial Intelligence Act) and amending certain union legislative acts.
[57] The aspects concerning classification of medical devices are governed by MDR Article 51 Classification of devices and Annex VIII Classification rules. For IVDR, the corresponding references are Article 47 and Annex VIII.

Function	RMT used by patient	x	x		x
	Software for MD or IVD			x	
	Software linking outcome data and processing data to the clinical site	X	x		
	Telemonitoring	x			
	Teleconferencing				X

Figure 3: Influence of the function of a device/software on its regulatory status.

The applicable legislative structure during the COVID-19 pandemic was mostly based on the legislation applicable at that time: the MDD[58], and for in vitro diagnostics on the IVD Directive.[59] The current legislative requirements and risk classification (in case of IVD) differ significantly from those applicable during the COVID-19 pandemic.[60] The present requirements are more extensive and complex. Simultaneously the risk classification for IVD has changed significantly as well. Due to the increasing role of European legislation, the role of national regulations[61] is currently limited. As of May 26, 2021 the Medical Device Regulation[62] came into force followed by the Medical Device Regulation for in-vitro diagnostics[63] on May 26, 2022, with a transition period. Regulation 2023/607[64] foresees in an extension of this transition period. Several devices (**'legacy devices'**) put on the market under the MDD regime, or IVDD regime may be kept in stock and offered under certain conditions up to respectively. The details are indicated in **Annex I.**

This report will take all rules under the IVDR and MDR, irrespective of any transition period for certification, as a starting point. Although there are differences between the regulatory framework and classification of the MDR and IVDR, these differences are of limited relevance for the conclusions of this report.
The pre-market regulations vary depending on the risk classification of the MD or IVD and consequently the role, purpose and positions of a RMT and software in the RMT chain. While during the COVID-19 pandemic (when the Directive was still in force) generally 80% of all IVDs were classified in the lowest category facilitating a conformity assessment statement of the manufacturer (facilitating a relatively faster regulatory pre- market track), only 20% of the IVD shall under the IVDR be classified in the lowest class. The other 80% of the IVD shall

[58] Council Directive 93/42/EEC of 14 June 1993 concerning medical devices.
[59] Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices.
[60] 'Europese verordeningen MDR en IVDR' <www.igj.nl/zorgsectoren/medische-technologie/nieuwe-europese-verordeningen-mdr-en-ivdr>
[61] Wet van 24 oktober 2019, houdende regels over de veiligheid en kwaliteit van medische hulpmiddelen (Wet medische hulpmiddelen); Besluit van 24 april 2020, houdende regels met betrekking tot de herverwerking en het verder gebruik van hulpmiddelen voor eenmalig gebruik in de zin van artikel 17 van Verordening (EU) 2017/745 en nadere regels over het gebruik van medische hulpmiddelen (Besluit medische hulpmiddelen); Regeling van de Minister voor Medische Zorg van 23 april 2020, kenmerk 1673023-204144, houdende de vaststelling van taaleisen en nadere regels in de zin van Verordening (EU) 2017/745 en Verordening (EU) 2017/746 (Regeling medische hulpmiddelen).
[62] 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.
[63] Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU.
[64] Regulation (EU) 2023/607 of the European Parliament and of the Council of 15 March 2023 amending Regulations (EU) 2017/745 and (EU) 2017/746 as regards the transitional provisions for certain medical devices and in vitro diagnostic medical devices.

have to follow more extensive pre-market procedures and studies and the manufacturer shall have to submit the data and information to the notified body for verification and monitoring after which the CE marking may be affixed. However, this does not include raw data.[65]

As a rule of thumb, a medical device falling under the scope of the MDR or IVDR may be placed on the market only if it fully complies with the requirements of the MDR and IVDR.[66] These requirements are related to the risk class assigned to the respective medical device or in vitro diagnostic taking into account the intended purpose, inherent risks, vulnerability of the human body and the potential risks associated with the devices.[67] For a medical device the risk classes are I, IIa, IIb, or III. For a product qualified as an IVD, the risk classes are A, B, C and D.

The general classification for IVD are:[68]

Class A	low individual and low public health risk
Class B	moderate individual and/or low public health risk
Class C	high individual and/or moderate public health risk
Class D	high individual and high public health risk

Figure 4: Classification of IVD according to risk to public or individual.

Class D devices cover essentially high-risk infectious agent testing (such as in blood transfusion or testing for life-threatening diseases) and blood/tissue compatibility testing. In addition to the overall assessment by a notified body, the performance of class D devices is to be verified by independent testing in EU reference laboratories, once those laboratories are designated by the European Commission. For novel class D devices, the performance evaluation has also to be reviewed by an IVD expert panel[69] . A European Database on Medical Devices (EUDAMED) containing most likely important information for policy making on devices on the market under MDR and IVDR is also under development.

For a medical device the risk classes are I, IIa, IIb, or III.[70] The risk classification of the MDR is case-specific, so the general classification is quite vague and broad. For more specific rules.[71]

[65] 'UDI Devices – User guide', EUDAMED V2.7 (April 2022); Nederlandse notified body: BSI-NL <www.bsigroup.com/globalassets/meddev/localfiles/en-gb/documents/bsi-md-mdr-best-practice-documentation-submissions-en-gb.pdf>; art. 77(6) MDR, waar de Commissie de opdracht krijgt richtlijnen te publiceren over het vrijwillig delen van raw data in het kader van clinical investigations: Commission Guidance on the content and structure of the summary of the clinical investigation report, 2023/C 163/06 C/2023/2622, OJ C 163, 8.5.2023.

[66] Details in annex I.

[67] MDCG 2021-24 Guidance on classification of medical devices, p. 4

[68] For IVDR, the corresponding references are Article 47 and Annex VIII.

[69] Expert panels on MDs and IVDs (EXPAMED) have been developed by the Joint Research Centre, the European Commission's internal scientific service, and will be managed by the European Medicines Agency.

[70] Classification is to be carried out in accordance with Annex VIII to the MDR. In addition, and according to Article 52(7)(a), (b) and (c), Class I devices can be further subdivided into Is – sterile condition, Im – measuring function and Ir – reusable surgical.

[71] See Chapter III of Annex VIII MDR.

Class I	Low risk
Class IIa	Medium risk dependent on application
Class IIb	Medium risk dependent on application
Class III	High risk

Figure 5: General classification of MD according to risk.

RMTs, regulatory classified as a MD or IVD, shall, when to be applied in the RMT dataflow most probably be classified as IIa, IIb or III depending on multiple factors of the device, including the intended use, and the IVD will probably be classified as C and most likely D, depending on the infectious disease during a (pre)pandemic.[72]

The regime applicable to software driving or influencing the use of a device shall most likely fall within the same class as the device.[73] Medical Device Software that both achieves its own intended purpose and also drives or influences the use of a (hardware) device for a medical purpose is classified on its own, based on the intended purpose achieved. In such a case, however, the risk class shall not be lower than the risk class of the hardware medical device.[74] For MDSW providing information for patient management different risk classifications may apply whereby the strictest rule or sub-rule should hence apply.[75]

All devices must comply with all relevant obligations of the MDR, such as:
- meet the general safety and performance requirements, including the requirements regarding the information to be supplied by the manufacturer.[76]
- be subject to the reporting requirements under the medical device vigilance system;

[72] Annex VIII IVDR: 2.4. Rule 4
Devices intended for self-testing are classified as class C, except for devices for the detection of pregnancy, for fertility testing and for determining cholesterol level, and devices for the detection of glucose, erythrocytes, leucocytes and bacteria in urine, which are classified as class B.
(b) Devices intended for near-patient testing are classified in their own right.
[73] Implementing rule 3.3 of Annex VIII.
[74] MDCG 2019-11 Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR, p. 12; Furthermore the risks related to the exchange of energy/substances between the body and diagnostic or therapeutic active devices, taking into account the different healthcare situations (condition of patients) are relevant for categorizing [rule 9, 10 and 12 of Annex VIII. MDSW, in the majority of cases, does not (directly) relate to such risks. It relates to the consequences of indirect harm from failure to provide correct information. Therefore, in line with Recital 5 of the Medical Device Regulation and international guidance from the IMDRF (International Medical Device Regulators Forum), Rule 11 was introduced into the MDR and is intended to address the risks related to the information provided by an active device, such as MDSW [Rule 11 , in particular, describes and categorises the significance of the information provided by the active device to the healthcare decision (patient management) in combination with the healthcare situation (patient condition).
[75] MDCG 2019-11 Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR, p. 12.
[76] Annex I of the MDR

- be CE marked (except custom-made devices and devices intended for clinical investigation);[77]
- be assigned a Unique Device Identifier (**UDI**) number and be registered in the electronic system.[78] The requirements are mostly equivalent to the rules for the IVD.

The CE marking of conformity[79] shall state that the requirements specified in this Regulation have been fulfilled in relation to the device that is covered. The manufacturer shall continuously update the EU declaration of conformity. The EU declaration of conformity shall, as a minimum, contain certain information[80] and shall be translated into an official Union language or languages required by the Member State(s) in which the device is made available.[81] Digital technologies, which may fall under the definition of "medical device", that are used in a clinical trial to support the development and approval of a medicinal product in a given therapeutic area as part of the dossier of a marketing authorisation will be assessed by the EMA and have gotten separate attention, due to their increased use.[82] These technologies may include sensors, wearables, tele-healthcare in clinical trials and digital record systems (such as apps that function as patient diaries). In summary, if a digital technology is used in the context of medicinal product development, evaluation or monitoring, and is expected to impact, even potentially, on the benefit-risk assessment of a Marketing Authorisation Application (**MAA**), then relevant aspects of the technology will be discussed at the time of MAA evaluation.[83] A qualification submission of the technology can also be pursued. In that case, it should provide insight into the reliability, accuracy, precision, clinical validity, generalisability and clinical applicability of the methodology to be qualified. However, this is not mandatory.

As indicated, prior to placing a device on the market, manufacturers of RMT (or IVD) shall have to undertake an assessment of the conformity of that device, in accordance with the applicable conformity assessment procedures as indicated for the respective class of the device.[84] These procedures contain items as general safety and performance requirements,[85] specification and justification of the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements, a clinical evaluation.[86]

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[77] In which case they should comply with the provisions of respectively Art. 52.8 and Annex XIII or Articles 62 – 80, 82 and Annex XV.

[78] Article 29, for implantable devices an extra obligation is applicable.

[79] As presented in Annex V, art. 10 MDR and art. 18 IVDR.

[80] Set out in Annex IV.

[81] Art. 19 MDR and art. 10 IVDR.

[82] EMA, 'Questions and answers: Qualification of digital technology-based methodologies to support approval of medicinal products (Status as of June 2020)', p. 3.

[83] EMA, 'Questions and answers: Qualification of digital technology-based methodologies to support approval of medicinal products (Status as of June 2020)', p. 4.

[84] Set out in Annexes IX to XI. [article 52. Manufacturers of class III devices, other than custom-made or investigational devices, shall be subject to a conformity assessment [as specified in Annex IX] or alternatively, the manufacturer may choose to apply a conformity assessment as specified in Annex X coupled with a conformity assessment as specified in Annex XI].
4. Manufacturers of class IIb devices, other than custom-made or investigational devices, shall be subject to a conformity assessment [as specified in Chapters I and III of Annex IX, and including an assessment of the technical documentation as specified in Section 4 of that Annex of at least one representative device per generic device group. Alternatively, the manufacturer may choose to apply a conformity assessment based on type examination as specified in Annex X coupled with a conformity assessment based on product conformity verification as specified in Annex XI].

[85] Annex I under the normal conditions of the intended use of the device, and the evaluation of the undesirable side-effects and of the acceptability of the benefit-risk ratio [referred to in Sections 1 and 8 of Annex I], shall be based on clinical data providing sufficient clinical evidence, including where applicable relevant data (as referred to in Annex III).

[86] In accordance with this Article and Part A of Annex XIV. See annex I.

After putting the MD or IVD on the market and into service, regulations for vigilance[87] (including for the reporting of any serious incident) apply.[88]

If the infectious pandemic disease presents a high individual risk and the RMT applied in the context of a DCT is combined with an IVD or function to improve the monitoring of this disease, EU reference laboratories shall need to perform an important and extra role in the pre-market and post market phases:

- They should be enabled to verify by laboratory testing the performance claimed by the manufacturer;[89]
- The notified body performing the assessment may request to verify by laboratory testing the performance claimed by the manufacturer and the compliance of the device with the applicable CS;[90]
- For specific devices, or a category or group of devices, or for specific hazards related to a category or group of devices, the Commission may designate, by means of implementing acts, one or more European Union reference laboratories (the 'EU reference laboratories'), that satisfy the criteria;[91]
- Within the scope of their designation, the EU reference laboratories shall, where appropriate, have tasks with respect to class D devices[92] to carry out appropriate tests on samples of manufactured class D devices or batches of class D devices;[93]
- to provide scientific and technical assistance to the Commission, the Medical Device Coordination Group (**MDCG**), the Member States and notified bodies in relation to the implementation of this Regulation;
- to provide scientific advice regarding the state of the art in relation to specific devices, or a category or group of devices.[94]

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[87] Art. 87 MDR, such as: reporting of any serious incident involving devices made available on the Union market, except expected side-effects which are clearly documented in the product information and quantified in the technical documentation trend reporting, pursuant to Article 88.

[88] As referred to in point (a) of paragraph 1 have to be reported immediately after they have established the causal relationship between that incident and their device or that such causal relationship is reasonably possible and not later than 15 days after they become aware of the incident. However, in the event of a serious public health threat the report referred to in paragraph 1 shall be provided immediately, and not later than 2 days after the manufacturer becomes aware of that threat.

[89] And the compliance of devices presenting the highest risk with the applicable CS, when such CS are available, or with other solutions chosen by the manufacturer to ensure a level of safety and performance that is at least equivalent.

[90] Referred to in paragraphs 3 and 4, for devices for which one or more EU reference laboratories have been designated in accordance with Article 100, the notified body performing the conformity assessment shall request one of the EU reference laboratories to verify by laboratory testing the performance claimed by the manufacturer and the compliance of the device with the applicable CS, or with other solutions chosen by the manufacturer to ensure a level of safety and performance that is at least equivalent, as specified in Section 4.9 of Annex IX and in point (j) of Section 3 of Annex X. Laboratory tests performed by an EU reference laboratory shall in particular focus on analytical and diagnostic sensitivity using the best available reference materials (Art. 48(5)).

[91] Set out in paragraph 4. The Commission shall only designate the EU reference laboratories for which a Member State or the Commission's Joint Research Centre have submitted an application for designation. (Art. 100).

[92] (a) to verify the performance claimed by the manufacturer and the compliance of class D devices with the applicable CS, when available, or with other solutions chosen by the manufacturer to ensure a level of safety and performance that is at least equivalent, as provided for in the third subparagraph of (Article 48(3)).

[93] As provided for in the Section 4.12 of Annex IX and in Section 5.1 of Annex XI.

[94] As well as: to set up and manage a network of national reference laboratories after consulting with the national authorities and publish a list of the participating national reference laboratories and their respective tasks;

Considering this role on EU level and their central knowledge role in regional healthcare areas of the Netherlands, the role and knowledge of laboratories qualified as EU reference laboratories shall be essential during a pandemic on national level as well.

These procedures for IVD and MD do not completely exclude the position or authority of The Health and Youth Care Inspectorate **(IGJ**). The IGJ remains responsible for monitoring, and supervising compliance alongside oversight counterparts from the other European Member States. Dutch manufacturers or authorised representatives of non-EU manufacturers established in the Netherlands are obliged to register (notify) certain risk classes of medical devices and IVDs nationally. National registration of a medical device is a statutory obligation[95] and helps the IGJ to carry out its supervisory remit in respect of these devices. Any incidents (via a Manufacturer incident report (**Mir**)) or Field Safety Corrective Actions (**FSCA**) regarding medical devices and IVDs should be reported to IGJ.[96]

3.6 Pharmaceutical legislation revisited

The regulatory framework for the development of medicinal products has not been changed significantly since the outbreak of the COVID-19 pandemic. However, on the 26th of April 2023, two proposals were released to amend the current European pharmaceutical regulatory framework.[97] The proposals are for a new directive replacing Directive 2001/83/EC (the primary EU law for human medicines) and a new regulation replacing Regulation 726/2004 (establishing the EMA and governing the centralised procedure), which will also consolidate the orphan and paediatric medicines regulations. The proposals seek to balance between supporting innovation and increasing the affordability and geographic availability of medicines by shortening regulatory protections.[98] Another noteworthy aspect is the streamlining of the regulatory procedures, whereby the standard review and approval timeline is reduced for centrally authorised products. Timelines for clinical approvals of for example clinical trial application are outside of the scope of this proposal.

Although this new instrument seems to be quite important for governmental instruments during a healthcare crises such as a pandemic, it is not likely that legislation promulgating from this proposal shall make it through adoption before late 2025 or 2026 and moreover this instrument is not directly related to the application of RMTs namely in the context of DCT either or not combined with monitoring of the infectious disease in a (pre) pandemic situation.

(f) to contribute to the development of appropriate testing and analysis methods to be applied for conformity assessment procedures and market surveillance;
(g) to collaborate with notified bodies in the development of best practices for the performance of conformity assessment procedures;
(h) to provide recommendations on suitable reference materials and reference measurement procedures of higher metrological order;
(i) to contribute to the development of CS and of international standards;
(j) to provide scientific opinions in response to consultations by notified bodies in accordance with this Regulation and publish them by electronic means having considered national provisions on confidentiality.

[95] Dutch Medical Devices Act, Section 24/25.

[96] 'Reporting serious incidents and corrective actions (FSCA)' <https://english.igj.nl/medical-technology/market-supervision/vigilance-reporting-incidents-and-corrective-actions/report-incidents-and-field-safety-corrective-actions>.

[97] 'Reform of the EU pharmaceutical legislation' 26 April 2023 <https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en>.

[98] The standard period for regulatory protection would be reduced from 10 years, including eight years of data protection and an additional two years of market exclusivity, to a total maximum period of eight years. "Basic" data exclusivity would be reduced from eight to six years, with an additional two years of market exclusivity, introducing a transferable data exclusivity voucher for antimicrobials, exemptions for hospital pharmacies with regards to preparing and dispensing products, transparency and disclosure requirements and the regulatory sandbox.

3.7 From Clinical Trials Directive to Clinical Trials Regulation

On 31 January 2022, the Clinical Trials Regulation[99] repealed the Clinical Trials Directive (EC) No. 2001/20/EC and national implementing legislation in the EU Member States, which regulated clinical trials in the EU until the Regulation's entry into application. Speaking from a legal perspective, no significant changes were introduced. However, in the operational execution of the Regulation, significant differences have been implemented with the goal to improve harmonisation in the execution of clinical trials across the EU.[100] As for now, this regulation only applies to clinical trials testing medicinal products.[101]

3.8 Tools for rapid access to suitable RMT on a national and EU scale

Before summarizing and analysing alternatives for urgent track procedures to shorten RMT and IVD development lines in case the market presents no adequate RMTs and IVD for the specific (pre)pandemic situation, it is important to stress that all pre-market and post market procedures and obligations are meant to procure and constantly monitor the adequate benefit/ risk performance of a MD and an IVD. Any deviation of those procedures may have an impact on the quality of the product, which should be outweighed against the benefit for governance and pandemic policy in terms of both public interest and individual risk. This process has to be monitored continuously as any stage of the pandemic may result in a different outcome of the benefit/risk performance and deviations to procedures.

An Ethical Advisory Board ("**EAB**") on both national and international level would support adequate considerations and possibly support public and individual capacity decision.

During the COVID-19 pandemic, IGJ released a guidance document related to the exemption to affix the CE mark in response to the limited availability of adequate IVDs. This policy was based under former legislation regulating an important higher number of IVD in the lowest class for which shorter pre-assessment procedure had to be followed.[102] It seems that IGJ balanced public and individual interest during the pandemic by facilitating the exemptions for a specific term.[103]

Important to note that an exemption to the obligation to affix the CE mark (bearing the number of the Notified Body after assessment and monitoring data of the manufacturer) does not automatically implicate that the manufacturer is exempted for other obligations such as related to quality, feasibility study, adequate data, research, post marketing surveillance etc of the product as well.

A retrospective analysis to support lessons learned from the COVID-19 period has been published on October 5th 2021 by the IGJ.[104] Moreover, the Temporary Committee Corona has been established, which will execute a 'parlementaire enquete' in order to be better prepared for a next public health crisis and learn lessons from

[99] Regulation (EU) 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.

[100] 'Clinical Trials Regulation', <www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-regulation> accessed 10 August 2023.

[101] Art. 2(1) Clinical Trials Regulation.

[102] 'Coronavirus: meer ruimte voor fabrikanten en leveranciers bij tekort aan medische hulpmiddelen' 23 March 2020 <www.igj.nl/actueel/nieuws/2020/03/23/coronavirus-meer-ruimte-voor-fabrikanten-en-leveranciers-bij-tekort-aan-medische-hulpmiddelen>.

[103] 'Geen uitzondering meer voor levering professionele mondkapjes en handschoenen aan de zorg zonder CE-markering' 30 September 2021 <www.igj.nl/actueel/nieuws/2021/09/30/geen-uitzondering-meer-voor-levering-professionele-mondkapjes-en-handschoenen-aan-de-zorg-zonder-ce-markering>; 'Medische hulpmiddelen vanaf 1 september weer alleen met CE-markering toegestaan' 21 October 2020 <www.igj.nl/actueel/nieuws/2020/08/11/medische-hulpmiddelen-vanaf-1-september-weer-alleen-met-ce-markering-toegestaan>.

[104] 'Lessen uit het toezicht tijdens de coronapandemie' 5 October 2021 <www.igj.nl/actueel/nieuws/2021/10/05/lessen-uit-het-toezicht-tijdens-de-coronapandemie>

the COVID-19 pandemic.[105]

In the context of DCT and RMTs, three regulatory and decision relevant aspects should be considered when considering measures in a (pre) pandemic phase:
1) Clinical trials are conducted on both national and international scale, most probably bearing as a consequence that the RMTs and at least the performance thereof should be equivalent in relation to the trial when deciding to move centrally executed clinical trials to a decentralised model using RMTs;
2) Manufacturers are not obliged to put any MD or IVD on the market in all Member States. For both national as international trials, this might complicate a rapid enrolment of RMTs when transferring trials to a POC or home situation;
3) Applying exempted IVD and or MD (in whatever form) in a DCT (either a national trial or international trial) during the pandemic for e.g. medicinal products in whatever stage of the clinical research, might have important and even unacceptable risks or consequences for a consistent and reliable data flow in itself or as a result of a stacked risk;
3) Exemption policies have to be coordinated for international DCTs.

The MDR and IVDR regulations introduce more exemptions and bodies involved with these procedures. The role of IGJ remains to certain extent a continuing factor.

Before analysing the possible exemptions on EU level, it is important to emphasize the new position (in comparison with the COVID-19 pandemic) and consequently monitoring/assessment role of the Notified Bodies under the IVDR and MDR. These entities mostly perform their activities on a commercial basis, however partly based on their exclusive role promulgating from EU regulation, and consequently function on the borderline of private and public activities. These bodies are consequently mostly private entities, to the extent that possibly several tasks may be interpreted as public tasks under open data regulations.[106]

The exemption rules of the MDR and IVDR show many similarities. Where the exemptions are identical, the corresponding article to the other regulation will be noted. The first set of not pandemic related exemption rules have been used for extending the transition period between the MDD and MDR.[107] The exemption of these products relies on the evaluation done by the competent authorities.

Furthermore, both the MDR and IVDR explicitly foresee in an exemption related to the conformity assessment procedures if the use of the product is in the interest of public health or patient safety or health.[108]
The respective Member State shall have to inform the Commission and the other Member States of any decision to authorise the placing on the market or putting into service of a device in accordance with paragraph 1 where such authorisation is granted for use other than for a single patient.[109]

Moreover, a competent authority (e.g. IGJ) may, by way of derogation,[110] authorise, on a duly justified request, the placing on the market or putting into service within the territory of the Member State concerned, of a specific device for which the procedures referred to in that Article have not been carried out, but of which the use is in the interest of public health or patient safety or health.[111] This derogation can also be used during the prepandemic phase. The exemption only gives the competent authority (in the Netherlands: the IGJ) the authority to apply this exemption on a duly justified request, so not on its own initiative. The manufacturer of the device will have to ask the competent authority to use the derogation. This derogation could be amended to better fit the (pre)pandemic phase.

As indicated above, Notified Bodies are important actors under the IVDR and MDR. Their role is not only related to the strengthened assessment and consequently pre-market phase. Where a Notified Body finds that

[105] 'Tijdelijke commissie Corona' <www.tweedekamer.nl/tcc>
[106] Art. 2(2) Open Data Directive; Data Governance Act; EHDS; Data Act.
[107] Art. 97 MDR.
[108] Art. 59 MDR, art. 54 IVDR.
[109] Art. 59(2) MDR.
[110] Art. 59 MDR.
[111] Art. 59 MDR and. 54 IVDR.

the requirements of a device are no longer met by the manufacturer, it shall, taking account of the principle of proportionality, suspend or withdraw the certificate issued or impose any restrictions on it unless compliance with such requirements is ensured by appropriate corrective action taken by the manufacturer within an appropriate deadline set by the Notified Body. The Notified Body shall give the reasons for its decision.[112]

Furthermore, though not an exemption for assessment, the Commission may, in exceptional cases relating to public health or patient safety or health, by means of implementing acts, extend for a limited period of time the validity of an authorisation granted by a Member State to the territory of the Union and set the conditions under which the device may be placed on the market or put into service.[113] Those implementing acts shall be adopted in accordance with an examination procedure.[114] Furthermore, the Commission shall, on duly justified imperative grounds of urgency relating to the health and safety of humans, adopt immediately applicable implementing acts in accordance with the procedure therefor.[115]

Another “exemption", though not in all respects related to an assessment procedure, is the confirmation of a non-compliance status of a device at the request of a manufacturer.[116] In case this situation occurs, the Member State shall inform the Commission and the other Member States of any decision to authorise the placing on the market or putting into service of a device where such authorisation is granted for use other than for a single patient. This decision can have an interaction on European level as the Commission may, following this notification in exceptional cases relating to public health or patient safety or health, by means of implementing acts, extend for a limited period of time the validity of an authorisation granted by a Member State into the territory of the Union and set the conditions under which the device may be placed on the market or put into service.[117]

Different Intellectual Property Rights might hinder rapid access to RMTs, for example because a manufacturer has a patent on a medical device. As a response to the COVID-19 pandemic, a legislative proposal was submitted in the Netherlands in April 2021, aiming to amend the Dutch Patent Act. Currently, the Minister of Economic affairs has the power to issue a compulsory licence if it serves the public interest. However, in this legislative proposal, the Dutch Minister of Health, Welfare and Sport (instead of the Minister of Economic Affairs) will become competent to grant a compulsory licence for a pharmaceutical product during a crisis or emergency.[118] The amendment has not been discussed in the Dutch Parliament yet.[119]

Although the regulatory landscape for exemptions and procedures, whether directly related to a healthcare crisis or not, provides several options for adequate (pre) pandemic preparedness, the key players might differ from national to international and governance (both national and EU level), for example competent authority, notified body and manufacturer. The combinations of options and actors may strengthen an efficient and

[112] Art. 56(4) MDR respectively Art. 51 (4) IVDR.
[113] Art. 59(3) MDR.
[114] Article 114(3) MDR.
[115] Article 114(4) MDR.
[116] This procedure might be relevant in the context of required exemptions as where a Competent Authority has applied this procedure (Article 97 MDR) with the effect that the device may be placed on the market despite its non-compliance, no additional derogation pursuant to Article 59 MDR, an exemption requested by the manufacturer is necessary. MDCG 2022-18**:** MDCG Position Paper on the application of Article 97 MDR to legacy devices for which the MDD or AIMDD certificate expires before the issuance of a MDR certificate.
[117] Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 107(3)). However, on duly justified imperative grounds of urgency relating to the health and safety of humans, the Commission shall adopt immediately applicable implementing acts (in accordance with the procedure referred to in Article 107(4)).
[118] *Kamerstukken II*, 2020-21, 35809-(R2152), nr. 2, amended in *Kamerstukken II* 2022/23, 36194, nr. A.
[119] Voorstel van rijkswet van de leden Ellemeet en Ploumen tot wijziging van de Rijksoctrooiwet 1995 in verband met de introductie van een bevoegdheid van de Minister van Volksgezondheid, Welzijn en Sport om ter bescherming van de volksgezondheid in een noodsituatie of crisis een dwanglicentie te kunnen verlenen voor een farmaceutisch product, een medisch hulpmiddel of een medisch hulpmiddel voor in-vitrodiagnostiek (Rijkswet dwanglicenties farmaceutische producten en medische hulpmiddelen)

effective approach of coordinated policy on a national level and between Member States with respect to RMTs.

Raw data are likely to become an important source of information when weighing possibilities and conditions for exemptions. It is important to note that premarket procedures do not foresee in the obligation for the manufacturer to provide raw data. However, guidelines regarding the content and structure of the summary of the clinical investigation report may be expected.[120] In addition, the Commission may issue guidelines for the formatting and sharing of raw data, for cases where the sponsor decides to share raw data on a voluntary basis. Those guidelines may adapt, where possible, existing guidelines for sharing of raw data in the field of clinical investigations.[121]

3.9 Exemptions for limited scale and defined users

Several possible options may be created for exemptions on a limited scale.

Clinical trials in emergency situations
In the CTR, the possibility is created to obtain informed consent and give information on the clinical trial after the decision to include the subject in the trial is taken.[122] All conditions have to be fulfilled, such as that the subject is unable to give prior informed consent due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition and the clinical trial has to pose minimal risk to the subject.[123]

In-house devices/health institute exemption
This exemption is general and, although it does not directly relate to a pandemic or public health, it might be relevant for the use of Remote Monitoring during a (re)pandemic phase. Medical devices can be manufactured and used within an EU health institution (in-house devices), on a non-industrial scale, to address the specific needs of target patient groups which cannot be met or cannot be met at the appropriate level of performance, by an equivalent CE-marked device available on the market. In-house medical devices are exempted from most of the provisions of the MD and IVD Regulations,[124] provided the health institution adheres to certain conditions,[125] to ensure the highest level of health protection, such as:

1) General safety and performance requirements: the relevant general safety and performance requirements of either the MDR or the IVDR are applicable to in-house devices;[126]

2) The definition of Health Institution for this exemption being an organisation the primary purpose of which is the care or treatment of patients or the promotion of public health.[127]

The health institution itself must determine how the requirements should be met but must also be prepared to provide detailed information to the competent authority.[128] The competent authority does not review the

[120] art. 77(6) MDR.
[121] Commission Guidance on the content and structure of the summary of the clinical investigation report, 2023/C 163/06 C/2023/2622, OJ C 163, 8.5.2023, p. 7–13.
[122] Art. 35, lid 1, CTR.
[123] Art. 35, lid 1, CTR.
[124] 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; Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU.
[125] Laid out in Article 5(5) of the relevant Regulation.
[126] Annex I of each Regulation.
[127] Definitions art. 2(36) MDR and art. 2(29) IVDR.
[128] MDCG 2023-1, January 2023, 'Guidance on the health institution exemption under Article 5(5) of Regulation (EU) 2017/745 and Regulation (EU) 2017/746', p. 10.

information beforehand. The authority verifies the documentation afterwards to ascertain that the general safety and performance requirements are met.[129]

This exemption might be relevant for a (pre)pandemic phase as, the words "health institutions" include hospitals as well as institutions, such as laboratories and public health institutes that support the healthcare system and/or address patient needs, but which do not treat or care for patients directly.[130]

This more extended explanation of a hospital to the executing key players in a (pre) pandemic phase might be useful for RMTs, and the software used in the RMT dataflow, as well as monitoring or controlling the pandemic disease when urgently needed. Although the clause clarifies as a condition the non-industrial scale, this limitation would not prevent inhouse software to be applied for a its patient group.[131] Moreover, in case of IVDs, the analysis of a large number of patient specimens does not automatically render an in-house IVD to a device produced on an industrial scale.[132]

Nonetheless in view of the central role of certain academic centres and top clinical hospitals, a European MDCG Guidance on in-house device in the interest of public health or a public health crisis would significantly support a rapid development of RMTs, especially in the early phases of a pandemic for either DCTs and/or monitoring the (presumed) symptoms of the (presumed) infectious disease more efficiently and thoroughly.

Off-label use of medical devices and IVD

Off-label is a well-known term and option in the field of medicinal products, although off-label use is only possible when protocols and legislation are strictly followed.[133] Although off-label use of medical devices and IVD might be an option for use in the event of shortages or absence of adequate devices during a pandemic period, no specific rules or guidelines apply on national or EU level.

Custom-made devices

The definition of custom-made devices limits the use for other than a particular patient, as a result of which this exemption could hardly be defined as a relevant exemption for a pandemic.[134]

Research only

This exemption seems to only apply to the MD and IVD for which the trial has been set up to investigate the safety and performance of that specific device and not the RMT facilitating this trial.[135]

Compassionate use

[129] Art. 5(5)(f) MDR and Art. 5(5)(e) IVDR.

[130] Recitals 29 and 30 of the IVDR and MDR, respectively.

[131] MDCG 2023-1, January 2023, 'Guidance on the health institution exemption under Article 5(5) of Regulation (EU) 2017/745 and Regulation (EU) 2017/746'.

[132] MDCG 2023-1, January 2023, 'Guidance on the health institution exemption under Article 5(5) of Regulation (EU) 2017/745 and Regulation (EU) 2017/746', p. 18.

[133] Art. 68 Geneesmiddelenwet; see also for the respective professional standards:
'Off-label voorschrijven' (Statement, 13 January 2018) <www.igj.nl/publicaties/standpunten/2018/01/13/off-label-voorschrijven>; 'Off-label voorschrijven' (Dossier, 10 June 2020) <www.knmg.nl/advies-richtlijnen/dossiers/off-label-voorschrijven>.

[134] 'custom-made device' means any device specifically made in accordance with a written prescription of any person authorised by national law by virtue of that person's professional qualifications which gives, under that person's responsibility, specific design characteristics, and is intended for the sole use of a particular patient exclusively to meet their individual conditions and needs, Art. 2(3) MDR.

[135] Investigational device is defined under art. 1(46) MDR as "a device that is assessed in a clinical investigation." investigational devices are exempted from the obligations to bear the CE marking of conformity (art. 20(1) MDR). Art. 52(3) MDR holds more exemptions for specific classes of devices and exemptions for investigational devices.

Member States may facilitate compassionate use of a medicinal product under specific conditions.[136]
The definition of compassionate use is based on the situation of an individual patient or a limited group of patients and not a public health crisis in whatever form. Compassionate use has not been regulated in the MDR or IVDR.

Named patient
Named patient has not been regulated in the MDR or IVDR. In view of the limited scale and restrictive conditions, it is not likely that this use shall be an adequate alternative for RMT needed for DCT during the pandemic.[137]

The health institution exemption is the most likely exemption to be used when a pandemic starts since the rules surrounding this exemption are clear and it is not limited to a small number of patients of the respective institution. However, an exemption should only be used as a temporary solution until an adequate alternative has been certified.

3.10 Data access for emergencies/emergency pathways

EUDAMED is the IT system developed by the European Commission, which was introduced in Regulation (EU) 2017/745 on medical devices (MDR) and Regulation (EU) 2017/746 on in vitro diagnosis medical devices (IVDR).[138]

The system is multipurpose. It is a collaborative and interoperable platform, that will function as a registration system, a collaboration and a dissemination system (partially open to the public). EUDAMED is instituted to improve transparency and coordination of information regarding medical devices available on the EU market. It consists of six modules: actor registration, unique device identification (UDI) and device registration, notified bodies and certificates, clinical investigations and performance studies, vigilance and market.[139]

Mandatory use of the system will start when the entire EUDAMED system (including all 6 modules) has been declared fully functional following an independent audit and a Commission notice to be published in the Official Journal and in accordance with the transitional provisions set out in the medical devices regulations.[140]

Although EUDAMED is not fully operational yet, it is planned to be used as a central data base during both non-pandemic as well as for a (pre)pandemic period, providing information on:

1) available devices on the EU market, their intended use, economic actors involved;
2) important post market surveillance data.[141]

[136] Art. 83 Regulation 726/2004: 1. By way of exemption from Article 6 of Directive 2001/83/EC Member States may make a medicinal product for human use belonging to the categories referred to in Article 3(1) and (2) of this Regulation available for compassionate use. Art. 3(1) refer to Annex 1.
[137] Art. 83 Medicinal Product Regulation.
[138] Art. 33 MDR & art. 30 IVDR.
[139] The obligations to register can be found in Articles 29 and Article 31. Article 31 requires economic operators (Manufacturers, Authorised Representatives and Importers) to register to obtain a Single Registration Number or "SRN". Article 29 requires manufacturers to upload information about each device, including its UDI information.
[140] Art. 123(3)(d) MDR & art. 113(3)(f) IVDR.
[141] 'EUDAMED database', <https://ec.europa.eu/tools/eudamed/#/screen/home> accessed 10 August 2023.

3.11 Data access regulations

Although the scope of the proposed Data Act[142] is "the internet of things" and a cornerstone of the European data regulations Open data Directive[143], Data Governance Act (**DGA**)[144] and European Health Data Space **(EHDS**) Regulation[145], it contains an important lead for access upon request by a public sector body or a Union institution to data held by commercial parties (such as the manufacturer of software or certain devices) in case of exceptional needs.

An exceptional need to use data within the meaning of this Chapter shall be deemed to exist in any of the following circumstances:
(a) where the data requested is necessary to respond to a public emergency;
(b) where the data request is limited in time and scope and necessary to prevent a public emergency or to assist the recovery from a public emergency;
(c) where the lack of available data prevents the public sector body or Union institution, agency or body from fulfilling a specific task in the public interest that has been explicitly provided by law.[146]

The laws would also give these bodies access to commercial data where needed to fulfil tasks in the public interest that they are legally obliged to carry out, and for which they could not obtain the necessary data in other ways. Small companies would be exempt from the requirements.[147]

The EHDS Regulation[148] proposal expressly states that health data contained in electronic health records ("**EHRs**") can be processed for training, testing and evaluating of algorithms, including in medical devices, AI systems and digital health applications.
However, there is a condition: this secondary use must satisfy any of certain purposes of which:

- contributing to the public health or social security;
- ensuring high levels of quality and safety of medical devices.[149]

The EHDS envisages a quite broad list of categories of data that shall be available to reuse, including; (i) EHRs, (ii) pathogen genomic data, (iii) genetic data, (iv) identification data related to health professionals, (v) electronic health data from clinical trials, and (vi) electronic health data from biobanks.[150] The EHDS regulation obliges the data holder to put the electronic health data at the disposal of the health data access body within two months from receiving the request from the health data access body. In exceptional cases, that period may be extended for an additional period of two months. However, this decision is made by the health data access body.[151] Health data access bodies and single data holders may charge fees for making electronic health data available for secondary use. Any fees shall include and be derived from the costs related to conducting the procedure for requests, including for assessing a data application or a data request, granting, refusing or amending a data permit or providing an answer to a data request.[152]

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[142] Proposal for a Regulation of the European Parliament and of the Council on harmonised rules on fair access to and use of data (Data Act), COM/2022/68 final.
[143] Directive (EU) 2019/1024 of the European Parliament and of the Council of 20 June 2019 on open data and the re-use of public sector information.
[144] Regulation (EU) 2022/868 of the European Parliament and of the Council of 30 May 2022 on European data governance and amending Regulation (EU) 2018/1724 (Data Governance Act).
[145] Proposal for a Regulation of the European Parliament and of the Council on the European Health Data Space, COM/2022/197 final.
[146] Art. 15 Data Act.
[147] N. Fleming, 'Proposed EU data laws leave researchers out in the cold' *Nature Index*, 9 May 2023 (doi: https://doi.org/10.1038/d41586-023-01572-2)
[148] Further discussed in next report.
[149] Art. 34 European Health Data Space Regulation.
[150] Art. 33 European Health Data Space Regulation.
[151] Art. 41(4) European Health Data Space Regulation.
[152] Art. 42 European Health Data Space Regulation.

4. Regulations and guidelines for clinical trials (TCT and DCT)

Clinical trials may be conducted only if the rights, safety, dignity and well-being of participants are protected and prevail over all other interests; and if the trial is designed to generate reliable and robust data.[153]

This strictly worded basis seems not to facilitate exemptions in the situation of a public health crisis. TCTs may be at risk during a pandemic due to the continuous concern of infection and extraordinary pressure on hospital treatments while the HCPs needed may be at risk of infection as well. Although a pandemic may realize considerably more patients, the decision to transfer trials to DCTs seems to be an adequate alternative during a pandemic period. However, several aspects have to be considered. These aspects differ when initiating new trials as DCT in comparison with the situation that already initiated TCTs have to be transferred to a DCT setting.

Furthermore, the process of weighing options and initiating procedures may be quite different for national trials compared to international trials involving more Member States or non-EU countries. Moreover, relevant factors influencing procedures and decisions for either starting a DCT or transferring a TCT to a DCT, might differ depending on the pandemic phase. The interest in the decentralised model has increased since the health crisis caused by the COVID-19 pandemic occurred. Several research consortia have been set up to analyse the potential, consequences, guidelines, patient perspective and the quality of the data in DCTs.[154] These consortia have often been set up outside of the context of a healthcare crisis, but lessons learned can still be applicable and of use to improve our pandemic preparedness. The advantages of DCTs should be weighed against the disadvantages, specifically when TCT are being transferred to a DCT as the patient may experience pressure in the public interest.

Relevant consequences to consider decisions on transferring trials to a decentralized set up in relation to the point of depart of the Clinical Trials Regulation (**CTR**) as reflected above are amongst others:

- More in general, DCTs may offer improvement in the collection of clinical evidence such as the ability to collect and collate data reliably and resourcefully (digital technologies) through the use of new technologies, such as mobile applications, RMTs, web pages and electronic consent, accelerating recruitment and improving retention of data and information.[155]
- DCTs could not only release the burden on hospitals in a pandemic phase, but also limit inter human contact in hospitals, reducing the risk of infection.
- For both the TCT as the DCT, international ethical guidelines have to be respected:
- The World Medical Association (**WMA**) Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects,
- The WMA Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks,
- The Council for International Organizations of Medical Sciences (**CIOMS**) International Ethical Guidelines for Health-Related Research Involving Humans.

However, these ethical regulations are based on regular situations and TCT.[156] The regulatory framework for DCTs is limited. Ethical considerations might get under pressure during a health crisis in which possible contact measures have been taken. The guidelines do not – yet - foresee in tools, guidance or aspects to consider when public health is at stake and patients might feel isolated.

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[153] Art. 3 Clinical Trials Regulation.

[154] Home - Trials@Home (trialsathome.com); IDEA-FAST.

[155] Y. Santa-Ana-Tellez and H. Gardarsdottir, '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' 29 March 2022 (V2.1), Trials@Home Consortium.

[156] CTR, WMO and guidelines as limited to the standards of good clinical practice and guidelines of National Competent Authority, International Conference on Harmonization of Good Clinical Practice (ICH GCP) (21,22), Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic (European Commission) (V.5, 10 February 2023)

4.1 Several relevant elements of DCT

For international DCTs, an important obstacle to consider is that not only regulations and guidelines might differ per participating research institute and country where the DCT is meant to be carried out, but also the phase and consequences of the healthcare crisis. Professional qualifications and certifications are not harmonized among countries. A transfer of cross border trials to DCT entails possibly longer processes for handling legislative and guideline differences. This is especially relevant for legislation on digital/electronic procedures and RMTs applied. This lack of legislative harmonisation is especially a barrier to the organisation of multinational trials at all levels: local, regional, national and European; as it requires coordination between different authorities (handling a pandemic as well).

A recommendation is for the Central Committee on Research Involving Human Subjects (**CCMO**) to cooperate with other research assessment committees in Europe in the (pre)pandemic phase. The CCMO does participate in the Heads of Medicines Agencies and other working groups at the European level.[157]

The element of fragmentation also relates to data protection: some legislative elements of data protection, particularly for health data, are divergently arranged at the EU member state level. The assumption of decrease of workload for healthcare professionals might be interpreted differently by the several participants in an international trial and cannot be argued as a rule of thumb for all participants.

Another item to consider is the coordinated decisions on clinical trials in an international context. More in general (international or national) the following elements are relevant for an adequate decision:

- Investigators and other healthcare professionals, should be sufficiently qualified to perform their task.[158]
- The facilities where the clinical trial is to be conducted, have to be suitable for the conduct of the clinical trial in compliance with the requirements of the CTR.[159]
- The national requirements on suitability of the facility are mostly implemented in the Central Committee on Research Involving Human Subjects (**CCMO**) richtlijn Toetsing Geschiktheid Onderzoeksinstelling.[160]
- Tasks and healthcare professionals might change during a, possibly fast, transfer to and during the DCT itself.
- The transfer is most likely to be qualified as a substantial amendment since it changes the safety of the trial and the reliability and robustness of the generated data for which a new approval from the CCMO is needed.[161] [162]
- The so called Verklaring Omtrent het Gedrag (Certificate of Conduct) (**VOG**) most probably will need a

[157] 'Europa', <www.ccmo.nl/over-de-ccmo/jaarverslagen/jaarverslag-2022/ontwikkelingen/europa> accessed 18 October 2023.

[158] Art. 49 CTR.

[159] Art. 50 CTR.

[160] CCMO-richtlijn Toetsing Geschiktheid Onderzoeksinstelling, 25 oktober 2021, Staatscourant 2021 nr. 44381.

[161] 'Wijzigingen onderzoeksdossier (amendementen)' <www.ccmo.nl/onderzoekers/tijdens-en-na-het-onderzoek/wijzigingen-onderzoeksdossier-amendementen>

[162] "*A **substantial modification** (SM) is defined as "any change to any aspect of the clinical trial which is made after notification of a decision referred to in Articles 8, 14, 19, 20 or 23 of the CTR and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial".*
*A **non-substantial modification** is a modification without substantial impact on the safety or rights of the subjects and/or the reliability and robustness of the data, and the information is not necessary for oversight. This modification should **not be reported** as such. The non-substantial changes should be listed and identified as such in the cover letter of the next substantial modification application. However, the changes do not have to be described in detail. (…) The non-substantial modifications will have to be recorded in the Trial Master File and made available on request for inspection purposes as appropriate*." This definition corresponds with clause 81(9) of the CTR: regulating substantial modifications and non-substantial modifications.

new chapter on DCT.

- DCTs, particularly those conducted in the home situation, require more front-end planning for the different professionals, patient and family and more and possibly adapted training, education and guidance for which standard documentation has to be set up beforehand.
- Possible required amendments for the liability insurance and clear rules for liabilities of the entities sponsoring and/or conducting trials in a situation in which the patient must rely importantly on RMT should be considered.
- Possible required amendments for the liability insurance and clear rules for liabilities of the entities sponsoring and/or conducting trials in a situation in which the patient must rely importantly on RMT should be considered.

The analysis of a "burden" remains an important aspect to consider for national trials as well. Several elements have to be considered to outweigh the burden and possibly emergency of a hospital against the point of depart of the CTR:

- Increased training for the various technologies, increased monitoring of the data and risk taking (e.g. risk of exposure to the disease in an uncontrolled home environment) rather than a reduction of an experienced burden during the pandemic.
- The information provided to the potential participant during the informed consent process should be available for consultation during their participation in the clinical trial and even after the trial has ended. The eConsent format can facilitate consultation if it is hosted on a website, an app or a study portal that can be accessed by the participant through a login process. This process might create extra workload or a more efficient process in case re-consent (renewed permission from the participants might be required[163], depending on the trial and the environment of the patient).
- Although real-time monitoring is possible as recording of parameters indicative of symptoms might be collected more frequently, the question arises whether this would be a benefit or a challenge for the trial.
- For both the international and national context an item to consider is that DCTs involve a strong awareness of the importance of authentication and verification of the identity of both the participants and the research team to ensure that privacy is maintained and that third parties do not access the information and data generated.
- One should ensure that data collected using the RMTs is only from the participant, who is possibly surrounded by other individuals. Possibly not all actions can be performed during home health visits or at home.
- The therapeutic area of the trial is also an important factor when deciding whether to apply this operational strategy (e.g., infusion medicines that need real time blood monitoring may not be suitable for a DCT approach). A DCT might limit the risk of contamination with the infectious disease in the hospital situation, but simultaneously increase the risk of a patient as the at home environment cannot be controlled.
- Some home tests may increase the risk of contamination of instruments and biosamples. Home health visits and self-sampling as well as storing medicinal products at home or transport to a home or POC, can complicate the management and preservation of biological samples and medicinal products. Furthermore, there is a risk of sample contamination in the participant's home environment, as it cannot be ensured that it is an aseptic environment during collection.

Consequently, adequate and differentiated risk assessments have to be performed before and during the disruption/pandemic when starting a DCT and when transferring a TCT to a DCT.

There is also a need for industry standards on how to responsibly handle many of the technologies and services

[163] Art. 6 WMO; and more information has to be provided to participants (art. 6(5) WMO lists the information that needs to be provided to participants and one is the risks for the participant's health that might come with the trial. Since these risks might change with the changing of the place the trial is being conducted, new information and informed consent both need to be given)

used in DCTs, in ways which allow for respecting both GCP requirements (aimed at protecting confidentiality, but also data integrity, etc.) and data protection requirements (stressing the need for data minimization, etc.). From 31 January 2023, all primary/initial submissions for research with a medicinal product are subject to CTR and must be submitted in the Clinical Trials Information System (**CTIS**).[164] By 31 January 2025, any ongoing trial approved under the Clinical Trials Directive will fall under the Clinical Trials Regulation.[165] At this moment there is not a specific legal framework for fast-track approval in case of a healthcare crisis or transfer of a TCT for medicinal, MDR or IVDR products trial to a DCT.[166]

Assessment of the application of the reporting Member State entails amongst others the anticipated therapeutic and public health benefits taking account of the reliability and robustness of the data generated in the clinical trial, for which, amongst others the design of the clinical trial and the suitability of the facilities where the clinical trial is to be conducted, may be qualified as an important factor.[167] These elements not only change to a limited extent when trials are being transferred to the home or POC situation, but possibly even importantly in combination with the consequences of a (pre)pandemic for individuals. Professional standards, such as related to the tasks and responsibilities of the researcher, hospital pharmacist and medical physicist are also to be considered for a prudent and justified (transfer to) DCT. Amended roles for all those involved have to be clear and embedded in guidelines respecting professional standards.[168] The role of the hospital pharmacist as embedded in guidelines[169] needs further exploration especially when medicinal products have to be distributed and administered at the home situation.[170]

National and international recommendations and guidelines[171] shall have to be implemented in the national guidelines and practice since RMTs are supposed to handle tasks of the hospital institutions and professionals in TCT and communication will importantly shift from face to face to telemonitoring and communication. Risk Assessment and possibly a prior SWOT analysis (Strength, Weaknesses, Opportunities and Threats) of the envisaged DCT, are essential in the process of initiating or transfer trials to DCT. All decisions made by the sponsor to adjust clinical trial conduct should follow a risk-based approach. A risk assessment should be routinely performed by the sponsor before the start of the clinical trial[172] and updated as necessary during the clinical trial. In their risk assessment, sponsors should cover the management of potential risks relating to e.g the loss of data. The ethical impact should also be addressed. In case of a major disruption, a transfer of a TCT to a DCT during a pandemic period might be qualified as such, it is expected that the sponsor performs a risk assessment of each individual ongoing clinical trial. The question arises whether the sponsor shall weigh elements of public health and the public emergency crisis as well. Trial participant rights, safety, dignity and well-being should always prevail, especially during a pandemic. Risks of continued participation in the clinical trial should be weighed against the anticipated benefit for the trial participants and society.[173]

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[164] 'Entry into application of the Clinical Trials Regulation' <https://health.ec.europa.eu/medicinal-products/clinical-trials/entry-application-clinical-trials-regulation_en>; 'Clinical trials in the European Union' <https://euclinicaltrials.eu/>; 'Clinical Trials Regulation (EU) No 536/2014: Questions and Answers' (July 2023, v6.5) <https://health.ec.europa.eu/system/files/2023-04/regulation5362014_qa_en.pdf>, Question 1.2.

[165] 'Clinical trials in the European Union' <https://euclinicaltrials.eu/>

[166] Was possible during COVID (national): 'Versnelde procedure (fast track) beoordeling onderzoeksdossiers coronavirus' (News, 27 March 2020) <www.ccmo.nl/actueel/nieuws/2020/03/13/versnelde-procedure-fast-track-beoordeling-onderzoeksdossiers-coronavirus>

[167] Art. 50 CTR & Art. 3(f) CTR.

[168] See Handreiking 'Verantwoordelijkheidsverdeling bij samenwerking in de zorg' (Herziening 2022)

[169] Beroepsstandaard Apotheken van het Ziekenhuis.

[170] Can only release a medicinal product upon prescription of a doctor (art. 61, lid 1, Geneesmiddelenwet), any medicinal product in the hospital can only be administered under the responsibility of a pharmacist art 61, lid 1, Geneesmiddelenwet. This applies as well to investigational medicine (art. 61, lid 2, Geneesmiddelenwet).

[171] Recommendation Paper on Decentralised elements in Clinical Trials, 13 December 2022.

[172] The principles of ICH GCP, integrated addendum to ICH E6(R1): Guidelines for good clinical practice ICH E6(R2), section 5.0.

[173] The principles of ICH GCP, integrated addendum to ICH E6(R1): Guidelines for good clinical practice ICH E6(R2), principle 2.2.

The Population Screening Act (Wet op het bevolkingsonderzoek, hereafter "Wbo") might be appliable where investigations are carried out in the entire population, or a category thereof, that involves screening. Moreover, according to art. 2(2) Wbo, the minister can decide that certain trials fall under the Wbo and have to comply with the rules of the Wbo. These screenings are subject to prior authorization. Screening might be related to sub (d) of a possible purpose of RMT, the controlling and monitoring of the whole population, of which the controlling and monitoring of the whole population is out of the scope of this report.

4.2 Clinical investigation and RMT

The Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk onderzoek met mensen (**WMO**)) governs:

Term used in WMO	Definition
Scientific research with medical devices	Clinical evaluation in the context of Regulation (EU) 2017/745: 'clinical investigation' means any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device.[174] Performance study in the context of Regulation (EU) 2017/746: 'performance study' means a study undertaken to establish or confirm the analytical or clinical performance of a device.[175]
Scientific research with medicinal products	Clinical trials in the context of Regulation (EU) 536/2014: 'Clinical trial' means a clinical study which fulfils any of the following conditions: (a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned; (b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or (c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

Figure 6: Subjects that the WMO governs.

The WMO has a broader scope than the MDR, IVDR and CTR, since it applies to medical scientific research in general and is not limited to research focused on medical devices, in-vitro diagnostic devices or medicinal products. Medical scientific research is not defined in the WMO itself. However, the CCMO (Central Committee on Research Involving Human Subjects) has defined the term as:

"M*edical/scientific research is research which is carried out with the aim of finding answers to a question in the field of illness and health (aetiology, pathogenesis, signs/symptoms, diagnosis, prevention, outcome or treatment of illness), by systematically collecting and analysing data. The research is carried out with the intention of contributing to medical knowledge which can also be applied to populations outside of the direct research population.*"

A central requirement of the WMO is informed consent of the participant.[176] The supervisory role has been attributed to the IGJ whereby the main focus is to ensure that trials are carried out safely and that the results of clinical trials are traceable, valid and reliable. The MDR contains specific rules for submission, assessment and conduct of clinical investigations into medical devices. The CCMO performs a pre-screening of all incoming documents. After screening the documents are sent to the (accredited) Medical Research Ethics Committee (MREC). The reviewing committee is either the CCMO or the MREC. The decentral review is taken at hand by the accredited MREC. The majority of MRECs is linked to an institution, for example, a university medical centre or a hospital. A number are not linked to an institution. In most cases research which is subject to the WMO

[174] Art. 2(45) MDR.
[175] Art. 2(42) IVDR.
[176] Art. 6, lid 1, WMO.

must be reviewed by an accredited MREC. The research which the CCMO has to review are listed in the Central Review of Medical Research Involving Human Subjects Decree.[177] More in general, the legislator chose to combine expertise in one single committee for certain types of research. This concerns the review of research with specific ethical, legal or social aspects and research in fields with limited expertise. An example is medical research with gametes or medical research focused on development of a vaccine.[178]

The question arises whether these procedures are adequate for decisions to transfer a TCT to a DCT during a (pre) pandemic phase. The process may even be a hurdle for a sponsor where international trials have to be transferred to a home or POC situation.

4.3 Safety of RMTs

Electronic safety reporting should be processed in the electronic database for safety reporting.[179] Specific guidelines for a transfer of TCT to DCT or a DCT for which RMTs are being applied in a home situation during a pandemic where the symptoms of the infectious disease might interfere with other effects, are still to be developed.[180] Transfer to DCT procedures for safety reporting, of which unexpected and serous reactions and side effects has to be developed or adapted as well. Specific guidelines for safety reporting in the home situation especially when responsibilities change importantly when TCTs are transferred to DCTs, are of the essence and should be developed. Guidelines for these safety reporting for DCT for which RMTs in development used, need to be captured as well.

The national competent authority in the Netherlands for medicinal products is the Dutch Medicines Evaluation Board (**MEB**), an independent administrative body. The MEB evaluates new medicines and acts as a gatekeeper. If new medicinal products need to be authorised by the MEB via the national or decentral procedure, the MEB shall assess the quality, efficacy and safety of such medicinal products. Supervision and enforcing the Medicines Act including rules pertaining to pharmacovigilance and good pharmacovigilance practice (**GPP**) is attributed to IGJ.[181] This last-mentioned competence applies as well for the Device vigilance. The earlier mentioned EMA evaluates new medicines via the centralised procedure within the EU, where Market Authorisations are granted by the EC. The EUDAMED system could provide the inspectorate and Minister (RIVM) certain performance information on Medical Devices and IVD on the European market that are useful for RMT either as the apparatus or diagnostics to be used or as an equivalent apparatus/IVD.

4.4 WGBO

The Wet op de Geneeskundige Behandelingovereenkomst[182] (**WGBO**) standards and handreikingen[183] contain clauses developed for a traditional medical environment. Rules on confidentiality and informed consent are not

[177] Besluit centrale beoordeling medisch-wetenschappelijk onderzoek met mensen

[178] Art. 1, onderdeel c en d Besluit centrale beoordeling medisch-wetenschappelijk onderzoek met mensen.

[179] Art 40 of Regulation 726/2004: the 'Agency' shall set up and maintain an electronic database for the reporting provided for in Articles 42 and 43. That database shall be a module of the database referred to in Article 24 of Regulation (EC) No 726/2004 (the 'Eudravigilance database').

[180] Best practices were identified in Trials@Home; though not published yet.

[181] *Spotlight: medicine and medical device pricing and reimbursement in Netherlands* (Lexology, 2 March 2023) <www.lexology.com/library/detail.aspx?g=554329d7-6f22-40a4-82a6-20310562edde&utm_source=Lexology+Daily+Newsfeed&utm_medium=HTML+email+-+Body+-+General+section&utm_campaign=Lexology+subscriber+daily+feed&utm_content=Lexology+Daily+Newsfeed+2023-04-19&utm_term=#footnote-031>.

[182] Wet op de geneeskundige behandelingsovereenkomst, Burgerlijk Wetboek boek 7, afdeling 5.

[183] Guidelines developed by KNMG (www.knmg.nl/)

completely in line with the essence of a DCT. The recommended guidelines, see 4.2, should be aligned with guidelines for implementing the WGBO.[184]

[184] See for example guidelines (handreikingen) KNMG; www.knmg.nl/, for example Guidelines on handling medical data: https://www.knmg.nl/web/file?uuid=043d8d9a-1d0e-46e0-a8e0-98092d764999&owner=5c945405-d6ca-4deb-aa16-7af2088aa173&contentid=411

5. Data protection, privacy and ethical aspects

5.1 National pandemic governance

Article 6c Wpg clarifies that the RIVM processes personal data, including health data[185], that are necessary for the execution of its task. These rules also apply to any reference laboratory that the RIVM will use for the execution of this task (art. 6c(5) Wpg).

5.2 RMT and MDR/IVDR or accessory software

Except for the General Data Protection Regulation **(GDPR**) and the national implementation acts, the MDR/IVDR contain privacy related clauses to be considered when using RMTs for DCT and/or controlling the infectious disease. Art. 72(3) MDR states that all clinical investigation information shall be recorded, processed, handled, and stored by the sponsor or investigator, as applicable, in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable law on personal data protection.

Art. 77(5) MDR states that "irrespective of the outcome of the clinical investigation, within one year of the end of the clinical investigation or within three months of the early termination or temporary halt, the sponsor shall submit to the Member States in which a clinical investigation was conducted a clinical investigation report as referred to in Section 2.8 of Chapter I and Section 7 of Chapter III of Annex XV." The clinical investigation report has to be accompanied by a summary. The Commission has also issued guidelines regarding the content and structure of the summary, based on art. 77(6) MDR.[186]

Furthermore, art. 57(3) IVDR states that Performance studies shall be designed and conducted in such a way that the rights, safety, dignity and well-being of the subjects participating in such performance studies are protected and prevail over all other interests and the data generated are scientifically valid, reliable and robust. Performance studies, including performance studies that use left-over samples, shall be conducted in accordance with applicable law on data protection. Moreover, the GDPR and Dutch GDPR Implementation Act (**UAVG**) apply to any trial or IVD and MD processing personal data in the Netherlands. As clinical trials mostly entail medical treatments, the WGBO is relevant as well.[187] The Clinical Trials Regulation refers to Directive 95/46/ EG (replaced by GDPR).[188]

5.3 Personal data, research and trials

Personal data will be processed for the purposes of conducting clinical trial trials. The dataflows follow several stages such as pre-screening of participants, trial enrolment trial execution and data analysis. The **GDPR** requires a legal basis whenever personal data are processed. Where explicit consent is relied upon as a legal basis under GDPR, in particular to process health and genetic data, this should be obtained separately from the informed consent under the CTR.[189] The lawfulness of data processing under the GDPR in subsequent stages relies on consent to participate in the clinical trial (hereinafter: CTR consent) and the legal obligations for data processing contained therein, with data processing based on the Clinical Trials Regulation and applicable by laws and regulations the following of which is mandatory according to these laws.[190] Privacy and data

[185] As defined in art. 4(15) GDPR: personal data related to the physical or mental health of a natural person.
[186] Commission Guidance on the content and structure of the summary of the clinical investigation report, 2023/C 163/06 C/2023/2622, OJ C 163, 8.5.2023, p. 7–13.
[187] Art. 7:457 BW & 7:458 BW.
[188] Art. 93 CTR.
[189] Art. 17(3)(b) GDPR.
[190] E.g., The principles of ICH GCP, integrated addendum to ICH E6(R1): Guidelines for good clinical practice ICH E6(R2).

protection are important items to be adequately covered when setting up trials. The WMO contains an explicit rule on adequate measures for the privacy of the subjects.[191]

5.4 Informed consent, DPIA and DMP

The Gedragscode gezondheidsonderzoek[192] (Code of conduct for health research) will most likely be interpreted as a national professional standard for health research. However, the code does not provide guidelines specifically for RMTs on the market and evaluations studies for RMTs. This Code further outlines the practical side of rules on informed consent and the withdrawing of informed consent has been explained, such as that the withdrawing of consent should be just as easy to do as giving consent.[193]

Sponsors should clearly distinguish between informed consent for purposes of conducting the trial, and consent obtained for purposes of data protection. The GDPR requires a legal basis whenever personal data are processed. Where explicit consent is relied upon as a legal basis under GDPR, in particular to process health and genetic data, this should be obtained separately from the informed consent under the CTR.

In the EU there is no clear consensus on whether explicit consent is always appropriate in a privacy context for the processing of personal data for research activities. In its opinion concerning the Q&A on the interplay between the CTR and the GDPR,[194] the European Data Protection Board (**EDPB**), a consortium of national EU data protection authorities, concluded that consent may not be the appropriate legal basis in some cases. Legal bases other than consent, such as public interests in the area of health or scientific research, should preferably be relied upon. However, these other legal bases require a corresponding implementation in national Member State law.[195] Apart from the informed consent, Data Management Plans **(DMPs**) and Data Protection Impact Assessments **(DPIAs**) remain important instruments to apply for all clinical trials involving more research institutions.

Informed consent, DMPs and DPIAs must be considered and mostly redrafted, adapted and signed when transferring TDT to DCTs. Dataflows change with regards to the complexity and parties involved, which may be most prominent for the research participants. The application of RMTs introduces an important key player processing data and mostly healthcare data: the manufacturer possibly situated in another Member State or even outside the EU. Online communication instruments may process more personal data than speech data. Possibly other HCPs than originally involved with the trial may be introduced. Patients may insert more data than necessary. The role of other third parties (e.g., for IMP, if an external company is used for transport, the participants' data is shared with a subcontractor) should be carefully considered from not only a Good Clinical Practice perspective but ethical and privacy perspective and rules as well. Recordings made and written conversations can only be accessed by those delegated to do so and cannot be stored or reviewed by third parties or vendors.[196]

Continuous monitoring of participants generates a large amount of data, some of which may be unnecessary, requiring resources and standardised procedures to review and analyse them properly. A separate protocol is needed for re-consent that may be realised by an electronic consent form.[197] [198] In addition, these clinical trials may also facilitate actions such as sharing information about the study with participants during and after study

[191] Art. 12 WMO.
[192] Gedragscode Gezondheidsonderzoek, januari 2022.
[193] See complete wording section 4.8 Gedragscode Gezondheidsonderzoek, januari 2022. However, already collected data may be processed for archiving and safety goals.
[194] EDPB, 'Opinion 3/2019 concerning the Questions and Answers on the interplay between the Clinical Trials Regulation (CTR) and the General Data Protection regulation (GDPR) (art. 70.1.b))' 23 January 2019.
[195] Art. 6(3)(b) GDPR.
[196] Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, v.5 February 10, 2022.
[197] Further report.
[198] Art. 6, lid 2, WMO; Recommendation Paper on decentralized elements in clinical trials, 13 December 2022, v.1; Guideline on computerised systems and electronic data in clinical trials, 9 March 2023.

completion or sending informative and motivational messages, which may have positive effects on participant engagement. The eConsent facilitates the storage and management of documentation, including the different versions of the informed consent used and signed during the trial in digital format. This allows clinical research assistants and auditors to review them remotely in an easier way. On the other hand, the lack of physical examinations and without non-verbal information it can be difficult to verify underlying conditions, check understanding or verify voluntary consent.

5.5 Privacy third countries

On July 10th, 2023, the European Commission adopted a new adequacy decision on the EU-US Data Privacy framework.[199]The European Commission has so far recognised Andorra, Argentina, Canada (commercial organisations), Faroe Islands, Guernsey, Israel, Isle of Man, Japan, Jersey, New Zealand, Republic of Korea, Switzerland , the United Kingdom under the GDPR and the LED, the United States (commercial organisations participating in the EU-US Data Privacy Framework) and Uruguay as providing adequate protection.[200]In 2023, a series of new laws will take effect or are to be drawn up in the EU that are of crucial importance for the legal framework for introducing various types of innovation. This will primarily affect cloud computing, the Internet of Things, and artificial intelligence. The new rules on innovation will govern activity that entails personal data processing as well as activity that involves non-personal data, while also observing the rule that laws on innovation will be without prejudice to the GDPR, and thus do not violate or amend it. In particular, these laws cannot be interpreted as forming new legal grounds for processing personal data in the case of regulated activity or as amending the information requirements provided for in the GDPR.

The most important innovation-related laws due to take effect in 2023 include the following:

1. an amendment to the National Cybersecurity System Act (the government plans to pass the amendment in QII 2023)
2. the Data Governance Act (EU Regulation to come into force as of 24 September 2023)

Meanwhile, the main pieces of legislation on which work is still in progress include:

1. the proposal for the Data Act.[201]
2. the proposal for the Regulation on Artificial Intelligence.[202]

The legal aspects of protection of data and privacy in the metaverse are becoming increasingly important. There is presently no legislation regulating data protection and privacy in the metaverse, and there are no plans to pass such legislation, while equally there are no guidelines in this respect issued by the European Data Protection Board or by national authorities.

There are specific issues concerning applicability of the GDPR to the metaverse, such as:

1. the processing of personal data of a special (sensitive) nature. Sensors built into VR sets to enable users to interact with the metaverse use an elaborate network of sensors that record the body's physical reactions to the designed world. Examples include face recognition systems (recognizing facial

[199] Commission implementing decision of 10 July 2023 pursuant to Regulation (EU) 2016/679 of the European Parliament and of the Council on the adequate level of protection of personal data under the EU-US Data Privacy Framework, C(2023) 4745 final.

[200] European Commission, 'Adequacy decisions' <https://commission.europa.eu/law/law-topic/data-protection/international-dimension-data-protection/adequacy-decisions_en#:~:text=The%20European%20Commission%20has%20so,commercial%20organisations%20participating%20in%20the> accessed 10 August 2023.

[201] Proposal for a regulation of the European Parliament and of the Council on harmonised rules on fair access to and use of data (Data Act), COM/2022/68 final.

[202] Proposal for a Regulation of the European Parliament and of the Council laying down harmonised rules on Artificial Intelligence (Artificial Intelligence Act) and amending certain union legislative acts.

expressions, geometry) and systems that track movement of the eyeball, retina, and entire body (position of head and hands, fingerprints, etc.), other physiological reactions (temperature, skin reaction, pulse, oxygen saturation, and electrical activity of muscles, and possibly in the near future brainwaves as well). The information that is collected and analysed by a face recognition system is biometric data as defined in article 4(14) of the GDPR and as such a category of data that is subject to special protection.

2. the status of particular parties that conduct data processing in virtual worlds (a controller, joint controller, processor).[203]

5.6 Ethical considerations

Most of the regulations referred to and or analysed in the context of a pandemic are based on or are manoeuvring between public interest on the one hand and the individual citizen on the other. The public interest is built on several layers of the health and wellbeing of individuals, both citizens and patients. Furthermore, citizens may also be qualified as patients. The MREC focuses on ethical aspects of clinical trials as well. However, the MREC is not instituted to consider public interest when weighing the individual interest.

Reorganising TDT to DCT or starting DCTs during a pandemic situation has consequences for the quality of the data, individual risks and individual interests and needs such as privacy in the home situation as well, personal contact with a HCP, clear and understandable communication based on the capacities and knowledge of an individual (with possibly technical illiteracy) and especially isolated patients or patients that should respect restrictions for personal contacts. Urgency driven decision making should nonetheless even in a pandemic be based on a thorough and prudent weighing of interests and respect personal welfare as much as possible.

For larger international clinical trials an Ethical Advisory Board (**EAB)** should be instituted to monitor phases and weighing the individual interests in the context of the purpose of the research.

An overarching EAB that monitors (a transfer to) DCTs in a pandemic period, RMTs development, RMT fast-tracking, RMT procurement procedures, and public healthcare measures, and adequately balances where public and individual interests, has not been instituted yet.

[203] More examples:

1. the means of compliance with the information requirement and determining the legal basis for processing personal data
2. rules on profiling natural persons represented by avatars in the metaverse,
3. transferring personal data to third countries.

6. Lessons learned, conclusions and recommendations

During the early phase of the COVID-19 pandemic the governance structure in the Netherlands appeared to be fragmented, though uniformity could be built and achieved by cooperation. Although the governance structure, key players and HCP`s showed impressive creativity and flexibility to handle the consequences of a worldwide spread of a relatively unknown infectious disease, one cannot exclude another health crisis resulting from a pandemic infectious disease, bringing within its wake new and unexpected side effects. Reflection on lessons learned against the backdrop of new developments in the field of key players, technological developments, such as RMTs and decentralised healthcare and research are likely to create adequate instruments for pandemic preparedness.

6.1 Lessons learned

The new legislative proposals on the national governance reflect an action for the possibly most vital lessons learned: a strong national legal basis for a national and coordinated approach for controlling infectious diseases classified as A1 or A2. The strengthened (future) governing and supporting roles for EU key players and WHO seem to reflect the lessons learned on an EU and worldwide level as well.

Although public procurement regulations for essential products, such as RMTs, foresee in shorter turnaround timelines and exemptions, even the application of those may be complicated if the infectious disease has not been fully analysed from a (bio) medical perspective. Furthermore, procurement legislation cannot prevent legal procedures putting the rapid and urgent application of required apparatus and tests at risk.

The third lesson learned related to shortages in the supply chain for vital healthcare products and a decreasing HCP workforce while the healthcare demand was increasing. This is only partly reflected and handled in new legislation. On one hand the new legislative framework for IVD and MD products will prolong development times of possible essential and adequate products. On the other hand, this new framework does foresee in more general exemptions and also more specifically related to an urgent public health need.

RMTs played a limited role in the COVID-19 pandemic. Only recently, a “hybrid” form for healthcare has been introduced in the national vision on strategy.[204] RMTs such as telecommunication and the Corona app were applied on a limited scale. Privacy issues had to be tackled urgently.[205] These solutions might release the burden of the HCP workforce but can also increase the workload if not prepared adequately or when trials are carried out in several countries. A Health Technology Assessment is crucial to evaluate the ultimate value of an innovative technology such as RMTs.

A specific EAB for decisions related to starting DCTs of transferring clinical trials to a DCT situation during a pandemic period was not instituted during the COVID-19 pandemic. Guidelines and standards for DCTs (either transfer or setting up) have not (completely) been developed yet.

The amendment of the Wpg related to the processing of data[206] reflects lessons learned from privacy issues. Other privacy and ethical issues will occur when DCTs shall be considered as an instrument for pandemic preparedness.

6.2 Conclusions and recommendations

Analysing regulatory and legal bottlenecks and opportunities of RMTs related to efficacy and safety of interventions during a non-pandemic and pandemic phase requires an integral approach starting from the regulatory framework for the governance and players involved on national, European and international level and leading to the analysis of the data flow from the subject to the hospital and/or laboratory, the supply chain of RMTs, the regulatory context of the RMTs and research, TCTs and DCTs and privacy and ethical

[204] *Nationale visie en strategie op het gezondheidsinformatiestelsel* (Ministerie van VWS, maart 2023), p 7.
[205] ‘CoronaMelder-app kan privacy niet waarborgen en is tijdelijk uitgeschakeld’, *Volkskrant* 28 april 2021.
[206] Art. 6c Wpg.

considerations related to public need and the individual position in a DCT.

Almost all these elements have been changed significantly since the last phase of the COVID-19 pandemic. Several changes related to the governance on national, EU and international level, are essential to the national pandemic preparedness policy. The legislative structure in the Netherlands during the years 2019 up to 2023 realized a fragmented approach strongly based on cooperation. The recent amendments to this framework are likely to streamline the governance structure, while also facilitating flexibility by instituting, a pandemic preparedness unit and the position of reference laboratories that may play a role in the context of the IVDR, and exemptions under the MDR and IVDR.

The most important governance changes on EU level might be the strengthened roles for HERA and EMA. The strengthened roles could bridge shortages in a tense market of increasing demand for products needed for testing, monitoring and devices required for the RMT data flow. However, at present one may assume that HERA and EMA will perform tasks within the EU spectrum rather than at the request or needs of an individual Member State. This element may necessitate an alignment of the national (pre) pandemic policy and measures based thereon with the policy, tasks and conditions of HERA and EMA in the (pre)pandemic phase during which a rapid response is essential.

RMTs entail the use of instruments and software on a large scale. These may be purchased by different stakeholders and persons involved. An important lesson learned from the COVID-19 pandemic is related to the centralized procurement of essential pandemic tests and equipment through a public body of an individual Member State. Procurement procedures by public bodies shall not only be a challenge as the exact characteristics of the infectious disease might be difficult to define to the extent as required by the procurement regulation. Even specific social and health procedures and exemptions in the field of innovative products might not be the right answer to the situation arisen. Moreover, any procedure or exemption chosen might provoke legal procedures of competitors which will put the rapid response needed at risk.

Depending on the exact use, these risks may be mitigated by putting a consumer product already used on a large scale as an element of the RMT dataflow. The dataflow of RMT entails the use of other instruments and software as well. These instruments might be on the market with the required intended use and CE mark. The use of existing consumer products cannot be qualified as a sure starting point for trials involving healthcare products needed to cure, suppress, or monitor the (symptoms of) the infectious disease. As shown during the COVID-19 pandemic, software, instruments and in vitro diagnostics shall have to be developed or adapted. Depending on the legal qualification of these instruments, consumer product, medical device and/or medical software, applicable regulations will facilitate a limited or more extensive development line and production possibilities.
Since the strengthened regulation applicable to medical devices and in vitro diagnostics, adopted before the COVID-19 pandemic however with a transition period ending in the very last phase thereof, the lessons learned from this pandemic are not or of limited relevance for an adequate (pre) pandemic preparation from today.

On one hand the strengthened premarket conditions for MDR and IVDR products entail most probably more challenges to handle during a future pandemic than during the COVID-19 pandemic. However, several clauses of the MDR and IVDR do foresee in adapted procedures where a health crisis occurs or were indicated in the interest of public health or patient safety or health. These may be initiated by several actors on national and international level.[193] These possibilities and options for exemptions could be the basis of solid preparational measures for a possible (pre)-pandemic phase. Still, more alternatives could be explored. There are several options for creating the elements of the dataflow from the individual at home or in a POC situation to the research team in a hospital or (reference) laboratory. When taking a consumer product as the device used by or for the individual, the central role of the RMT flow is likely to be the software element.

The legal framework leaves room for several exemptions for reference laboratories and hospitals to develop RMTs. This could be a temporarily suitable approach in case that there are no devices on the market with the correct regulatory status (CE marking) under MDR or IVDR.

Nonetheless, the ideal set up (weighing all options, alternatives and back-up scenarios) for RMT during a (pre)pandemic phase should be further explored.

The application of RMTs for running or new trials during the (pre)pandemic phase requires thorough considerations, preparations of guidelines, risk analysis, guidelines and standard forms for informed consent, Data Privacy Impact Assessment (**DPIA**) and Data Management Plans (**DMP**), clear division and allocation of responsibilities of all healthcare providers (including hospital pharmacists and laboratory specialists) involved, approval/notification procedures in possible different jurisdictions and mostly standards of instruction to procure balanced decisions based on the correct balance between the interest and safety of the individual (patient) and the public health crisis having impact on other patients in hospitals and the whole population as well. These considerations and documentation should be evaluated and reconsidered preferably before a possible future pandemic situation occurs. Ethical aspects of these decisions could be considered during the (pre)pandemic phase. The applicable regulation puts the position and rights of the individual central in the trial, while the (pre)pandemic phase requires weighing of interests of individuals on different levels. As this aspect must be weighed continuously, leading to different outcomes in the different phases and development of a pandemic, an EAB might be helpful or even a necessity to procure a balanced and widely supported outcome. Although the amendments of the Wpg (as further outlined in Chapter 1), as lessons learned do foresee in a legal basis for certain data flows, RMT will create more privacy questions that need to be considered as an element of pandemic preparedness.

	General	**National**	**International**
Governance	Structure for items that can solely be handled on national level on the one hand and items that can/shall be procured on European or international level. Ch 2.1, 2.2	Structure and alternative structures reflecting their roles in the supply chain, DCT and in house developments of software, diagnostics and medical devices. Ch 2.1, 3.5 Prepare possible use and access to EUDAMED Ch 3.10, 4.3	Prepare Communication framework and tasks allocation related to ECDC/ HERA/EMA/WHO/European Commission for all products needed during a pandemic. Ch 2.2, 2.3, 3.2, 6.1
RMTs		Develop and design ideal dataflow and alternatives weighing risks of non-availability, shortages and disruption in the supply chain. Ch 3.3 Develop guidelines for off label and named patient use. Ch 3.8	Inventorize options for alternatives and exemptions MDR/IVDR. Prepare rapid interaction possibly in cooperation with national and international bodies and reference laboratories. Ch 3.8, 6.1
TCT/DCT	Prepare guidelines for DCTs and transfers from TCT to DCTs, Guidelines for decisions making, responsibilities, informed consent, and -benefit analysis.	Prepare guidelines for DCTs and transfers from TCT to DCTs and align with international guidelines.	Align with international guidelines for DCTs and transfers from TCT to DCTs/harmonise across EU member states.

	Prepare an analysis for priorities of DCTs. Ch 4, 4.1, 4.4 Prepare a SWOT analysis for decisions on transferring TCT to DCT. Align where possible with European and international guidelines and standards. Prepare fast track and central decision making METC/CCMO. Prepare POC structure for: elderly, disabled, illiteracy, non-Dutch speaking citizens. Prepare responsibility guidelines (keten- verantwoordelijkheid) for the (transfer to) DCTs. Ch 4, 4.2	Ch 4.1	Realize central procedures at least in the EU, "one stop approval". Ch 4, 4.1, 4.2
	Prepare Risk analysis RMT and ideally several alternatives followed by preferred data flows and elements thereof as well as alternatives for urgent RMT, POC, Home, running trials, new trials monitoring possible infectious diseases. Ch 4		
Ethical and Privacy	Continuously monitor the benefit and individual risk during the (pre) pandemic phase. Ch 3.8, 4	Draft standard models for DPIAs. Ch 5.4, 6.1 Prepare an Ethical Advisory Board (tasks, nominations, legislative context, protocol) Ch 3.8, 5.6, 6.1	Draft guidelines for cross border or cross continent dataflows during a (pre)pandemic. Ch 5.5

Figure 7: Recommendations.

Deliverable 3: Interviews with Innovators and Regulators

Disclaimer: Please note that the information presented in this deliverable are responses gathered during an interview. The aim of the interview was to capture knowledge from different organizations regarding the regulatory field. All answers/opinions shared by the interviewees are of their own and may not reflect the opinions of their organization or that of Lygature.

Key definitions:

***Remote monitoring technologies (RMT)**: wearable sensors, sensors that can be placed in home or in the car, wearable monitors for telemonitoring, algorithms, and models that process data and make them insightful and usable for different end users*

***Regulatory**: the system of laws, regulations and directives and the structures and bodies that monitor and enforce these laws, regulations and directives.*

Abstract

We interviewed a small software company that is developing apps for smartphones for clinical decision-making. From the interview, we found that the organization is struggling with the complexity of the newly implemented Medical Device Regulation. This dramatically slows down the development due to a lack of knowledge regarding the requirements of the MDR, increased costs, longer waiting times at notified bodies, difficultly providing necessary data. Furthermore, the requirements of the validity of the clinical endpoint is poorly described by the regulator. This leaves many SMEs wondering if their innovation will be actually be accepted by the regulators. Suggested solutions include working with (expensive) consultants and knowledge sharing with other SMEs. Currently, this company feels that the safety and efficacy requirements for approval are too stringent for software. They suggest a further broadening of the classifications within the MDR whereby software used in decision supported therapy would be less stringently assessed. This would greatly help in bringing helpful innovations to patients faster, and would help resource-constrained SMEs.

We also interviewed a large international pharmaceutical company that develops many medicinal products for various therapeutic areas. As of yet, not many RMTs have been used as a primary endpoint in clinical trials for medicinal products. More frequently, these devices are used as exploratory endpoints as they lack of regulatory acceptance, due to lack of clinical validation and standardization across the industry. The innovator/company also mentioned that the requirements of the validity of the clinical endpoint is poorly described by the regulator. From the interview, we found that regulators are not the bottleneck in the adoption of digital health technologies in clinical trials. However, there is a lack of harmonization between sponsors resulting in multiple sponsors attempting to develop their own digital health technology at risk of redundancy and differences in the definition of the standards. The solution to this problem would be to standardize the measurements and build an open repository with all the measurements and technologies that have been validated. This would avoid fragmentation and lower the risk and cost of sponsors in developing their own digital biomarkers and increase wide spread adoption.

The MDR/IVDR consultancy assists various types of organizations to navigate the complex regulatory landscape to bring innovation to the EU market. Given that RMTs are classified as a medical device or an in vitro diagnostic device, the two largest regulatory obstacles that the consultancy assists with are firstly clearly defining the claims of the product to define the appropriate regulatory pathway and secondly building technical documentation (TD) with the evidence for the claims and ensuring a quality management system (QMS) is in place to guarantee the quality of related processes. With the recent implementation of the new MDR/IVDR the waiting times at notified bodies has increased and at the same time, more evidence is required for CE marking. Less stringent regulation may promote innovation yet at the same time the safety and reliability of a device or software needs to be ensured by the manufacturer. During a pandemic, when clinical studies required for generating evidence for CE-marking may be difficult to come by, an alternative process to allow devices on the market might be required. A proposed solution would be to allow devices to have an emergency use authorization, as with medicinal products, thereby speeding up access to devices that may help during a pandemic. However, if the device product is not consistent enough in its measurements then it may even cause more harm than good. As a result, a risk-reward assessment should be done by the national competent authorities, expert groups, notified bodies, and in close communication with the manufacturer.

The European Medical Agency (EMA) is an agency of the European Union responsible for the scientific evaluation, supervision and safety monitoring of medicines. As RMTs are relatively new to the pharmaceutical sector the EMA not been able to define the biggest regulatory hurdles that RMT innovators face. However, the EMA has published many guidelines and recommendations on their website and support innovators to approach the EMA for scientific advice as early as possible. While large pharmaceutical companies are aware of the EMA's scientific advice recommendations; academics and SME are usually less familiar with the mode of interaction. One aspect that the EMA stresses is that if the endpoint measured by the RMT is not regulatorily acceptable yet, then a clinical study should contribute to the endpoint validation work. Before the RMT has been regulatorily accepted, the endpoint the RMT is collecting should be used as an exploratory endpoint until eventual regulatory qualification. Importantly, considerations on Context of Use (CoU), sensitivity of the measure to detect change and characterisation of a minimal important difference are key parameters regarding regulatory acceptability. Lastly, one aspect that the EMA struggles with is the lack of deep expertise (AI algorithms, data privacy and GDPR) to evaluate the impact of certain technologies and methodologies.

Interview with an SME

Date: 15 February 2023

Background of the interviewee:

We interviewed the chief clinical officer from a digital medicine SME located in the Netherlands. Digital medicine is the intersection of applied data science and the development of digital biomarkers to enable personalized healthcare, leading to decision supported therapy.

1. *What were the regulatory hurdles you faced during the development of your digital biomarker/RMT? And how did you address them?*

There are different hinderances to the development of a novel digital biomarker. For eHealth solutions, the transition from the MDD (Medical Devices Directive) to the MDR (Medical Device Regulation) is rather difficult. In addition, getting your innovative solution registered under the MDR is a difficult trajectory itself. Overall the legislation that innovators need to follow is quite complex.

Change can be hard, but in the case of transitioning from MDD to MDR it is especially difficult. The new MDR legislation is significantly longer and more rigorous. It puts more emphasis on the safety of the end user and on clinical evidence. The MDR is replacing the MDD and will come into full effect end of 2027 or 2028. Innovators, even with an MDD approved product, are required to re-submit their application for approval by notified bodies, commercial companies that evaluate whether the developed technologies comply with the European legislation on behalf of the European Commission. Our interviewee indicated that timelines for review of a technology are considerable (currently running up to 85 weeks). At the time of writing, there were just 37 notified bodies that are accredited to assess the technology according to the MDR.[1]

Furthermore, once an application has been submitted the product may no longer be altered as it needs to be evaluated “as is”. For traditional medicinal products (such as small molecules) or certain medical devices (such as implants) this process makes sense. However, in the case of software products being used in the healthcare environment (such as to support clinical decision making), it could be beneficial to re-evaluate the legislation and review process, and reassess whether it needs to be as stringent as it currently is. Too stringent rules can result in the slowing down of innovation, and causes delays in patients receiving medical products. As a side effect, some innovations might not reach patients at all if innovators fail to navigate the review process for their product.

The legislation around the MDR has become increasingly complex, while transparent information or guidance on how notified bodies handle the MDR (eg. which information is needed in a submission) is difficult to come by. The interviewee explained that at the start of the review process, it experienced somewhat of a mismatch in what is expected to comply with the legislation, and the capacity for an innovator to provide the necessary information. Smaller innovators such as start-ups and scale-ups do not always have the regulatory knowledge and ability to assimilate all the necessary information. In those cases, the legislation and the way that it is enforced can lead to innovations being shelved until resources become available. To overcome this hurdle, start-ups and scale-ups frequently hire

consultants to aid in the application process. They also try to learn from other innovators such as Luscii or follow MDR and ISO13485 trainings offered by Peercode.

Trainings, either self-study or ones given by an accredited MDR trainer, are possible solutions for innovators to get a better understanding of the transition from MDD to MDR and the overall review process for medical devices (including software products). Alternatively, together with consultants, conducting a gap analysis of what changes are required to transition from MDD to MDR may also be required. However, many SMEs don't have the resources to cope with the legislation change and to comply with the regulations implemented via the MDR. Notified bodies only approve or deny applications, and do not offer scientific advice in case of a product rejection. Coupled with a cost of ~20,000-35,000 euros per review request, this represents a significant expense to developing novel digital therapies.

2. *According to the SMEs analysis/experience, what are the different regulatory requirements associated with validation of endpoints in the context of drug development vs validation of biomarker for personal monitoring/shared decision making in clinical practice?*

When looking at the regulatory hurdles in the context of developing a new digital biomarker for clinical trials of novel therapies, it comes down to endpoint validation. The EMA/FDA need to be presented with sufficient evidence that a novel digital endpoint is as good as or better than the current gold standard. The requirements, however, for validation of novel digital endpoints are poorly defined by the regulatory bodies, leaving innovators with the question: "when is good enough, good enough?".

The lack of a programmer's knowledge of MDR can be an additional hinderance. People working on digital tools are usually driven by technical opportunities, and are not always aware of the regulatory requirements they are expected to comply with when their innovations are to be implemented in the clinical environment. Down the road, they will have to spend significant time deciphering the MDR, rather than developing new digital endpoints. Once a digital biomarker is technically and clinically validated for a specific disease, the digital biomarker needs to be clinically validated for each new disease. This is understandable in a clinical setting (eg. for drug development or for diagnostic tools), but for monitoring patients' disease progression the SME argues that the current set of regulations might be superfluous, especially with a general digital biomarker such as fatigue.

Doctors are starting to use the SMEs and CE marked products in their clinics as they find the digital biomarkers relevant to monitor disease progression from afar. Unfortunately, for product reimbursement (and broad acceptance of technologies by health care providers, and implementation in standard clinical care) often real-world evidence (outside of interventional trials) is required. To gather real-world evidence, an innovator needs to have sufficient funding to power such a real-world evidence data collection study, plus sufficient buy-in from doctors. This leads to a chicken or egg conundrum. Funding may come from a variety of sources such as an innovation fund, health insurances or even the patients themselves, but it still provides a bottleneck. The COVID-19 pandemic has emphasized the importance of telemonitoring, which is now more frequently reimbursed. Easier access to funds that would allow to power studies focussed on gathering real-world evidence, leading to acceptance by health technology assessment bodies and insurers would help to overcome this hurdle.

3. *In your opinion, what future regulatory changes might make it easier to develop new digital biomarkers and RMTs?*

With regard to patient safety and data privacy, the SME does see the value of having tools and devices assessed by a third party (such as the notified bodies) before they are allowed on the market. This helps to ensure that only products with a certain quality are allowed to be used. Under the MDR the requirements for clinical evidence have become more stringent. Gathering clinical evidence is a lengthy and costly process, and hence a hurdle for innovators. In addition, for each product risk class (Class I-Class III) the same level of evidence is needed. Currently, the SME feels that the safety and efficacy requirements for approval are too stringent. They suggest a further broadening of the classifications within the MDR whereby software used in decision supported therapy would be less stringently assessed. For example, for devices falling in Class I and Class IIa it would be beneficial if another level of evidence would be required compared to Class IIb and Class III devices: more evidence and a more stringent assessment for high-risk class devices, and a more lenient approach for lower risk class devices. This would greatly help in bringing helpful innovations to patients faster, and would help resource-constrained SMEs. Moreover, additional support from organizations such as Regulatory Affairs Netherlands (REGNED) can greatly help SMEs during the navigation of the regulatory landscape.

Interview with large innovator/pharmaceutical company

Date: 10 May 2023

General

1. *Can you briefly introduce yourself and explain what your work entails?*

The interviewee has worked his entire career for various pharmaceutical companies. This has enabled him to work in many specialized roles and build a deep understanding of drug development, regulatory and market knowledge. He always worked in a clinical setting and in the last 8 years transitioned to a patient centric role. This innovator/company is one of the industry front runners aligning patients' wants, needs and preferences when designing a clinical trial. Recently, the interviewee has become involved in the digital health space and has been driving the adoption of patient connected technologies in clinical trials both inside and outside of a hospital setting. He has worked on electronic clinical outcome assessments (eCOAs), and digital biomarkers.

The use of digital measurements is growing in clinical trials but requires both regulatory and practical standardization as well as harmonization. According to the interviewee, the entire ecosystem of pharmaceutical players would need to strive to develop the same standards. Currently, the EMA and EFPIA have been aiming to achieve this through various programs to standardize the digital health space in clinical trials.

Opportunities and regulatory hurdles for RMTs in clinical trials

1. *To what extent is The innovator/company investigating and implementing Remote Monitoring Technologies in clinical trials? Can you elaborate on how these technologies are developed and assessed (eg. in house, in a public private partnership, etc).*

The innovator/company has a broad portfolio with six therapeutic areas, for which they are developing medicinal products. In all cases the interviewee and his team are exploring where they can employ digital health technologies to better characterize disease states and stratify patient populations. At the same time digital health technology can be used to quantitatively measure patient functionality, which is often subjective and difficult to measure by clinicians. This may give doctors an extra tool in their arsenal, in addition to existing ones, to make informed medical decisions. In the therapeutic domains of diabetes and cardiovascular disease, the use of digital health technologies has been more widely adopted than in oncology. As of yet, these technologies are used to measure exploratory endpoints and are often not developed enough to be used as primary endpoints in the absence of regulatory acceptance, and/or due to lack of clinical validation and standardization across the industry.

The interviewee notes that the regulators are usually not the bottleneck in the adoption of digital health technologies in clinical trials. The regulator's expectations are clear to sponsors, but regulators are not able to facilitate the harmonization across the ecosystem. Many sponsors are attempting to develop digital health technologies at risk of redundancy and differences in the definition of the standards. Large public-private partnerships such as IDEA-FAST and Mobilize-D aim to harmonize these standards of digital health technologies. These consortia are both politically and financially interesting for big pharmaceutical companies, as they can help showcase what is possible, and where potential hurdles might be. Unfortunately, these consortia usually don't have a long term outlook once the projects are

finished, and there is no overarching sustainability strategy following these IMI projects. However, bringing these pharmaceutical companies together to work in a precompetitive space does help to push the field forward, and is a strong tool to work towards harmonisation of measures and standards. The output of projects can be limited with long durations, administratively heavy and expensive, leading to mainly big pharmaceutical companies participating. Newer, smaller pharmaceutical companies do not always have the resources and overhead to participate in these programmes.

The innovator/company does not develop their own technologies inhouse, but instead procures from third parties. These technology firms are often SMEs that lack the resources to successfully scale up production and make it available in multiple countries. There are numerous examples of technology startups from the last 5 years who received funding for initial product offerings and failed during scale-up, now no longer exist. This has generally made sponsors reluctant to perform large scale clinical trials with technology startups, preferentially working together with larger more established technologies companies.

Technology has been shown to be useful in exploratory and proof of concept studies, phase 0 and 1 studies. Often the upscaling of the product is the issue, as well as the lack of MDR CE marking. Lastly, the use of real-world data from consumer grade devices is not well managed, often has missing data, poor signal to noise ratio and the expectations of regulators is less clear.

2. *When designing a clinical trial that uses RMTs, what interactions have you had with regulators (EMA, CBG, CCMO/METCs) and how did that impact the design of your study? Were there any regulatory hurdles that you had to overcome?*

The innovator/company has mainly interacted with the FDA and the EMA, using the qualification process to discuss new outcome measures. Discussions with the FDA are more frequent, as the FDA has a bigger impact with global presence. Anecdotally, the interviewee thinks that its easier for the EMA to follow the FDA's decision than it is for the FDA to follow the EMA's decision. The FDA has been seen as more approachable and easier for discussing processes for both devices and drugs.

Sponsors want to discuss with regulators as early as possible if a novel biomarker would be accepted, often without being able yet to demonstrate that its works. To which the regulators request proof that the technology works as expected, which leads to a catch-22. Additionally, the logistics and associated costs around validating your technology can be an issue. Many sponsors are currently learning from each other for example via working groups in EFPIA's digital endpoint sub-group on how to implement technology whilst keeping it cost effective, as well as harmonization and standardization of clinical endpoints. Furthermore, TUFTS university is conducting research to determine the net present value of digital measures which will be published later this year.

3. *What opportunities do you foresee in the validation and development of new digital biomarkers using RMTs? And what problems?*

For patients with dermatological issues, itching, a subjective patient outcome, can be quantified with a RMT. More specifically, night-time scratching can be objectively measured and easily communicated with a physician. This new biomarker has been discussed with the digital medicine society (DiME) and is specifically designed with the patient's needs in mind, while attempting to harmonize and standardize the measurement. Furthermore, this digital measure has been presented to the EMA, indicating

patient's preferences, enabling the creation of a new research platform and defining a new relevant clinical endpoint.

The interviewee notes that the use of RMTs in pandemic preparedness is going to be difficult. For one, the costs would be high, as population screening in general is a costly activity. A cost-benefit analysis would need to be done to identify which high risk population groups would benefit most from monitoring. Another factor to consider is who would ultimately bear the costs of monitoring. This is more a political issue than a technical or a regulatory one. Finally, it might even be easier to have a pandemic *response* plan in place rather than a pandemic *preparedness* plan.

Future State

1. *What changes would make the development and validation of novel digital biomarkers and RMTs in clinical trials easier?*

The interviewee suggests that two things are needed to facilitate the development of RMTs. First, there should be a clearly defined standard. In the standard is should be clearly explained what and how the technology is measuring, as well as a description of the technology and the evidence gathered through clinical validation, like an ISO standard. Second, an open library or repository should be created with all the possible measurements and technologies that have been validated and that are reproducible. This will enable sponsors to evaluate if they want to invest in new digital biomarkers or re-use existing approved ones. Furthermore, this would avoid fragmentation with many sponsors developing their own digital biomarker. Lastly, this would also create a specialized service ecosystem which would be cheaper, more efficient and of higher quality. The adoption of these validated biomarkers would be faster and more widely accepted. The EFPIA already has a digital endpoints working sub-group that is currently exploring this approach.

Interview with MDR/IVDR Consultant

Date: 22 May 2023

General

1. *Can you briefly introduce yourself and explain what your work entails?*

The consultancy works with medical device related startups, SMEs and larger companies, and is giving advice on how to comply with the MDR/IVDR. They work with both European based companies as well as companies trying to enter the European market. Many organizations find the complex legislation difficult to work with and therefore the consultancy offers support with the writing of product technical documentation for regulatory approval, set up of quality management systems, and related product or process validation studies. Furthermore, they train organizations on-the-job.

Opportunities and regulatory hurdles for RMTs

1. *What are in your experience the most common regulatory hurdles innovators face during the development of digital biomarkers/RMTs? And how do you advise innovators to address those regulatory hurdles?*

Generally speaking, there are two main regulatory hurdles that innovators face during the development of digital biomarkers/RMTs (presuming they fall under the definition of a medical device), namely, first step - clearly defining the claims and related functionality/mode of action of their product in order to assess what Regulation is applicable; and, second step - building technical documentation (TD) with the evidence for the claims and ensuring a quality management system (QMS) is in place to guarantee the quality of related processes.

For CE marking of a medical device (including IVDs), the claims of what the device does and what medical needs it tackles, need to be clearly defined. Without a clearly defined claim the appropriate validation tests might be overlooked. Clearly defining the claims needs to be planned early on in the development process to avoid frustrations, stress with timelines, complications with investors, and issues with the quality of the product. With the introduction of the MDR/IVDR it can also be difficult to interpret if the product in question is considered a medical device or not. Consultancies can assist with the detailing the product claims and help understanding how the definitions or requirement of MDR/IVDR apply.

The implementation of a quality management system is essential. How processes are documented and quality is ensured is a vital part of achieving the CE marking. Consultancies can also assist in the setup of a quality management system.

The consultancy helps many innovators that develop i.e. medical software products towards MDR/IVDR CE approval. The speed at which the software is developed is sometimes unmatched by the regulatory timelines. Often it is difficult for developers to understand why the rules are so stringent and the regulatory approval rates are so slow. Some software products and RMTs can be seen as innovations with a low risk to the user by the innovator, but still require the same approval process as devices falling into a higher MDR risk category. To help improve the knowledge gap and understanding of regulatory procedures, a suggestion would be to include this topic in the university curriculums of relevant studies.

Between innovators and regulators tension can arise. During a pandemic, many technologies were needed “yesterday” so the question arises how can we speed up the process of approval. Platform technologies have been suggested of which once the technology works for one disease area, the technology can be implemented for another disease area with defined but relative limited effort. When the product technology and processes within the organization already exist, it enables line-extensions. The setting up of processes or quality management systems takes a lot of start up time, which in the case of these types of established platform technologies can be skipped.

Currently there are long waiting times at the notified bodies. There used to be over 70 notified bodies under the MDD/IVDD. Due to the implementation of the MDR/IVDR, they will have to, amongst others, adjust their internal processes and get designated under MDR/IVDR, which can take several years. With the introduction of the MDR/IVDR, all previous medical device products that had a MDD/IVDD certification required to be reassessed under the MDR/IVDR, effectively requiring >25 years of work to be “redone”. In addition, some products (a lot of software products and IVDs) are up-classified and do need a NB to obtain CE under MDR/IVDR, which under the “old” Directives could be “self-certified”. In addition, systems like EUDAMED or the MDCG guidelines were not available the first couple of years after the MDR/IVDR came into force, which has created extra challenges for the industry and NB’s. COVID in parallel did not help either. As a result, it is expected that the coming 5 years innovators will still face limited capacity at notified bodies. Recently an amendment to the MDR/IVDR has been published (REGULATION (EU) 2023/607) allowing longer transfer periods for certain devices under conditions.

2. *What interactions as a consultant do you have with regulators (e.g. EMA, CBG, METC)? And what interactions do you have with notified bodies?*

The consultancy can have contact with the CBG, in case the product is composed of both a medical device and a medicinal product. The consultancy does not have contact with the EMA but they do have contact with representatives of the VWS, IGJ, notified bodies at e.g. regulatory professional meetings (seminars, conferences) in the Netherlands or Europe or as part of client projects.

<u>Future State</u>

1. *In your opinion, what future regulatory changes might make it easier to develop new digital biomarkers and RMTs?*

(Presuming RMTs fall within the definition of a medical device). The consequences of the stricter MDR/IVDR (as compared to the “old” MDD/IVDD) are only now being felt, during the transfer period. The field is increasing its understanding on what exactly is written in the legislation and how is it interpreted. Less strict legislation might help innovators, but the bar still needs to be set high enough to ensure the safety and reliability of a device or software tool to achieve its claimed intended purpose.

Over the last years (under MDD/IVDD), the harmonization between the notified bodies and authorities of various countries in EU has not been optimal. This is improved with the implementation of the MDR/IVDR. It is a welcomed change that there will be more harmonization across Europe.

<u>Pandemic</u>

1. *During a pandemic, would it be possible to certify a consumer device/software as a device under the MDR/IVDR so that it can, for example, be used as a diagnostic tool or in a clinical trial investigating medicinal products such as vaccines?*

In urgent pandemic situations, it is expected that in the end the national competent authority (most likely the IGJ and VWS in the Netherlands) will make the final decision. Consumer products may be used but only with a specific goal in mind. The consumer product doesn't necessarily need to be used/validated in a clinical setting, unless it contains a medical claim. If the product is not consistent enough in its e.g. measurements then it may even cause more harm than good. It could even lead to a false sense of security due to the quality of the measurement. In any case, transparency by the manufacturer on the capabilities and limitations of a device (also a consumer device) will in such a case help in making informed decisions. A risk-reward assessment should be done by the national competent authorities, their expert groups, involved notified bodies, in close communication with the legal manufacturer.

2. *Is it possible to add another indication for a MDR/IVDR marked device?*

It is possible to add another indication, which is considered a substantial change. This change needs to be validated and the technical documentation needs to be adjusted in alignment (and when relevant the QMS as well). A notified body is required to review/approve this change and related documentation (for device risk classes that need an NB for CE approval).

3. *During a pandemic, do certain products get preferential fast-track approval at the notified bodies?*

The MDR legislation requires clinical validation of the product. This has become a bigger part of the requirement and sometimes requires a clinical study to be done. During a pandemic the healthcare system is under enormous pressure with doctors and healthcare professionals taking care of patients, not having time to spend on additional clinical trials for medical devices.

A solution to this problem, would be an emergency use authorization followed by a full authorization later. Innovators would need to discuss their clinical trials with notified bodies/authorities/CCMO beforehand and receive approval. Notified bodies currently do not offer sparring/review on the study plan upfront, but in case of an emergency situation such as a pandemic, it could be beneficial if there would be opportunity to offer this.

The regulatory system in the USA differs from the system in the European Union. Whereas notified bodies are not allowed to provide advice to avoid conflicts of interest by simultaneously assessing and advising, the FDA is able to do so. However, some initiatives are currently being set up to allow the notified bodies earlier involvement, such as, for example, reviewing clinical protocols as part of the technical validation. It would be beneficial if there would be more opportunity for notified bodies to provide this service.

Interview with European Medicines Agency

Date: 5 September 2023

This interview was a written interview where the interviewees directly responded to the questions in written format.

Opportunities and regulatory hurdles for RMTs in clinical trials

1. *What are, in general, frequent issues or mistakes (ethical, legal, privacy, feasibility) that the EMA recognizes surrounding applications for market authorization for an IMP that involve RMTs to measure a clinical endpoint?*

The use of remote or wearable technologies is relatively new to the pharmaceutical sector. As a consequence, to date, there have not been many submissions where pivotal trials have utilized endpoints measured using such devices. It is therefore too early to establish trends.

However, the existing guidance and recommendations derive from experiences and examples seen by regulators. The following references may be useful when considering the potential risks/critical points in planning the use of technologies for remote collection of data from trial participants:

- Guideline on computerized systems and electronic data in clinical trials: https://www.ema.europa.eu/documents/regulatory-procedural-guideline/guideline-computerised-systems-electronic-data-clinical-trials_en.pdf
- Recommendation paper on decentralized elements in clinical trials: https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en

If a device used falls under MDR, the applicable requirements also need to be taken into account.

It should also be noted that ICH GCP E6 is currently undergoing revision, and will have a dedicated annex covering how GCP principles may be applied across a variety of trial designs and data sources, including the use of decentralized elements.

- Concept paper for ICH E6 (R3) Guideline for Good Clinical Practice Annex-2: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Annex2_ConceptPaper_2023_0405.pdf

2. *Is there alignment in the regulatory requirements for clinical endpoints in the context of drug development (clinical trials) for medical devices between the EMA and notified bodies; given they follow the MDR/IVDR? Is there a platform on which notified bodies and the EMA discuss the evaluation of medical devices? Does the EMA request data (e.g. outcomes from feasibility studies) from notified bodies?*

Endpoints measured by RMTs need to be clinically relevant, either in themselves or as surrogate to a clinically significant endpoint, in order to be accepted for regulatory purposes. An RMT may be measuring a known and already accepted by the scientific community endpoint or an endpoint the clinical relevance of which is self-explanatory.

However, the RMT may be measuring an endpoint that would require regulatory qualification before it can be accepted. In these cases, the assessment of the clinical performance of the RMT by a notified body may be complicated by the need for regulatory qualification of the novel endpoint measured by the RMT first, but given that such qualification may take time, the endpoint should only be used as exploratory (i.e. not with the intent to guide clinical decisions) until such time that it is considered qualified.

There is no platform, during either medicine development or evaluation/authorisation where notified bodies and the EMA discuss the evaluation of RMTs, but the evaluation of a medical device cannot and should not require the acceptability of the RMT for regulatory purposes; instead, the intended use of the device should be adapted until the regulatory qualification of the RMT (only possible via medicines regulators).

Also see MDCG 2022-10 Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR) https://health.ec.europa.eu/system/files/2022-05/mdcg_2022-10_en.pdf

3. *The EMA's document: "Q&A on the Qualification of digital technology-based methodologies to support approval of medicinal products" was last published in June 2020. To what extent is this document still applicable and does the EMA have additional updates to share?*

The Q&A was intended as a living document reflecting experience as it is gained.

Following the workshop on the Qualification of Novel Methodologies, and the increasing experience the EMA is gaining through SA and ITF, the intention is to update the document.

4. *According to the Emergency Task Force (ETF), to what extent are RMTs considered as a tool for monitoring patients during a pandemic and to what extent are they used to measure clinical endpoints? During a public health emergency, how does the EMA deal with non-CE MDR marked RMTs in a clinical trial used under public emergency clauses?*

We have seen increasing numbers of proposals for remote monitoring, seeking scientific advice and qualification advice / opinion.

5. *HERA signed an agreement with EMA to cooperate on health emergency preparedness and response. During a public health emergency, what is the role of EMA regarding devices? Is that limited to devices used in clinical trials and/or administering medicinal products? Or something else?*

Regulation (EU) 2022/123 provides the legislative framework for activities to be established by EMA to monitor and mitigate potential and actual shortages of medical devices considered to be critical during a declared public health emergency. This includes coordinating the identification and publication of a list of critical medical devices which is adopted by the Executive Steering Group on Shortages of Medical Devices (MDSSG). Medical devices included in this list are subject to reporting obligations by

relevant Economic Operators, National Competent Authorities and Notified Bodies to closely monitor supply and demand with an aim to ensure availability as needed throughout the EU/EEA.

The methodology used to identify critical medical devices is published on the EMA website (https://www.ema.europa.eu/en/documents/other/methodology-establishment-public-health-emergency-critical-medical-devices-list_en.pdf) and states that only CE marked devices placed on the market in the EU/EEA are in scope. This means that if the device has a CE mark and has been placed on the market in the EU, it is in scope of this Regulation regardless of its intended use.

HERA's scope in a public health emergency is on medical countermeasures, which differs from that of EMA as it encompasses not only CE marked devices, but also potentially other types of devices such as laboratory developed tests. In addition, availability of critical raw materials and components is also within HERA's scope but outside the scope of EMA's work.

EMA and HERA work closely together to ensure no duplication of data collection efforts, and will therefore share relevant data and knowledge. To prepare for this, EMA and HERA co-chair a Joint Industrial Cooperation Forum Working Group on data collection, which aims to align data collection efforts across organizations and reduce data submission burden on industry stakeholders.

6. *What lessons would you like to share with us (or investigators/innovators/sponsors) regarding designing a study that incorporates RMTs to measure clinical endpoints?*

The study design would depend on the relationship of the RMT with acceptable clinical endpoints.

If the RMT simply provides an alternative way to measure a regulatorily acceptable clinical endpoint, then the use of the RMT only has implications for the conduct of the study in collecting endpoint-related data (e.g., less or no study visits, if the RMT allows continuous or more intensive measurement of the endpoint that can be automatically uploaded).

If the endpoint measured by the RMT is not regulatorily acceptable yet, then the clinical study should contribute to the endpoint validation work, i.e. the endpoint should be used as exploratory and an attempt made to correlate (or anchor) it to acceptable clinical endpoints towards eventual regulatory qualification of the endpoint.

In any case, it is recommended to scientific or qualification advice in advance of the clinical trial start to confirm validity of the measure and sound implementation in protocol.

Consideration should be given to key guidance documents, as follows:

- CTCG recommendations on decentralised elements in clinical trials,
- NfG on computerized systems and electronic data in CTs, ICH-E6 (see response to Q1) as well as to the
- Qualification opinion on eSource Direct Data Capture (DDC) (EMA/CHMP/SAWP/483349/2019).

7. *In a study performed by the CBG (Dekker et al., 2021), qualification opinions, qualification advices, and scientific advices were evaluated to gain insight in the types of devices that are intended to be used in clinical trials for supporting/submitting application for obtaining marketing authorization (registration trials) and the main recommendations of the CHMP. It was found that the main recommendations of the CHMP were related to relevance of the (novel) outcome measure; validation; precision, accuracy, sensitivity, and specificity; compliance; sampling interval; and data handling and privacy. Can you comment on these findings? Are there any other common issues that you come across?*

The CHMP recommendation on the relevance of the novel outcome measure relates to its qualification or regulatory acceptability in general which would involve considerations on Context of Use (CoU), sensitivity of the measure to detect change (as a result of natural history and/or pharmaceutical intervention) and characterisation of a minimal important difference (MID).

The remaining aforementioned issues constitute important aspects of the clinical performance of RMTs as well as aspects relating to the conduct of *clinical performance studies* to support the conformity assessment of RMTs used to measure (novel) endpoints or outcome measures.

The CHMP takes such aspects into consideration (but does not assess towards conformity assessment per se) in the course of the qualification of the novel endpoint or outcome measure.

8. *What regulatory changes might make it easier to develop novel digital biomarkers and RMTs for measuring clinical endpoints?*

The development of the digital biomarkers does not conceptually differ greatly from other biomarkers. There is however a grey area concerning the remit of EMA versus other actors (e.g. Notified bodies), including the appropriateness and capability to exchange confidential information if needed.

There is also a lack of expertise in the network to evaluate the impact of certain technologies and methodologies on the areas pertaining to the remit of the different bodies. Examples could be: difficulties for medicines regulatory network to evaluate the effect of (potential) biases introduced by algorithms or self-learning systems; capability to understand and protect personal information according to both GDPR and GCP (who accesses what and when); expertise within notified bodies to go beyond safe performance of a device and consider effectiveness, if needed.

9. *RMTs are often mentioned as technologies that carry the potential to help develop new biomarkers in areas of unmet medical need, to lower participant burden in clinical trials, to support clinical decision making, to better stratify patient groups, to help pick up on the benefit/risk profile of treatments, and to make clinical trials faster and cheaper. Can you share your opinion on this proposition?*

(We could not develop a specific answer but aspects are alluded to in answer 6, and we generally welcome developers to discuss these their proposals and how these are may improve development approaches.)

10. *In a clinical trial that uses RMTs, how does the EMA look at the clinical validity of an endpoint measured with a RMT, if there was a software update and upgrades during the clinical trial? Is there already a decision towards AI generated clinical endpoints?*

As a general rule, the clinical validity should be established regardless of the technology used to measure the endpoint. The impact of updates and upgrades to all computerized systems used in the clinical trial should be assessed by the sponsor/investigator before their implementation. The guideline on computerized systems elaborates the expectations for these aspects. The same expectations for suitability for the purpose and reliability of the data apply to any technology.

There is a draft reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle, currently under public consultation, which outlines the current thinking on the use of AI to support the safe and effective development of medicines. AI is a field which is rapidly developing, and thinking may change.

- Draft Reflection Paper on the use of AI in medicinal product lifecycle https://www.ema.europa.eu/documents/scientific-guideline/draft-reflection-paper-use-artificial-intelligence-ai-medicinal-product-lifecycle_en.pdf

11. *How concerned is the EMA about data quality during a decentralized clinical trial?*

Decentralized elements have been used in clinical trials for a considerable number of years, and may facilitate better conduct of trials and collection of data. The risk related to data quality depends on what the decentralized element is used for and how well the technology is fit for its purpose. The same standards are applied to trials conducted by traditional means or by making use of new technologies and a decentralized setting. The Recommendation paper on decentralized elements (see answer to question 1) in clinical trials is a useful reference which addresses some of the identified concerns related to the use of decentralized elements.

12. *When should sponsors or investigators reach out to the EMA for scientific advice, and what is the best way to do so? Do you think sponsors or investigators are aware of your role in giving scientific advice? [RH: on RMTs]*

Scientific advice can be requested at any point during development, i.e., as soon as a sponsor or investigator starts planning a study or formulating a development plan and ideally the interaction should commence early.

Submissions can follow the formal pathway following registration of the sponsor with EMA and acquisition of a Research Product Identifier (RPI) for the product under development (see Requesting scientific advice or protocol assistance from EMA), but initial contact may be sought directly with the EMA scientific advice (scientificadvice@ema.europa.eu).

Medicine developers are well aware of the option for EMA/CHMP/SAWP/centralised scientific advice and Qualification of Novel Methodologies. On the other hand, academic developers, MedTech and

small companies (pharma or medtech) may be less familiar with the existence or the mode of interaction with EMA scientific advice.

Deliverable 4: Literature study on decentralised clinical trials

Abstract

The landscape of clinical trials has undergone a notable transformation, shifting from traditional in-clinic setups to embrace decentralized elements such as Remote Monitoring Technologies (RMTs). This transition, enabled by digital innovations, has prompted the Trials@Home consortium to explore the regulatory implications of using RMTs into European clinical trials. This literature study delves into the regulatory opportunities and hurdles presented by RMT adoption.

The opportunities presented by RMTs are multifaceted. Regulatory bodies have demonstrated a willingness to accept telemedicine, particularly evident during the COVID-19 pandemic, where telemedicine was adopted to ensure trial continuity and lower infection risk. Decentralized trial methods, including telemedicine visits and direct-to-patient drug supply, have gained traction. Regulatory bodies like the European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA), National Competent Authorities (NCAs) have provided guidance, facilitating the incorporation of RMTs in pilot Decentralised Clinical Trials (DCTs). Initiatives such as the EMA's Innovation Task force or Clinical trials transformation initiative underline a concerted effort to foster collaboration between regulators and sponsors. RMTs enable recruitment of diverse participant populations and decreased travel burden, have the potential to increase trial adherence and decrease dropouts. Furthermore, RMTs can also be used in low risk chronic disease trials due to the participants' ability to self-manage their condition.

Conversely, many hurdles have been noted related to RMT adoption in clinical trials. Sponsors are hesitant to employ DCTs as they are currently no standardized or well-established implementation techniques. There is a lack of clarity in validation requirements of using RMTs in a clinical trial to achieve a market authorization for a medicinal product as well as uncertainty about the acceptability of novel digital endpoints. Regulators only accept RMT-based clinical endpoints to support regulatory decision making in a trial when a RMT used is sufficiently validated. Without proper validation, RMTs can be used for measuring exploratory endpoints in a clinical trial. The sharing and protection of participants' personal data, the ownership of data generated by RMTs, and compliance with the General Data Protection Regulation (GDPR) all contribute to the complexity. It is recommended to consult a data protection officer during the setup of a clinical trial. Both the participants and trial staff face new burdens with the introduction of RMTs. While RMTs can offer convenient data collection, it can potentially overwhelm participants, particularly those with limited digital literacy. Participants in DCT have become responsible certain aspects of data collection. Site staff have to be trained to use devices and handle technological issues. We propose that specific studies should be conducted to measure the participants' and trial staffs' burden. RMTs may also weaken the trust and relationship between investigators and participants possibly affecting adherence and dropout rates.

This study highlights the evolving regulatory landscape surrounding RMTs in European clinical trials. Contradictory findings exist in the literature, wherein regulators show openness to RMTs whilst simultaneously expressing concerns about safety, privacy, and validity. It is currently unknown if the concerns are due to regulator hesitancy, or due to innovations not meeting the required standards. To lower participant burden, sponsors could provide concierge support services and collaborate with patient organizations for patient-oriented trial designs. Striking a balance between innovation and regulatory compliance is crucial to realizing the full potential of RMTs in advancing clinical research.

Introduction

Clinical trials are an indispensable tool to evaluate the safety and efficacy of new medicines and medical devices. In the past, clinical trials were exclusively performed in a hospital or clinic by a supervising principal investigator requiring participants to frequently travel for a scheduled visit. However, over time the clinical trial activities have been slowly moving from the clinic into the participants immediate surroundings, usually the home. This transition has been enabled by the adoption of digital technologies, such as apps, devices and wearables that are used for data collection and communication between the investigator and the trial participant (van Rijssel et al., 2022). Recruitment of trial participants has been facilitated via social media, direct to participant shipment of investigational drug product (IMP) as well as home nurse visits are all examples of decentralized trial elements that enable the transition from in-clinic trials to trials conducted in the participants home (De Jong et al., 2022).

Introducing remote monitoring technology (RMTs) into clinical trials to facilitate decentralised trial elements can offer many opportunities but may add additional complexity to clinical trials conducted remotely. Some challenges include participants becoming responsible for timely communication of safety information as well as insufficient trust building between the investigator and participant (de Jong et al., 2022). Yet, at the same time the regulatory system needs time to catch up with the rapid technological developments. The Trials@Home consortium aims to provide insights into the possible opportunities and challenges of Decentralised Clinical Trials (DCTs) in Europe. The aim of this literature study is to evaluate the opportunities and hurdles involved in the adoption of RMTs into clinical trials from a European regulatory perspective.

Method

During April 2023 we collected all the publicly available peer-reviewed papers published on the Trials@Home website (https://trialsathome.com/). All these papers were used in the literature search. Additionally, using PubMed, we ran a database search with the key words: “Trials@Home Consortium” to ensure we collected all the literature regarding this topic and any literature that referenced the Trials@Home consortium. All the papers were carefully read, and the key regulatory contexts of clinical trials were summarized in a table. The resulting regulatory topics were subsequently classified into two categories: regulatory opportunities and hurdles of using RMTs in clinical trials. Within these categories, common themes were identified which are elaborated in the results section.

Results & Discussion

Our search resulted in 10 publications and 1 work package deliverable that are publicly available (see table 1). All but one of the literature published mentions regulatory topics suggesting the importance of the regulatory context.

Number	Study Name	Author	Mentioning of regulatory topics?
1	COVID-19 and the Emerging Regulatory Guidance for Ongoing Clinical Trials in the European Union	De Jong, 2021	Yes
2	Learning from remote decentralised clinical trial experiences: A qualitative analysis of interviews with trial personnel, patient representatives and other stakeholders	Coyle, 2021	Yes

3	A systematic review of methods used to conduct decentralised clinical trials	Rogers, 2022	Yes
4	Opportunities and Challenges for Decentralized Clinical Trials: European Regulators' Perspective	De Jong, 2022	Yes
6	Ethics review of decentralized clinical trials (DCTs): Results of a mock ethics review	Van Rijssel, 2022	Yes
7	A secondary qualitative analysis of stakeholder views about participant recruitment, retention, and adherence in decentralised clinical trials (DCTs)	Coyle, 2022	Yes
8	Which decentralised trial activities are reported in clinical trial protocols of drug trials initiated in 2019-2020? A cross-sectional study in ClinicalTrials.gov	de Jong, 2022	Yes
9	A cross-sectional survey on the early impact of COVID-19 on the uptake of decentralised trial methods in the conduct of clinical trials	Suman, 2022	Yes
10	Decentralised, patient-centric, site-less, virtual, and digital clinical trials? From confusion to consensus	Santa-Ana-Tellez, 2023	No
11	WP4 – 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	Santa-Ana-Tellez, 2021	yes

Table 1: List of literature published by the Trials@Home consortium and their respective mentioning of regulatory topics.

Opportunities

Regulatory and Sponsor Acceptance

De Jong et al, 2021 showed that regulators (notably, the French and German NCAs as well as EMA) had readily accepted telemedicine (albeit temporarily during the COVID-19 pandemic) and enhanced remote clinical trial monitoring to ensure trial continuity (De Jong et al., 2021). On-site visits were replaced with telemedicine calls reducing chance of infection and lowering patient burden. In a survey study investigating the COVID-19 impact on the use of decentralized trial elements, the authors note that 31% of the organizations surveyed adopted a fully decentralized trial approach to ensure continuity during COVID-19, indicating that sponsors are incorporating decentralized elements in their trials (Suman et al., 2022).

Decentralized data collection and remote monitoring were expected to remain in future trials with 33% and 27%, respectively (Suman et al., 2022). This is, of course, only true if digital solutions and technology were well established and implemented, and which have been reported to work well in the early phase of the pandemic. The survey study showed a large uptake of tried and tested decentralized methods, yet there was only a small shift in uptake of innovative, fully decentralized clinical trials (Suman et al., 2022). Most frequently mentioned decentralized methods included: telemedicine health visits, direct-to-patient IMP supply and decentralized data collection.

Remote source document verification (rSDV) is typically not allowed in Europe, but in the case of COVID-19 studies and other life-threatening diseases with no satisfactory treatment options this was allowed to be monitored remotely. Interestingly, not all EU member states agreed on harmonizing

the rSDV approach citing participant privacy concerns and unnecessary site burden (De Jong et al., 2021).

Both the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) are supportive of decentralized elements, such as RMTs, in clinical trials. Regulatory guidance papers such as the EMA's recommendation paper on decentralized trial elements, (https://health.ec.europa.eu/system/files/2023-03/mp_decentralised-elements_clinical-trials_rec_en.pdf) are published to help sponsors and investigators navigate the regulatory landscape (Rogers et al., 2022). The EMA encourages early contact to assist prospective applicants in identifying the most appropriate regulatory interaction route. The EMA's procedures to receive feedback are, among others, the qualification of novel methodologies for drug development tools and the Innovation Task Force (Gelis et al., 2023). The Danish, Swedish and Swiss National Competent Authorities have also expressed interest in DCTs and issued guidance for conducting DCT pilot studies (de Jong et al., 2022).

Furthermore, various initiatives, workshops, and programmes such as the EMA's Innovation Task force have been set up by the regulators to facilitate the dialogue with sponsors (Rogers et al., 2022). In addition, local METCs or ethics boards regularly receive trainings to stay up to date with the regulatory legislation changes (Rosa et al., 2015). Lastly, many formal regulations, such as the FDA's approval to use medical devices for home use, enable the adoption of RMTs in clinical trials (Smalley, 2018). Initiatives such as the Trials@Home, RADAR-AD and Mobilise-D consortia as well as the Clinical Trials Transformation Initiative aim to develop novel end points and decentralized trial elements.

Participant Population and Indications

RMTs allow clinical trials to be conducted in rare diseases for which participants might be difficult to come by due to geographical dispersion (de Jong et al., 2022; Rogers et al., 2022). Moreover, the recruitment of a more diverse participant population is enabled which, in turn, is more representative form of data collection in a real-world setting (de Jong et al., 2022). Chronic diseases with low risk are better suited for clinical trials with RMTs due to the participants' ability to self-manage their condition (de Jong et al., 2022; van Rijssel et al., 2022). Other diseases with more risks and requiring more care are less well-suited for clinical trials involving RMTs.

In a paper describing the decentralized trial elements for studies started in 2019 and 2020, the authors report that only 15.3% of the trails used wearables devices, sensors, or biomarker kits (De Jong et al., 2022). Interestingly, of these trials that included wearable devices, 46% were in phase 2, 41% were in phase 3 and only 12% were in phase 4 (De Jong et al., 2022). This might be explained by the fact that the majority of the disease areas for these trials were infectious diseases and metabolic diseases (Diabetes type 1 & 2) leading to more frequent use of RMTs in phase 2 and 3 studies. Three of the five phase 4 studies were for diabetes. It is possible that due to the ability to self-manage, and the relative low risk to the participant, RMTs were chosen for these phase 4 trials.

Participant engagement and adherence

Less travel burden as well as a more seamless integration in the participant's life are frequently mentioned opportunities that RMTs offer in clinical trials potentially resulting in higher trial adherence and less dropouts (Coyle et al., 2022b; de Jong et al., 2022). Continuous safety monitoring, reduced recall and observer bias, the possibility for increased patient engagement through digital platforms were also described and may reduce trial timelines (Coyle et al., 2022b; de Jong et al., 2022; Khozin & Coravos, 2019; van Rijssel et al., 2022).

Hurdles

Regulatory and Sponsor Hesitancy

A high level of regulatory requirements, and a low perceived degree of acceptance by the FDA and EMA may be limiting the implementation of decentralized trial elements (de Jong et al., 2022). Investigators and sponsors seem hesitant to implement RMTs and DCTs as they are currently no standardized or well-established implementation approaches (Coert et al., 2021; Gelis et al., 2023; van Rijssel et al., 2022). Furthermore, sponsors report limited regulatory guidance from regulators (Gelis et al., 2023), as well as lack of clarity of overall responsibility under the ICH (de Jong et al., 2022).

Until recently, clinical trial sponsors had to submit clinical trial applications to each local Medical Research Ethics Committee (MREC) in each country where they were interested to perform a study to gain approval to run a clinical trial (*Clinical Trials Regulation | European Medicines Agency*, n.d.). However, each local MREC could have different views on the implementation of decentralized trial elements such as the acceptability of devices used regarding data privacy or the clinical validity of a specific device used (de Jong et al., 2022). With the implementation of the new Clinical Trials Regulation (CTR), a great step forward to harmonise the process of clinical trial applications, assessment and supervision was made. The introduction of the CTR also included the introduction of a central system (the Clinical Trials Information System, CTIS) which allows sponsors to submit one application to multiple EU countries, facilitating applying for a multinational trial (*Clinical Trials Regulation | European Medicines Agency*, n.d.). The CTR will help facilitate harmonization of the process for assessment and supervision of clinical trials throughout the EU, although local differences in regulation interpretation can still cause some differences (de Jong et al., 2022; Muurling et al., 2023).

A literature study focusing on decentralized trial elements showed that only 1.6% of protocols included fully decentralized data collection through mobile devices, which could indicate hesitancy of sponsors to adopt these technologies (De Jong et al., 2022). Comparing pre-COVID-19 pandemic trials to post-COVID-19 trials, there was only an uptick ~1% in the use of wearables and telemedicine visits (De Jong et al., 2022). This is in line with previous research, where private sponsors are less frequently incorporating wearables and telemedicine than public sponsored trials (Marra et al., 2021). In addition, private sponsors also tend to employ fewer phase 4 trials than public sponsors (Marra et al., 2021).

Clinical validity and reliability

Sponsors need to prove to regulators that the RMTs used in a clinical trial are reliable and validated if the RMT is used in studies aimed to achieve a market authorization for a medicinal product. Furthermore, the outcome measures must be relevant to the indication and sensitive enough to be able to assist clinicians in interpreting changes in a patient that are clinically meaningful (Haberkamp et al., 2019; Viceconti et al., 2022). However, there is a lack of clarity in validation requirements of using RMTs compared to traditional measurements (Apostolaros et al., 2020) as well as uncertainty about the acceptability of novel endpoints (de Jong et al., 2022). Validity testing of digital biomarkers is essential; however, validity does not ensure that a selected technology will perform as expected in a specific remote clinical trial context (Coyle et al., 2022b).

Sponsors may not know what clinical validation is necessary for a novel digital outcome to be accepted by regulators and therefore may be less willing to invest in technology when conventional alternatives are readily accepted (de Jong et al., 2022). The EMA is known to only accept clinical endpoints in a trial when a RMT device is sufficiently validated (de Jong et al., 2022; Dekker et al.,

2021). A CE mark can give regulators a certain level of reassurance (Gelis et al., 2023). At the same time, the EMA will make their own assessment to see if the data gathered via an RMT is solid enough to use for regulatory decision making. Using a non-CE marked device as an exploratory endpoint or during the early phase in drug development can also be accepted by regulators. However, in general it is recommended to use a CE marked device in its intended use to collect data to support regulatory decision making (Gelis et al., 2023). For a sponsor to use a non-CE marked digital device as a primary or secondary endpoint in a clinical trial a possible separate application may be requested by the regulators. This dramatically increases the regulatory burden for sponsors as they would have to submit two applications in parallel, one for the medicinal product and one for the medical device (Gelis et al., 2023).

With the recent introduction of Artificial Intelligence (AI) and algorithms to analyse data, the complex interplay between the hardware, sensors, and algorithm makes evaluation by regulators even more difficult (Coravos et al., 2019). In addition, the generation of "Big Data" from RMTs could unnecessarily burden participants to capture the data but also the dataset could be challenging to interpret and difficult to extract meaning (de Jong et al., 2022; Gelis et al., 2023).

Data & Privacy

During the beginning of the COVID-19 pandemic many sponsors tried adopting decentralized trial elements, notably rSDV, to ensure trial continuity. However, due to the nature of the data, privacy concerns and ethical considerations, regulators did not always accept rSDV. Furthermore, delivery of IMP to patients as well as data verification and privacy concerns were also seen as a burden to the adoption of RMTs due to regulatory restrictions (Suman et al., 2022). The issue of data integrity and validity remained a point of contention for data collected unsupervised by participants using remote monitoring digital technology (Rogers et al., 2020)

For the delivery of IMP as well as shipment of devices to participant homes and good distribution practices (GDP), the EMA's recommendation paper states that the personal data of trial participants should be processed in accordance with the General Data Protection Regulation (GDPR) on a need-to-know basis (*Recommendation Paper on Decentralised Elements in Clinical Trials*, n.d.). Furthermore, various NCAs, due to variations in national legislation, have different rules about distribution, returning and destroying of IMP (Apostolaros et al., 2020; de Jong et al., 2022).

One barrier to the adoption of RMTs in clinical trials is the question of data ownership. It is not always clear who owns the data generated by the RMT, as ownership could sit with the patient or the manufacturer of the device (Coyle et al., 2022b; Messmer et al., 2017). Regardless of who owns the data, EMA states in their recommendation paper that the sponsor needs to ensure adequate protection of the participants personal data in compliance with the GDPR (*Recommendation Paper on Decentralised Elements in Clinical Trials*, n.d.).

Aside from practical considerations (e.g., physical assessment) or regulator restrictions (e.g., e-Consent not always permitted) in a fully decentralized clinical trial, data collected remotely remains a point of contention. Ensuring data completeness and data privacy can be difficult to control in an unsupervised trial participant using RMTs (Rogers et al., 2020). Furthermore, given the complexity of the legal language used in the GDPR legislation the appointment of a data protection officer to ensure privacy compliance would be recommended in a DCT (Lalova-Spinks et al., 2022).

Participant and site staff burden

One interesting finding is the mentioning of burden shift from the site staff to the trial participants. In traditional trials, participants are expected to come to the site for measurements, which may be

seen as burdensome to the trial participant. In decentralised trials, some argue that trial participants are being overburdened with digital technology, "digital overload" when participants are asked to use multiple devices to track their disease progression (Coyle et al., 2022a; Donnelly et al., 2018). Digital overload may be exacerbated by reduced access to digital technologies in some participant groups, such as, older adults, economically deprived or people with disabilities (Coyle et al., 2022b). Coupled with small errors and frustrations of failed data uploads or errors in the device menus could lead to participants dropping out of trials (Coyle et al., 2022b).

Others have noted that participants are responsible to activate, charge and wear the RMTs for long periods which presents a significant burden on the participant (Galarnyk et al., 2019; Rogers et al., 2022). Participant burden further increases with RMTs as they are also responsible for timely communicating relevant safety information (de Jong et al., 2022). Certain participant groups, based on low levels of digital literacy and use of online recruitment methods, may be excluded thus limiting the generalizability of the trial results (de Jong et al., 2022; van Rijssel et al., 2022).

In some cases, it was recommended to perform many smaller feasibility and exploratory trials instead of one large trial to see which RMTs were well suited. On the other hand, the reduction of burden trial activities on the participants may have been shifted to the individual site staff to deal with the technological issues that participants are facing. This requires site staff to undergo additional training. Site staff have also noted feeling isolated or helpless when the technology is experiencing errors while the participant might be trying to report a serious adverse event (SAE) (Coyle et al., 2022b). The inability of timely safety monitoring and recording of SAEs due to technical failures of RMTs is unacceptable to the regulators (de Jong et al., 2022). As both participants and site staff experience new difficulties it might not be a burden shift from one to the other but more a change in the type of burden.

Investigator-participant relationship

Using RMTs in trials may also weaken the trust and relationship between investigators and participants. As a result, compliance and trial adherence may be lower in participants in a trial with decentralized elements (Coyle et al., 2022a; de Jong et al., 2022; van Rijssel et al., 2022). It has been noted that patient advisory panels and focus groups have been found to have the lowest cost and highest impact on the clinical research relative to other patient-centric initiatives (Stergiopoulos et al., 2020).

Conclusion

The Trials@Home consortium took a deep dive into many regulatory aspects of DCTs. Looking at the both the opportunities and hurdles for RMTs adoption from a regulatory perspective in Europe, we can conclude that the situation is complex, and requires nuance. Many articles have contradictory findings such as the fact that regulators are open to RMTs and see the use case, whilst they simultaneously express concerns related to safety, privacy, and validity (Coyle et al., 2022b; de Jong et al., 2022; Rogers et al., 2022). Moreover, the increased perception of bearing more burden, the trial participant or the site-staff, also leads to disagreements between authors. However, this might just be two sides of the same coin.

Based on the findings from this Trials@Home literature search, there is a slight reluctant tendency from regulators towards RMT adoption in clinical trials. This may be because the technology used is not well established yet and lacks standardization and harmonization. In a mock ethics review executed in Trials@Home, regulators expressed predominately hesitant attitudes towards the DCTs. DCTs were considered more burdensome and less safe, due to the responsibility being shifted

towards the participant with in-person contact lacking (van Rijssel et al., 2022). The benefits of RMTs did not carry much weight, whereas the integrity of the data safety of the participants were prioritized (van Rijssel et al., 2022). It is currently unknown if the concerns are due to regulator hesitancy, or due to innovations not meeting the required standards.

Given the hesitancy to adopt RMTs in clinical trials a structured approach to the problem is required. The implementation of the CTR is meant to help with harmonizing the assessment and supervision of clinical trials in the EU. Other efforts might be needed to further solve this issue from both a regulator and an innovator perspective.

Given the frequent mentioning of increased burden of the participant and site staff during a DCT, it remains unclear who is bearing the burden due to the use of RMTs (Coyle et al., 2022a; de Jong et al., 2022). One solution for minimizing participant burden would be for sponsors to offer a participant concierge support service where participants are guided through the clinical trial and offer support for the devices used. This might also help with building trust between the patient and the investigator. Sponsors should be required to work with participants and patient organizations to really understand their burden and preferences to design their trials more patient-oriented. One study looked at the technology burden between sites staff and participants in DCTs and found similar levels of frustrations among site staff and participants resulting from technological issues. One suggestion was to streamline study technologies into one adaptive platform experience instead of using disparate DCT technologies at the site (*Easing the Clinical Trial Technology Burden on Patients and Sites*, n.d.). However, further studies should be conducted to investigate the real burden levels placed on site staff and participants in a DCT.

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Deliverable 5: Studying EU-wide, multi-centre clinical trials on RMTs using the learnings from RADAR-AD

Abstract

The IMI funded RADAR-AD project investigated the potential of RMTs in Alzheimer's Disease. Many findings coming from this project are also useful for other disease areas, and can hence be considered for the use of RMTs in the context of future pandemics. We investigated the publications and deliverables produced by the RADAR-AD project and evaluated whether they discussed topics with relevance to the regulatory ecosystem.

It was found that the MREC feedback on the research protocol differed on issues raised, evaluation run times, and the level of scrutiny. Recommendations to improve the review process leading to a sound research protocol included engaging an institutional data protection officer, a patient advisory board review of the protocol, stimulating a strategy for ethical reflections during the study, and working on a mutual understanding with the MRECs on the definition of a medical device. Our review showed that the regulatory status of a device was not considered in the selection of devices for the project. If one plans to apply for a market authorisation application for a therapeutical product and information gathered via apps or devices is used to support the application, the relevant regulatory and legal will have to be met. Innovators and investigators are advised to consider the regulatory status of devices early on, so that informed decisions can be taken.
The evaluation of qualification opinions (QOs), qualification advices (QAs) and scientific advices (SAs) of the Committee for Medicinal Products for Human Use (CHMP) performed by the RADAR-AD consortium showed that accelerometers to measure activity and/or sleep were the most frequently used devices, followed by mobile applications and glucose monitoring devices. When investigating these parameters, there is already a body of knowledge one could build on. It should be kept in mind that such a technology will have to be validated for its specific context of use.
The project's ITF meeting report provides valuable feedback, indicating the value of meeting with the ITF. Manufacturers, investigators or sponsors working on RMTs in the context of infectious diseases are advised to reflect on these topics early on, and engage with regulators as early as possible. In addition, sufficient resources will have to be made available to support such a qualification process. Engaging with regulators early on in the development process is imperative to the success of developing novel tools and technologies. Both the ITF and the qualification advice procedure are good pathways to engage with the EMA in the early stages of development.

Introduction

The Innovative Medicines Initiative (IM) is a European public-private partnership aimed to improve the competitive position in the field of pharmaceutical research, and to speed up the development of better and safer medicines. They fund programmes that investigate and develop innovative novel diagnostic tools, biomarkers, or therapies in a pre-competitive space (*IMI Webpage*, n.d.). Over the years, a number of programmes investigating opportunities and challenges of remote monitoring technologies (also under the name of eHealth technologies or digital technologies) to assess disease have been initiated. These include the projects RADAR-CNS, IDEA-FAST, Mobilise-D, Trials@Home, and RADAR-AD (*IDEA-FAST Website*, 2023; *Mobilise-D Website*, 2023; *RADAR-AD Website*, 2023; *RADAR-CNS Website*, 2023; *Trials@Home Website*, 2023). These projects often include interactions with regulators or studies on the regulatory landscape (Broekmans, n.d.; Mikolaizak et al., 2022; Viceconti et al., n.d., 2020). Learnings from these projects can help to understand the opportunities and challenges of remote monitoring, and the regulatory bottlenecks that can hamper the use and implementation of these technologies.

In this deliverable, we review the publications and deliverables produced by the RADAR-AD project. This project was selected because of the following reasons:

- The project had a regulatory strategy right from the start (Verheij, 2019) and had interactions with the EMA via the Innovation Task Force and by applying for scientific advice. Evaluating the regulatory strategy as well as the feedback provided by the Innovation Task Force gives starting points for innovators interested in digital endpoints(Stolk, 2020b). Often, these feedback points are disease-agnostic and are hence also relevant for infectious diseases and future pandemics.
- As part of the project, an evaluation was made of qualification opinions (QOs) and qualification advices (QAs) as well as scientific advices (SAs) of the Committee for Medicinal Products for Human Use (CHMP) on remote monitoring technologies (Dekker et al., 2021). This gives insight in both the technologies and endpoints for which innovators are asking opinions and advice, and insight in the opinions and advice provided by the EMA. Also here findings can potentially be extended to infectious diseases and future pandemics.
- RADAR-AD is a large study comparing various consumer-grade and medical CE marked devices for their performance. The study contains a multi-centre trial executed in 9 different European countries, providing insight into how medical ethical committees interpret EU legislation and evaluate clinical trial applications with remote monitoring technologies (Muurling et al., 2021, 2023).

RADAR-AD investigates the potential of RMT to assess cognitive and functional decline in Alzheimer's Disease (AD). AD is a progressive neurodegenerative disorder, and the main cause of dementia. Drug development work in the Alzheimer's field has been very challenging (van Bokhoven et al., 2021), and until the recent registrations of Aducanumab (*Aducanumab Approval Letter*, n.d.) and Lecanemab (*Lecanemab Approval Letter*, n.d.) (currently only by the FDA) no disease modifying drugs have been available for the disease.

It is the aim of the RADAR-AD project to assess whether RMTs can discriminate between different stages of the disease, whether this could help to support patients and caregivers, and improve the way clinical trials in AD are set up and executed (Muurling et al., 2021). It does so by evaluating various RMTs in 3 different study tiers (wearable sensors, homebased sensors, and a smart-home environment) across different stages of the disease, in different countries, and by applying different modelling approaches (Brem et al., 2023). Engagement with regulatory agencies, ethics specialists and patient advocacy groups has been weaved into the project right from the start.

Method

During July 2023 we collected all the publicly available peer-reviewed papers published on the RADAR-AD website (*RADAR-AD Website*, 2023) and on Cordis (*Cordis Website*, 2023). All these papers were used in the literature search. Additionally, using PubMed, we ran a database search with the key words: "RADAR-AD" to ensure we collected all the literature regarding this topic and any literature that referenced the RADAR-AD project. All the papers were carefully read and evaluated for the mentioning of regulatory opportunities or hurdles related to RMTs, and summarized in a table. We also reviewed the deliverable reports that are publicly available on Cordis, to evaluate whether they contain references to regulatory considerations (*Cordis Website*, 2023). All references to regulatory topics are described in the results section below.

Results

Our search resulted in 11 publications and 18 deliverables that are publicly available (see table 1). From the publications, 1 publication is fully dedicated to the topic of regulatory hurdles and opportunities (Dekker et al., 2021). One publication briefly mentions that it is important to collaborate with regulators to ensure that appropriate regulatory frameworks are in place for digital technologies (T. G. Stavropoulos et al., 2019). Another publication reports on the feedback received from the medical ethical committees following the review of the research protocol (Muurling et al., 2023). A recently published review contains a brief section on regulatory learnings (Brem et al., 2023). Other publications do not refer to regulatory strategies, considerations, opportunities or hurdles, although they sometimes refer to topics that also come back in regulatory discussions.

No.	Pubmed and website	Author	Mentioning of regulatory topics?
1	Remote monitoring technologies in Alzheimer's disease: design of the RADAR-AD study	Muurling et al., 2021	no
2	The Role of Heart Rate Variability in the Future of Remote Digital Biomarkers	Owens et al., 2020	no
3	Exploring Network Properties Across Preclinical Stages of Alzheimer's Disease Using a Visual Short-Term Memory and Attention Task with High-Density Electroencephalography: A BrainConnectome Neurophysiological Study	Lazarou et al., 2022	no
4	Wearable Devices for Assessing Function in Alzheimer's Disease: A European Public Involvement Activity About the Features and Preferences of Patients and Caregivers	Stavropoulos et al 2021	No
5	The Use of Remote Monitoring Technologies: A Review of Recent Regulatory Scientific Advices, Qualification Opinions, and Qualification Advices Issued by the European Medicines Agency	Dekker et al., 2021	yes
6	Selecting remote measurement technologies to optimise assessment of function in early Alzheimer's disease: A case study	Owens et al., 2020	No
7	IoT Wearable Sensors and Devices in Elderly Care: A Literature Review	Stavropoulos et al., 2020	No
8	Robust Motor Imagery Classification Using Sparse Representations and Grouping Structures	Oikonomou et al., 2020	No
9	Sensors in Everyday Objects for Dementia Care	Stavropoulos et al., 2019	Yes
10	Ethical challenges of using remote monitoring technologies for clinical research: A case study of the	Muurling et al., 2023	Yes

	role of local research ethics committees in the RADAR-AD study		
11	Digital endpoints in clinical trials of Alzheimer's disease and other neurodegenerative diseases: challenges and opportunities	Brem et al., 2023	Yes
	Deliverables		
	D4.01 device selection	Not applicable	Yes
	D3.09 Briefing package for stakeholders	Not applicable	Yes
	D3.10 First meeting report of the standing regulatory and policy advisory group	Not applicable	yes
	D3.08 Report with assessment of regulatory situation	Not applicable	Yes

Table 1: Overview of publicly available publications and deliverables of RADAR-AD that include references to regulatory topics

From the deliverables, 4 include topics of regulatory relevance. Some of the information described in the deliverables have later on been published in peer-reviewed papers, causing overlap in content in some of the publications and deliverables. Key deliverables on this topic are D3.8) reporting on the assessment of the currently regulatory situation (Pasmooij, 2021) (which was published as a peer review article well, see (Dekker et al., 2021)) D3.9) reporting on the briefing package used in the meeting with the EMA's innovation task force (Stolk, 2020a), D3.10) reporting on the actual ITF meeting (Stolk, 2020b), and D4.1) reporting on the device selection procedure (T. Stavropoulos, 2020). See also table 1.

Analysis of the regulator's viewpoints – Medical Research Ethics Committees

Following the declaration of Helsinki and the Clinical Trial Regulation, medical research is only allowed when the research protocol has been reviewed by an independent committee (Carlson et al., 2004) (European Parliament, 2022). This task is executed by Medical Research Ethics Committees (MRECs). How local MRECs across Europe apply and interpret the clinical trial regulation (and its predecessor, the clinical trial directive) when reviewing applications for studies with RMTs has been underrepresented in the current literature, which is why this was investigated by the RADAR-AD consortium. The MREC feedback and documents on the review process from 10 sites in 9 European countries from the were analysed. Upon analysis, 4 key themes emerged on which the MRECs raised questions. These are data management, participant's wellbeing, methodological issues, and issues pertaining to the regulatory category of RMTs. Review run times and scrutiny differed considerably across sites and countries: process duration varied from 71 to 423 days, some MRECs did not raise any issues, whereas others raised up to 35 concerns, and the approval by a data protection officer was needed in half of the sites.

The differences in the topics of concern raised, the review run times, and level of scrutiny of the same study protocol across MRECs in different countries suggest that a multi-site study would greatly benefit from a harmonization in research ethics governance processes. In addition, the authors suggest that some best practices could be included in ethical reviews across institutional, national and international contexts, such as including an institutional data protection officer in the early stages of trial design, including patient advisory board reviews of the research protocol, stimulating a strategy for ethical reflections within the study, and working on a mutual understanding with the MRECs on when a device is considered a medical device and when not (Muurling et al., 2023)

Device selection and regulatory status

In RADAR-AD deliverable report 4.1, which reports on the device selection procedure for the clinical study, it is noted that one of the selected devices has received class II medical device qualification from the FDA, which makes it the only RMT that is classified as a medical device in the context of AD. Moreover, in the deliverable it is mentioned that the regulatory status (for example, whether the device carries a CE-mark or not) of the respective technologies was not one of the selection criteria in the study (T. Stavropoulos, 2020).

Regulatory perspective - EMA

The publication by Dekker et al., 2021 reports on evaluating qualification opinions (QOs) and advices (QAs) as well as scientific advices (SAs) of the Committee for Medicinal Products for Human Use (CHMP). This study was performed to gain insight in the types of devices that are intended to be used in clinical trials for supporting/submitting application for obtaining marketing authorization (registration trials) and the main recommendations of the CHMP. In the SAs, accelerometers to measure activity and/or sleep parameters were the most frequently used devices, followed by mobile applications and glucose monitoring devices. Usually, these measures were proposed as secondary or exploratory endpoints. The main recommendations of the CHMP were related to relevance of the (novel) outcome measure; validation, precision, accuracy, sensitivity, and specificity; compliance; sampling interval; and data handling and privacy. Despite a trend in increased use over time, the use of RMTs in registration trials is still relatively rare. Insights in the main recommendations of the CHMP may stimulate the use of novel RMTs in a regulatory context (Dekker et al., 2021).

Lessons learned from engaging with the Innovation Task Force

RADAR-AD deliverable report 3.9 describes the information package that was compiled to brief regulators and HTA bodies on the project. It was specifically used for an interaction with the Innovation Task Force of the EMA. The consortium prepared high-level questions for the EMA, pertaining to 1) the collection of data from multiple data sources; 2) stratification of patients based on RMTs and RMT- based endpoints; 3) regulatory acceptance of data coming from consumer-grade (non-medical grade) devices for the measurement of clinical outcomes; 4) acceptability of aggregated data coming from consumer grade (non-medical grade) devices 5) regulatory requirements for open-source based platforms for data collection (Stolk, 2020a). The ITF meeting is reported on in D3.10 (Stolk, 2020b). It contains valuable insights into regulatory considerations when developing RMTs and RMT-based endpoints, which is why we have summarised the feedback in a detailed way in the table below (table 2).

Table 2: Summary of ITF feedback on the RADAR-AD project

Topic	*Advice*
Collecting data from multiple sources	- Focus on one aspect with the most promising evidence - Noting that the validation of novel endpoints and biomarkers is a resource- and time intensive task - Convincing evidence from prospective studies in the context of use (CoU) is needed - For the introduction of a new endpoint, validation should be in comparison to the

	existing accepted (gold) standard, and claims should be specific and unambiguous - Further guidance could be provided by the EMA using the qualification advice process
Stratification of patients based on RMTs and RMT- based endpoints	- Currently, patient reported outcome (PRO) data is not sufficient for MAA in the CNS domain except for headache - PRO can only complement objective, primary outcomes. The PRO as secondary outcome should be validated in studies, where it is important to assure sufficient adherence and address missing data and the timing of data collection
Regulatory acceptance of data coming from consumer-grade (non-medical grade) devices for the measurement of clinical outcomes	- Regulators would like to have assurance of the quality of the data generated. Algorithms using data of non-validated devices will be challenged. The use of devices CE-marked for medical use is hence recommended.
Acceptability of aggregated data coming from consumer grade (non-medical grade) devices	- In the meantime, a guideline on computerised systems and electronic data in clinical trials has been published, which touches on topics related to data and devices (European Medicines Agency, 2023) - Main issues are the traceability to the individual person, and the quality and integrity of data. Within the International Conference on Harmonization (ICH) a revision of the E6 guideline (Good Clinical Practice) is addressing the issue of utilisation and verification of other sources of data.
Regulatory requirements for open-source based platforms for data collection	- An open-source platform is likely acceptable as long as the system complies with a number of aspects that could be reviewed by the EMA Scientific Advice Working Party, including the principles of Good Clinical Practice. Attention should be paid to the requirements of the General Data Protection Regulation (GDPR). - Within the European Commission, initiatives are considered for setting standards with the aim of ultimately seeking international harmonisation, for example via the ICH.

The concluding notes of the ITF meeting mention that the work done by the consortium is very much appreciated, as innovation is needed in this area. Regulators, however, need to take a cautionary

approach in accepting new innovations and endpoints. These need to be secure and reliable to measure and scientifically thoroughly validated (Stolk, 2020b).

Discussion and conclusion

The evaluation of the deliverables and publications of the RADAR-AD project provide important insights in topics of relevance to innovators, regulators and consortia investigating the opportunities and hurdles of RMTs. Many findings are also useful for other disease areas, and can hence be considered for the use of RMTs in the development of medicinal products against future pandemic causing pathogens.

The evaluation of MREC feedback on the research protocol showed that there are similarities in points of concern raised, but also differences between MRECs. In addition, run times and the level of scrutiny has been considerably different across MRECs. Multi-site/multi-country studies executed in the EU would greatly benefit from a harmonization in research ethics governance processes. The change from Clinical Trial Directive to Clinical Trial Regulation was partly fuelled by the widely recognised problems arising from the lack of harmonisation under the Clinical Trial Directive (Petrini, 2014). However, as it only entered its application by 31st January 2022, it remains to be determined to what extend harmonisation and a swifter review of multi-centre clinical trials working with RMTs will be achieved under the new legislative framework of the Clinical Trial Regulation.

Best practices that can help innovators, manufacturers and investigators in this type of study to establish a sound research protocol and achieve smooth review include engaging an institutional data protection officer in the early stages of trial design, including patient advisory board reviews of the research protocol, stimulating a strategy for ethical reflections within the study, and working on a mutual understanding with the MRECs on when a device is considered a medical device and when not (Muurling et al., 2023). These best practices can be implemented in studies focussing on drug development against novel pathogens as well.

On the topic of devices, our review showed that the regulatory status of a device (whether it was CE marked or not) was not a consideration in the selection of devices by the consortium. The relevance of the regulatory status of a device depends on the stage of research. In earlier phases of research and when going for advice to the EMA, devices are not yet required to carry a CE mark. However, if one plans to apply for a market authorisation application for a therapeutical product and information gathered via apps or devices is used to support the application, the relevant regulatory and legal requirements (such as using a sufficiently validated device) will have to be met (*Questions and Answers: Qualification of Digital Technology-Based Methodologies to Support Approval of Medicinal Products*, 2020). Having a CE marked device is a reassurance that the device has been evaluated and complies with general safety and performance requirements as laid out in the MDR, which is important information for regulators. On the other hand, the MDR puts the bar high for medical device software to pass regulatory scrutiny (Gelis et al., 2023). The evaluation of devices or software tools and CE marking them as a medical device falls within the remit of the notified bodies, and not the EMA. We hence advise innovators, manufacturers and investigators to think about the regulatory status of devices (CE marked or not, and whether the data collected can comply with the requirements set out by regulators) early on, so that an informed decision can be taken when a research protocol is developed and devices are selected.

The publication by Dekker et al., 2021 provides an important overview of the advice and opinions of the CHMP on RMTs. In addition, innovators and consortia can consult this publication early on to educate themselves, and to understand which factors are deemed important by the EMA. The 2021

analysis shows that accelerometers to measure activity and/or sleep were the most frequently used devices, followed by mobile applications and glucose monitoring devices. Hence, when investigating these parameters, there is already a body of knowledge one could build on. However, one should keep in mind that such a technology will have to be validated for its specific context of use (European Medicines Agency, 2020). For example, as accelerometers have been frequently mentioned in scientific advice, it could be explored whether these could also play a role in drug trials for treatments against future pandemics. Vice versa, given the importance of oxygen saturation as an indicator of deterioration in COVID-19 patients (Alboksmaty et al., 2022; Shah et al., 2020) it could be worthwhile to investigate these in the context of future pandemics causing respiratory complications.

The ITF meeting report of the consortium also provides valuable feedback on different regulatory topics, indicating the value of meeting with the ITF when developing RMTs in the context of drug registration trials. Topics of attention mentioned during the RADAR-AD ITF meeting have also been addressed in a publication on insights coming from the qualification of the SV95C in Duchenne muscular dystrophy (Servais et al., 2022). The first wearable-derived digital clinical outcome assessment qualified by the EMA was the qualification for the use of stride velocity 95th centile (SV95C) measured by a suitable device for use as a secondary endpoint in trials for Duchenne muscular dystrophy (European Medicines Agency, 2019). Topics of attention include the importance of thorough validation of the data collection devices, issues pertaining to privacy, selecting the most promising evidence, and comparing it to the gold standard (Servais et al., 2022). These points are essential to take into consideration when developing digital biomarkers to support market authorisation applications for medicinal products. Manufacturers, investigators or sponsors working on RMTs in the context of infectious diseases are advised to reflect on these topics early on, and engage with regulators as early as possible. In addition, sufficient resources will have to be made available to support such a qualification process. It was also recommended to address certain topics again at a qualification advice meeting, which is a more formal and in-depth process compared to a meeting with the ITF. Engaging with regulators early on in the development process is imperative to the success of developing novel tools and technologies, which has been mentioned elsewhere as well (Izmailova et al., 2021). Both the ITF and the qualification advice procedure are good pathways to engage with the EMA in the early stages of development (Gelis et al., 2023).

When developing novel endpoints, especially when there is time pressure as during a pandemic, there are different topics to take into consideration. Firstly, it is important to decide whether the endpoint is an exploratory one, or a primary one. For both options, it can be an advantage to select devices and technologies that are already qualified and certified for assessing parameters of relevance to that specific disease, or have a clear strategy ready to certify them as a medical device. Still then, the process of getting a methodology qualified to support regulatory decision making is quite lengthy and not easy (Servais et al., 2022). An alternative is to ask for scientific advice for a development programme in which an RMT is used, and achieve feedback on both the development programme and the use of the RMT simultaneously.

During a pandemic, regulators could consider fast-tracking scientific advice, qualification advice, and applications for devices and medicinal products that are relevant to tackling the pandemic, as was done during the COVID-19 pandemic (*Coronavirus Disease - EMA Webpage*, n.d.). Recently, the Role of EMA in crisis preparedness has been strengthened in 2022 by Regulation (EU) 2022/123 of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness.

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Deliverable 6: Interviews with researchers working on RMTs and DCTs, and interview with members of the Central Committee on Research involving Human Subjects (CCMO)

***Disclaimer**: The information presented in this deliverable are responses gathered during an interview. The aim of the interview was to capture knowledge from different organizations regarding the regulatory field. All answers/opinions shared by the interviewees are of their own and may not reflect the opinions of their organization or those of Lygature.*

Abstract

The Trials@Home consortium aims to provide insights into the possible opportunities and challenges of Decentralized Clinical Trials (DCTs) in Europe. During the project, the consortium has had many interactions with regulators, notably medical research ethics committees and national competent authorities from various countries as well as the EMA. From the interview we found that each EU member state has different local laws governing various aspects of a clinical trial. As of January 2022, the Clinical Trial Directive from 2001 was replace by the Clinical Trials Regulation (CTR) and aims to harmonize the different local laws in the EU member states. To help implement the CTR, the clinical trials information system (CTIS) was launched in January 2022 which aims to make clinical trial applications easier for sponsors in the EU. DCTs carry many benefits but from a regulatory perspective, sponsors need to demonstrate the added value of the remote aspects as well as ensuring that data privacy regulations are followed. The findings of the Trials@Home consortium can be used to develop hybrid and remote trials which enable clinical trials to continue even during a pandemic.

The RADAR-AD consortium investigates the development of new digital endpoints in Alzheimer's disease using RMTs in a multinational clinical trial. Due to the nature of the multinational trial the consortium requested approval from various medical research ethical commissions. Each country interpreted the trial protocol differently and this required adaptations per country. For example, the camera used by patients was not accepted in every country. From the interview, we noted that when designing a multinational clinical trial with devices, an adaptable protocol should be used to accommodate the different national laws governing clinical trials. The study also emphasized the importance of ensuring a data protection officer was consulted for data privacy concerns as well as patient representatives to ensure the patient desires are taken into account. Lastly, the RADAR-AD trial also demonstrated the importance of site engagement and training of the site personnel to adequately assist the trial participants when technological issues arose with the devices.

The Central Committee on Research involving Human Subjects (CCMO) is the Dutch governmental organization that assesses if a clinical trial is law abiding. Furthermore, they are the central medical ethical organization that manages all the medical research ethical commissions throughout the Netherlands. CCMO is usually assessing early phase clinical trials involving gene or cell therapy as well as complex ethical questions such as embryos or involving children. The CCMO has had very little experience assessing trials using RMTs as these are usually incorporated in phase 2 or 3 trials and used to measure exploratory endpoints. When designing trials with RMTs, it is important to consult the EMA's recommendation paper on decentralized trials elements and allow for adaptable trial design. Finally, the introduction of the CTR last year aimed to harmonize national legislation on research involving human

subjects in various EU member states. The central application of clinical trials via CTIS is a first start in this.

Interview with coordinator, Trials@Home

Date: 27 March 2023

General

1. *Can you briefly explain the outline of your project and its key objectives?*

The Trials@Home consortium aims to provide insights into the possible opportunities and challenges of Decentralized Clinical Trials (DCTs) in Europe. Investigating what is accepted by regulators is also part of the project (for example, investigating remote consent). Together with a large consortium, led by UMCU and Sanofi, a pharmaceutical company and a partner in the project, they are conducting a trial on investigating different levels of decentralization with three arms of varying in-person contact: fully remote, hybrid and classical.

2. *From your perspective, where do you see an added value of remote clinical trials?*

Decentralized clinical trials can be especially useful in targeting patients that are hard to find, such as for example, orphan disease patients. The use of the fully remote trial may also enhance the retention and adherence, as the technology enables a more seamless integration in the patient's life without the need for frequent clinic visits. The interviewee also acknowledged that fully remote clinical trials are not always the best option depending on the specific requirements of the trial and patient. Hybrid trials, on the other hand, will probably be the dominant future form.

Opportunities and regulatory hurdles for RMTs in clinical trials

1. *Which interactions have you had with regulators (EMA, CCMO, notified bodies), and how did that impact the design of your study? If you were to design the study again, which modifications would you make, based on your lessons learned?*

The Trials@Home consortium had many discussions with regulators. Firstly, they had a mock ethics review to better understand the MREC's points of concern. Secondly, they had discussions with the EMA's innovative task force where they discussed various aspects of the trial, such as e-consent, safety monitoring, data privacy & quality, as well direct-to-patient shipment. Interestingly, direct-to-patient shipment of medicine was not always accepted by all countries. Additionally, the BfArM, the Federal Institute for Drugs and Medical Devices in Germany, extended scientific advice to the Trials@Home consortium and had concerns about physical examinations (e.g. could these be trustworthy enough) during the fully remote arm of the trial. Lastly, regulators also had concerns about data quality and how to ensure that adverse events were being recorded by the patient.

The interviewee reported that the RADIAL trial was designed during the COVID-19 pandemic. This pandemic catalyzed the adoption of more flexible trial design elements, such as direct-to-patient shipments and the use of remote monitoring tools.

2. *As of 31st January 2022 the Clinical Trials Directive has been replaced by the Clinical Trials Regulation, with the aim to harmonize the submission, assessment and supervision processes for clinical trials in the European Union (EU). To what extent do you feel that this would benefit DCTs?*

The main advantage is that the trial does not need to be approved in every EU country. A single point of application makes the process simpler.

However, the Trials@Home study still experienced some setbacks during the submission of the study under the CTR in March 2022. Namely, the German local committees interpreted the law differently than the German BfArM. Specifically, the direct-to-patient shipment element was rejected. Furthermore, not all countries have adopted the CTR in their respective national laws yet, which might change over the next couple of months. As the approval has shifted from a national level to a centralized EU level, the ability to contact the regulators directly through CTIS has been difficult. Lastly, the new regulatory framework needs to work for all items, and needs to be interpreted in a consistent way. However, the "human factor" in decision making is not always transparent or comprehensible, which can lead to inconsistencies.

3. *What changes, from a regulatory perspective, would make setting up and conducting DCTs easier and more efficient?*

In general, we are on the right path to changing the regulatory dialogue with countries wanting to harmonize. The EMA has set out a workplan to accelerate Clinical trials in the EU (ACT-EU), with Denmark leading this. Some regulators have little experience working with DCTs so having discussions starts to build trust and understanding. Overtime, with more data becoming available from DCTs, trust is developed.

DCTs' data collection standards are very strict, as is also the case for a conventional trial. However, the interviewee argues that these strict standards can become unrealistic. Interpreting impact of missing data and comparing these between a trial with scheduled visits or a DCT with continuous monitoring is challenging. It would be good to have an open discussion on this topic with the regulators, and take context into consideration.

The interviewee also notes that devices used in DCTs need the EU's medical device CE marking to be used for clinical endpoints. However, the Trials@Home trial is using CE marked devices as a proof of concept of what is possible in remote trials, and less so in developing novel digital clinical endpoints.

4. *Can you elaborate a bit on what it was like to set up a DCT with a multidisciplinary team? Do you have any tips for teams with a similar objective?*

It has been an incredibly complicated yet enjoyable process where most of the learning was done simply by doing it. The team is extremely motivated to make the consortium a success, but the project is large and fragmented. Unfortunately, the trial was delayed, partly due to COVID-19 but also due to other factors such as the legal agreements that needed to be made with the various vendors.

<u>Study design</u>

1. *What are some general points to consider when designing a DCT with RMTs?*

When designing a DCT with RMTs two major points should be considered. First, the study may attract a more diverse patient population which should be taken into account. Secondly, it's crucial to incorporate a patient expert panel in the study design. The panel will be able to think along in the design

of the trial regarding patient preferences, the materials used in the trial and the data that will be collected.

Many pharmaceutical companies use external vendors for their remote monitoring technologies. This has led to concerns with the regulators regarding privacy and accountability for the data, as often different apps or platforms need to work together. Questions arise such as: “Who is accountable?” and “how to you guarantee the data quality?”

2. *To what extent do software updates and/or upgrades impact your study? How do the regulators look at this?*

Regulators want to be informed about the possible risks and mitigation strategies. Furthermore, regulators are also interested seeing the changes in the software over time. Software updates were not as much of a concern as the fragmentation of the data sources of RMTs. Unfortunately, the data from RMTs in DCTs are not originally collected all in one place such as an electronic case report form (eCRF) but are spread over multiple databases. This fragmentation is also something that one should take into account when designing a DCT.

Future State

1. *What regulatory standards updates can you share with us looking towards the future of DCTs in Europe?*

The EMA has published a guidance paper on DCTs, “Recommendation paper on decentralised elements in clinical trials” in December 2022. In general, the regulators are not against DCTs and see lots of potential for their use. DCTs will probably be used less frequently in early stage trials which carry more risk to the participant. It is expected that DCTs will more likely be used in later stage trials to relieve the burden to the participant.

There are two main regulatory standards that need to be considered looking towards the future of DCTs. Firstly, researchers need to be able to clearly explain the added value of the remote aspects. Secondly, a data management plan needs to be available to demonstrate knowledge of the various data streams and privacy concerns.

2. *Which lessons learned from your experience in DCTs could also be used to improve the pandemic preparedness of the Netherlands and/or the European Union?*

In the future, more trials will be hybrid trials, meaning that part of the trial will be done remote. The COVID-19 pandemic showed that decentralized aspects of trials were essential for the continuity of many trials. Unfortunately, many trials without remote aspects were halted to the detriment of the patients. The pandemic catalysed the adoption of remote monitoring tools in clinical trials and should be implemented for pandemic preparedness.

A health technology assessment, a literature study on all the decentralized trials as well as a SWOT analysis will be completed by the Trials@Home consortium. Once these deliverables are completed, more lessons learned can be shared.

Disclaimers and acknowledgements:

This interview reflects the views of the interviewee and neither Trials@Home consortium, IMI nor the EU and EFPIA are liable for any use that may be made of the information contained herein.

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Interview with investigators, RADAR-AD

Date: 10 March 2023

RADAR-AD investigates the development of new digital endpoints in AD using RMTs.

Opportunities and regulatory hurdles for RMTs in clinical trials

1. *Which interactions have you had with regulators (EMA, CCMO, notified bodies), and how did that impact the design of your study? If you were to design the study again, which modifications would you make, based on your lessons learned? Was the regulatory landscape easy to navigate?*

Since the RADAR-AD was a multicenter international trial, the investigators had many interactions with the different regulators. Specifically, they interacted (either direct or indirect) with the local medical research ethics committees (MREC) in different countries. Per country, these committees can be slightly differently organized. They can for example be linked to regions, such as in England, or per university or hospital, such as in the Netherlands. Each country involved had a different approach, and as a result, varying levels of regulatory involvement were experienced.

The interviewees observed a discrepancy between what the patient advisory boards (PAB) and MREC thought was too taxing in the context of RMT usage for the study participants. Patients on PABs are not always representative of the average patient; they are generally more active and involved. Patient representatives also take a seat in the MREC which is how the patient voice is represented. Furthermore, they also were in contact with Central Committee on Research Involving Human Subjects (CCMO) in the Netherlands. For consultations regarding the General Data Protection Regulation (GDPR) data privacy officers would be involved in the assessment of the trial, however, not all countries involved data privacy officers.

If they were to design the study again, the interviewees both agreed that they would simplify the trial with less sites involved. At the beginning of the trial, it wasn't clear what the regulatory expectations were on a country level and how complex it was to get approval. For example, the approval for camera usage in different countries in RADAR-AD was often a point of contention by different MRECs as the GDPR was interpreted differently. Another recommendation for future studies is to select recruitment sites based on their experience with treating Alzheimer's disease (AD) patients as well as their recruitment strategies. Furthermore, it is recommended to consult data privacy officers during the trial design process, hopefully smoothening the approval process. Since the goal of the RADAR-AD was to investigate a mix of off-the-shelf available devices and medical devices in their potential to pick up signals relevant to functional decline in AD, they indicated that the study served well for that purpose. They would not change the trial design itself or the selected devices, even though some devices were not MDR CE marked, if they were to perform the study again.

2. *What were the regulatory hurdles you faced during your research on digital endpoints and RMT? And how did you address them?*

The main regulatory hurdle faced with the RADAR-AD study was receiving approval in all the different countries involved. This required the trial protocol to be adapted to local regulations.

3. *As of 31st January 2022, the Clinical Trials Directive has been replaced by the Clinical Trials Regulation, with the aim to harmonize the submission, assessment and supervision processes for*

clinical trials in the European Union (EU). What opportunities do you foresee in the validation and development of new digital endpoints? And what problems?

This transition is indeed a good development. However, the CTR mainly applies to interventional rather than observational trials. Given what the interviewees experienced during RADAR-AD, some cultural differences need to be taken into account, even though the regulation will be rolled out in an EU wide way. Often slight local adaptations needed to be done. For example, ensuring that the apps for testing were available in the local languages. More importantly, each country has their own approach to defining diseases. In the Netherlands, AD is considered a neurobiological disease where doctors use endpoints together with clinical symptoms to diagnose the disease. Whereas in the UK, AD is considered psychiatric disease where mainly behavior and clinical symptoms are used in the diagnosis. As a result, special attention needs to be paid when defining disease stages in different countries.

4. *What changes -from a regulatory perspective- would make the development and validation of digital endpoints in multi-center trials easier?*

In the future, it would be good to have a clear harmonization between the local MRECs whereby definitions are aligned, and cultural differences are considered. It would also be beneficial for researchers to know which sites are good to work with. For example, in the south of Europe fewer older participants had smartphones, which required extra site involvement.

5. *Frequently mentioned regulatory concerns in clinical trials using RMTs are data quality, data completeness, correct user adoption, timely central-monitoring, processing and analysis of real-time data. How did you ensure that these concerns were mitigated?*

One of the key mitigation actions is to ensure that recruitment sites know what they need to do, i.e., clear standard operating procedures. This was achieved using manuals and videos to instruct the sites. Next, when patients came to the sites, the necessary apps were installed on their devices, were taught how to use them and were closely remotely monitored. Where possible, devices were chosen that could automatically upload data to the cloud, so that participants would be contacted by the local site coordinator when there were more than 2 consecutive days with missing or bad quality data. Moreover, the participant's partners were requested to help where possible, performing the daily tasks together which helped with adherence. Lastly, ensuring an interim analysis of the data was started as early as possible as well as rolling data review ensured data quality.

<u>Clinical validation</u>

6. *How did you select the remote monitoring technologies used in your study?*

When selecting the RMTs used in the study, the biological and symptomatic components of AD were considered. First, functional domains that are relevant to measure in AD were mapped based on clinical symptoms and patient reported information. Then, RMTs were selected that could measure the functional domains accordingly. Lastly, practical considerations were made, such as, data availability, battery life, data sharing, price, looks or functionality. A more patient-centric focus was taken in the selection of the clinical endpoints as quality of life was valued more than the individual digital endpoints. One important challenge was the lack of clear expectations of how "good" the new digital endpoint had to be. It was difficult to match the digital endpoint with the clinical gold standard.

7. *To what extent did software updates and/or upgrades impact your study? What does that mean for your validation of your digital endpoint?*

Software updates negatively impacted the study. Ideally, you want to collect data the same way for all the research participants. However, with a software update the layout or instructions changed or even the algorithm used to analyze the raw data. This led to new manuals and trainings that had to be created for the apps that were used. In some cases, languages were not included in the automatic update leading to sites dropping the RMT. Understandably, device manufacturers have a technical approach to refining their product with updates. This unfortunately clashed with the needs of the study, namely consistent measuring. In the future, the interviewees would like to discuss with producers of devices to not have automatic updates. Ultimately, it is unclear what the software updates mean for the validity of the digital endpoints and will be considered as a limitation of the study.

8. *Were the regulator's expectations of clinical relevance of the novel digital endpoint clear to you before you started the trial? Did you know when "good enough" was "good enough"?*

Unfortunately, it was not clear when "good enough" was "good enough". The regulators are building up knowledge of what the patient needs and acknowledge that the RADAR-AD study is a step in the right direction. From the MREC's perspective there were no comments regarding the clinical relevance of the novel digital endpoints. This was most likely the case as RADAR-AD is an IMI funded project such that a scientific committee had already approved the clinical relevance. The European Medical Agency was pragmatically positive about the study, noting that it was an important exploratory trial with a lot of potential.

9. *Which lessons learned in your study could also be used to improve the pandemic preparedness of the Netherlands and/or the European Union?*

RMTs could be used to measure symptoms, behavior, cognition or even act as reminders for participants to take their medication from afar. Moreover, RMTs could act as a surrogate for in-person measured endpoints. Another advantage, such as telemedicine, enables contact with research participants without requiring them to physically visit the clinic. RADAR-AD has successfully demonstrated that the trial was able to start during the COVID-19 pandemic as well as ensuring proper contact with patients, clinical trial sites and overall study continuation.

10. *Some devices used have CE marking, however, only one device is certified as medical device. How did the regulators respond to the proposal for novel digital endpoints using these devices in RADAR-AD?*

To measure an endpoint and have it accepted by the EMA, the devices will have to comply with relevant regulations, often meaning that they should be CE marked medical devices. Although it is understandable that this is the current standard of the EMA, a bit more leniency could eventually also bring value to participants. Relevant data regarding a disease can be generated even if the device is not CE marked as a medical device but shall be considered an exploratory endpoint.

11. *How do you envision the results of this study will impact the lives of AD patients?*

There has been a massive increase in technical developments in healthcare which could reduce the burden of healthcare practitioners. The use of apps and devices to monitor AD patients can be very

beneficial. It gives patients more insights regarding their condition, allows them to be monitored remotely and can be assisted by doctors faster via telemedicine.

Data Privacy and Security

12. *What regulatory standards regarding privacy and security concerning the data of the end user did you struggle with in RADAR-AD clinical trial?*

In the Netherlands, the wet medisch-wetenschappelijk onderzoek met mensen and GDPR standards for data privacy and security are very clear so this wasn't a real concern. Important is to separate the patients' data from the identification of the patient. In addition, it was important to have clear agreements between different stakeholders involved. The only real concern was the camera used by patients. This was an issue as the camera was taking images of people's surroundings, and hence these pictures could also include pictures of people that did not consent to having their picture taken. This problem was mitigated by making the camera optional and using software to blur the faces of the photographed individuals.

13. *From a regulatory concern, how did you handle different types of data coming from various devices used in RADAR-AD?*

The data had to be pseudonymized ensuring that the data could not be traced back to a specific patient. For example, the GPS sensor in one of the devices was recalibrated to be set at the north pole. Before the study, devices were clearly mapped to functional domains of AD. This led to less queries from the regulators and made the analysis more specific to AD.

Disclaimer

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Interview with CCMO

Date: 14 April 2023

Background:

One interviewee has worked with MREC in Utrecht in the past, and now she started as a pre-clinical studies assessor at the CCMO and helped to write the EMA's recommendation paper on Decentralized Clinical Trials published December 2022.
The other interviewee assesses various MDR/IVDR dossiers that come to CCMO.

General

1. *Can you explain what your work entails and the key responsibilities of the CCMO?*

Following the Dutch law on medical research involving human subjects act (*Wet medisch-wetenschappelijk onderzoek met mensen;* WMO) the CCMO assesses whether a clinical study is law abiding. Moreover, the CCMO assesses whether the pre-clinical studies give enough ground to safely start a given clinical trial. The Central Review of Medical Research Involving Human Subjects Decree (*Besluit centrale beoordeling medisch-wetenschappelijk onderzoek met mensen*; BCB) stipulates which types of research have to be reviewed by the CCMO: clinical trials that cover complex questions, such as working with genetic modifications, embryos, children (non-therapeutic intervention) or other complex ethical topics. In the Netherlands there are also 14 accredited MRECs, spread out through the Netherlands. These are involved in the evaluation of all the other clinical trials.

The CCMO is involved in creating policies, supervision of MRECs and gives guidance on certain topics. Furthermore, the CCMO also acts as a liaison between the European competent authorities (involved in assessing clinical trials) and the Dutch MRECs. CCMO is involved in implementing the European regulations (CTR/MDR/IVDR) and supporting the MRECs with any questions they might have.
With the introduction of the CTR, the online platform Clinical Trials Information System (CTIS) is used to validate and assess clinical trials which will be performed in the EU. If the Netherlands is chosen to be the lead country of the assessment of the clinical trial, the CCMO is responsible for the evaluation of the protocol.

Opportunities and regulatory hurdles for RMTs in clinical trials

2. *As of 31st January 2022 the Clinical Trials Directive has been replaced by the Clinical Trials Regulation, with the aim to harmonize the submission, assessment and supervision processes for clinical trials in the European Union. Can you describe how the CCMO has implemented the Regulation? Are investigators aware of the implications of this change?*

The introduction of the CTR has enhanced communication between the CCMO and the MRECs in the Netherlands. One benefit is that the resulting system can speed up the assessment timelines for clinical trials. However, sponsors have to handle incredibly short timelines, a mere twelve days to answer questions that the MRECs might have. Large pharmaceutical companies that set up multinational clinical trials profit from the CTR, but smaller academic studies with fewer resources are hindered by the tight timelines. Additionally, the online system is not very stable and frequently experiences technical problems.

The interviewees note that the EU countries have a different approach to how they assess clinical trials. National laws and guidances can be slightly different, and the interpretation by national committees of

certain topics can differ. For international studies, consensus on these topics has to be reached. The harmonization in legislation is welcomed. However, this will take some time.

3. *To what extent do you feel that the adoption of CTR would benefit trials using RMTs?*

Local laws and ethical concerns differ per country at the moment. That means for now that studies that use RMTs should have adaptable protocols to allow for differences in local laws and ethical concerns. It is advised that study designers use the EMA's recommendation paper published in December 2022 for guidance on decentralized clinical trial elements (https://health.ec.europa.eu/system/files/2023-03/mp_decentralised-elements_clinical-trials_rec_en.pdf).

4. *Do you have a view on the most frequent issues that surround applications of studies involving RMTs? If so, what are the most frequent issues (ethical, legal, privacy, feasibility) you see at CCMO regarding these applications?*

The CCMO has not yet evaluated many studies using RMTs. Most frequently evaluated studies by CCMO are phase 1 and 2 studies which usually do not include RMTs in the study design. Phase 1 and 2 studies generally assess the safety of an intervention. RMTs are usually included in a trial during later phases, such as 3 or 4, to lower patient burden. MRECs assess more phase 3 or 4 studies that fit the use of RMT, and would thus be a more suitable candidate to answer this question.

5. *From our research (evaluation of studies registered in clinicaltrials.gov), we see very few phase 4 clinical trials using RMTs. From your point of view, can you think of reasons why RMTs are not widely studied in phase 4 trials?*

Phase 4 studies are typically larger and therefore more complex. Sponsors might feel less inclined to add to the complexity of the trials by introducing RMTs which may also lead to missing or errors in the data.

6. *What lessons would you like to share with us (or investigators/innovators) regarding designing a study that incorporates RMTs?*

The CCMO assesses the feasibility of studies on medical ethical questions. Its mandate does not cover acceptance of endpoints in the context of drug development. Therefore, it is possible that the study design is sound, but the CBG or EMA would not accept the clinical endpoints to allow for a market authorization of a medicinal product. In some cases, sponsors may use a device that is not validated as a medical device (CE marking) in a clinical trial and use the readout for clinically relevant endpoints. However, this endpoint may be rejected by the CBG or EMA as the device is not clinically validated as a CE-marked medical device. CCMO and CBG are different institutions, and sponsors are requested to reach out to the CBG or the EMA for questions related to the validity of clinical endpoints. Lastly, the CCMO assesses whether a clinical endpoint is relevant for the study itself, which is another point of view than the market authorization point of view.

<u>Study design</u>

7. *From your experience, do investigators/innovators have a good understanding of the terms and conditions that their study set-up needs to comply with, especially for studies investigating RMTs?*

The knowledge of investigators regarding RMTs used in clinical studies varies widely. Patient participation is crucial in the study design and should be implemented early on during the design phase. The CCMO also requests patient perspectives in the application process. For Dutch studies (that are not clinical trials involving a medicinal product), the ABR form is used that contains some questions on patient participation.

Future State

8. *Are there any upcoming regulation changes (that you know of) that may impact the way RMTs are assessed?*

The European commission has proposed the European Health Data Space regulation which might make it easier to exchange and share medical data. The regulation may help to share anonymized data which would alleviate some privacy concerns regarding data generated by RMTs.

9. *What are your thoughts on software being used as a medical device?*

The safety and performance of the software when used as a medical device are paramount. The software needs to correctly and accurately convey data especially if it is used in a medical decision. Upcoming software techniques offer exciting possibilities but also come with new types of risks that need to be evaluated. Harmonization and lawmaking will take time.

10. *In your opinion, what future regulatory changes might make it easier to develop new digital endpoints and RMTs?*

The EMA's recommendation paper for decentralized trial elements contains recommendations that could facilitate the safe and effective use of RMTs. This paper contains many starting points that can help to harmonize the national implementation of legislation in different member states within the EU. Currently, countries' local laws still differ considerably. It will take some time to align on laws and regulations. How "open" local regulators are to allow for RMTs is partly driven by the benefit a country can potentially have from implementing decentralized elements. For example, countries that have a low population density (and thus long travel times to specialized hospitals) could benefit in a different way than countries that have a denser population.

11. *To what extent can remote monitoring technology be used to improve the pandemic preparedness of the Netherlands and/or European Union?*

It is probably not feasible to have enough infrastructure ready during the beginning of a pandemic to be able to fully remote monitor patients. A cost-benefit analysis could be done to see if the government should invest in the remote aspect. The COVID-19 pandemic has accelerated the adoption of RMTs and proven that the technology can be successfully incorporated in clinical trials.

Deliverable 8: RMT use in phase 4 studies

Abstract

Clinical trials are vital in the development of new medicines and medical devices. Phase 4 clinical trials can be conducted to collect additional safety and real-world efficacy data after market authorization of a drug. In this literature study we investigated the use of RMTs in phase 4 studies conducted in the European Union (EU). Using the database clinicaltrials.gov we searched for studies between 2013 and 2022 that used RMTs in clinical trials that were classified as a phase 4 clinical trial. Twelve clinical trials met our inclusion criteria. 66% of the studies used an RMT to measure patients' adherence to medication, and 33% of the studies used RMTs to measure a biomarker, such as sleep or blood glucose levels. Of the 12 studies included, six (50%) of the sponsors were either pharmaceutical companies or medical device companies. The other 50% of the sponsors were university hospitals or research institutions. Relating to pandemic preparedness, our search resulted in only one study that met the inclusion criteria relating to infectious diseases. The clinical trial search that we performed did not result in devices that measured parameters (for example oxygen saturation, respiratory rate and temperature) related to infectious diseases. Looking at the total number of phase 4 clinical trials executed in the EU, we found relatively little phase 4 classified studies using RMTs. This could partly be due to a methodological limitation of our study. Another explanation is that regulatory expectations are not always clear, which could lead to sponsor hesitancy in developing novel digital biomarkers. Another observation is that the majority of phase 4 studies using RMTs are executed in the USA. A potential explanation for this is that the regulatory landscape for RMTs in the USA is less scattered compared to the EU. Further research is recommended to better understand the factors influencing sponsors' decisions to use (or not use) RMTs in their clinical trials, particularly in phase 4 studies.

Introduction

Clinical trials are indispensable in demonstrating the benefits and risks of new medicines, medical devices, and nonpharmacological interventions. Once medicines are approved by regulators, sponsors are required to conduct post-market surveillance (phase 4 clinical trials) to ensure safety, record any adverse events, and collect additional data on efficacy (Suvarna, 2010. A similar concept applies to RMTs, with the EU reporting all the adverse events, modifications and possible recalls of the medical device via a central database called EUDAMED (Van Norman, 2016).

During phase 4 clinical trials, additional data can be collected regarding medical therapies and vaccines in the post-marketing phase. RMTs may be used to collect additional data to get additional insights on the safety and efficacy profile of a medicinal product in a real-world environment (Clinical Trials Transformation Directive, 2017).

A thorough review on the global use of "connected digital products" (which follows a definition similar to what we refer to as RMTs) has been performed by Marra and colleagues in 2020, investigating the use of RMTs in clinical trials up to 2018 (Marra et al., 2020). In order to get the latest view on RMTs used in phase 4 trials in the EU, we performed a structured search using the ClinicalTrials.gov website.

We expected that by examining which phase 4 clinical trials are conducted using RMTs (and specifically in Europe), we will gain insight on what kind of trial designs, investigators and sponsors are most interested in, and are approved by medical research ethical committees (MRECs).

Method

In March 2023 we searched the Clinicaltrials.gov electronic databases for phase 4 clinical trials that included RMTs. The search terms were selected based on the author's knowledge regarding wearable devices and search terms from Dekker et al. 2021 (Dekker et al., 2021). The search terms used can be found in **table 1**. Phase 4 clinical trials were included if the start date was between 1 January 2013 and 31st December 2022 and studies that took place within Europe. Protocols showing randomized control trials and observational studies were eligible for inclusion if an electronic device was used in remote monitoring by a clinician. All disease areas were included during the search. As a benchmark, a search was done to identify all phase 4 studies with a study start between 1 January 2013 and 31 December 202, yielding 15.570 results. To benchmark phase 4 studies performed in the EU, the same search was done with a location filter on Europe, yielding 1.515 studies in total. All disease areas were included during the search.

Search terms	Inclusion criteria	Exclusion criteria
“wearable”	Phase 4 study	
“remote monitoring”	Study start between 1 January 2013 and 31 December 2022	
“mobile device”	Location: Europe	Outside of Europe
“smart phone”	Electronic device used in remote monitoring by clinicians	Electronic device used to collect data but without remote monitoring by clinician
“electronic device”		
“sensor”		
“actimeter”		
“actigraphy”		
“actimetry”		
“accelerometer”		
“Global positioning system”		
“software”		

Table 1: Search terms used during the clinical trial search and inclusion/exclusion criteria for data collection.

Results

Search Term	Number of Trials Worldwide	Number of Trials USA	Number of Trials Europe	Number of Trials Eligible
“wearable”	14	9	1	1
“remote monitoring”	3	1	2	2
“mobile device”	11	5	1	1
“smart phone”	26	18	7	3
“electronic device”	15	9	4	0
“sensor”	34	16	10	3
“actimeter”	0	0	0	0
“actigraphy”	6	5	1	1
“actimetry”	0	0	0	0
“accelerometer”	1	0	0	0
“Global positioning system”	0	0	0	0
“software”	34	11	12	1
Total	**144**	**74 (51%)**	**38 (26%)**	**12 (8%)**

Table 2: Phase 4 clinical trial frequency with the respective search term worldwide and in Europe as well as number of eligible trials.

As seen in **table 2**, the 12 search terms used returned 144 phase 4 clinical trials worldwide that were conducted between 2013 and 2022. Of these 144 trials, only 38 (26%) were conducted in Europe and only 12 (8%) were eligible based on the aforementioned inclusion criteria. The studies that were excluded because the data that the electronic device captured was not remotely monitored by clinician. The majority of trials (51%) were conducted in the USA and as a result also excluded.

Table 3 lists a detailed overview of all the phase 4 clinical trials that were included in this study as they met the inclusion criteria. RMTs were used in various disease areas ranging from sleep, cardiovascular disease, mental disorders as well as infectious diseases. The RMTs used in the phase 4

clinical trials can broadly be classified into two categories: measuring medication adherence (8/12) and/or monitoring patients' disease state using (digital) biomarkers (e.g. blood glucose concentration, activity measurements and sleep levels) (4/12).

Two of the clinical trials were terminated prematurely due to low enrolment of patients. The remaining studies were either recruiting at the time of the search or had been completed.

Search Term	Study Name	Year	Country	Device used	Disease area	Outcome measure	Sponsor	Study type	Status	Link
wearable	A Trial to Explore Acceptance and Performance of Using a Digital Medicine System With Healthcare Professionals and Adults With Schizophrenia, Schizoaffective Disorder, or First Episode Psychosis on an Oral Atypical Antipsychotic	2018	UK	Digital medicine systems used to measure medication adherence and potentially enhance adherence wearable sensor patch	Schizophrenia Psychosis	Percentage Of Days With Good Patch Coverage Patient adherence	Pharmaceutical company	Interventional (Phase 4)	Completed	Link
remote monitoring	Assessment of the Prognosis of Persistent Left Bundle Branch Block (LBBB)After Transcatheter Aortic Valve Implantation (TAVI) by an Electrophysiological and Remote Monitoring Risk-adapted Algorithm (LBBB-TAVI)	2015	France	Holter with remote monitoring	Cardiovascular aortic stenosis	To assess the rate and deadline time after Atri ventricular high-grade conductive disorders	University Hospital	Interventional (Phase 4)	Unknown	Link
remote monitoring	COVID-19 Primary Care Platform for Early Treatment and Recovery (COPPER) Study (COPPER)	2021	Netherlands	Device to measure dexamethasone saturation and signs and symptoms	COVID-19	Hospitalization/death Recovery Disease severity	General Practitioners Research Institute	Interventional (Phase 4)	Terminated	Link
electronic device	Assessment of SMS and Smartphone Interventions for OneTouch Reveal® Experiences	2015	UK	OneTouch Reveal® Mobile APP OneTouch Verio® Flex BGMS	Diabetes type 1 & 2	A1c change from baseline	Medical Device Company	Interventional (Phase 4)	Completed	Link
Smartphone	Smartphone App and CO Self-monitoring for Smoking Cessation (SMART-CO)	2017	Switzerland	Smartphone app and carbon monoxide self-monitoring (personal device)	Smoking cessation within HIV patients	Self-reported abstinence biochemically verified by a carbon monoxide test in-person	University Hospital	Interventional (Phase 4)	terminated	Link
Smartphone	A Clinical Study to Evaluate the Effect of the Connected Inhaler System (CIS) on Adherence to Maintenance Therapy in Poorly Controlled Asthmatic Subjects	2018	Pan-Europe	Smart phone app and online dashboard for HCP	Asthma	Percentage of ELLIPTA Doses Taken (Daily Adherence)	Pharmaceutical Company	Interventional (Phase 4)	completed	Link
Smartphone	Adherence in Topical Treatment of Psoriasis	2017	Denmark	App with electronic monitor to improve medical adherence to treatment	psoriasis	Percentage of Adherent Participants	University Hospital	Interventional (Phase 4)	Completed	Link
sensor	Automate Detection of Sleep Apnea by ApneascanTM (AIRLESS)	2014	France	Autoscoring algorithms with automatic detection of sleep apnea by the Apneascan TM	Sleep apnea	Apnea-hypopnea index	University Hospital	Interventional (Phase 4)	Completed	Link
sensor	Effect of Electronic Monitoring and Feedback on Adherence to Easyhaler Controller Medication in Patients With Asthma (eMOFEE)	2021	Germany	sensor attached to Easyhaler inhaler and mobile application	Asthma	Mean weekly adherence to controller medication	Pharmaceutical Company	Interventional (Phase 4)	Recruiting	Link
Sensor	Fiasp® Versus NovoRapid® in Children With Type 1 Diabetes on MiniMed 640G Pump With Sensor	2019	Greece	Insulin pump equipped with sensor	Diabetes type 1	1-hour post-prandial glucose levels	University Hospital	Interventional (Phase 4)	Unknown	Link
actigraphy	Effect of Selexipag on Daily Life Physical Activity of Patients With Pulmonary Arterial Hypertension. (TRACE)	2017	Pan-Europe	actigraphy to measure physical activity and sleep	pulmonary arterial hypertension	activity levels and sleep	Pharmaceutical Company	Interventional (Phase 4)	Completed	Link
software	Post Marketing Study for the Evaluation of Predictix Antidepressant Clinician Software Support Tool in Prescribing Antidepressant Medication/s for the Treatment of Patients Suffering From Major Depressive Disorder	2019	France	Predictix Antidepressant Software tool (RMT)	Depression	success rate of the Predictix tool usability	Medical Device Company	Interventional (Phase 4)	unknown	Link

Table 3: Overview of clinical trials eligible for inclusion.

Results and Discussion

Based on the clinical trial search and inclusion criteria, we found relatively few phase 4 studies (8%) that included RMTs in European clinical trials. This is in line with earlier findings in a paper describing the decentralized trial elements for studies started in 2019 and 2020. The study reported that only 15.3% of the trails used wearables devices, sensors or biomarker kits with only 12% of trials being phase 4 for trials conducted in the USA or the EU (De Jong et al., 2022).

The results in this study also demonstrated that RMTs used in phase 4 studies are generally for chronic diseases such as diabetes, skin diseases and neurological disorders. This is also in line with previous publications, describing that chronic diseases with low risk are better suited for clinical trials with RMTs due to the participants' ability to self-manage their condition(de Jong et al., 2022; van Rijssel et al., 2022). Furthermore, this is also in line with previous findings where the use of RMTs in registration trials was found to be relatively rare, and, where applied, were mainly used in neurological disorders (Dekker et al., 2021) and deliverable 7 of this project. Of the 12 studies included, six (50%) of the sponsors were either pharmaceutical companies or medical device companies. The other 50% of the sponsors were university hospitals or research institutions.

There might be several explanations for the relatively low number of phase 4 clinical trials registered in Europe using RMTs. Firstly, our study set-up cannot exclude the possibility that we missed studies because they are not labelled as phase 4 study in the database. A study similar to our study investigating the use of "connected digital products" ran into a similar issue, noting that many studies in the database are not labelled with the study phase (Marra et al., 2020). This could be resolved by expanding the search to include the "not applicable" phase, which "describes trials without FDA-defined phases, including trials of devices or behavioural interventions". As it requires a considerable effort to go through all the studies that are labelled "not applicable" (for example: the search term "wearable' in combination with the phase "not applicable" yields 1401 results), this was considered out of the scope of this deliverable. Another limitation is that the term phase 4 study may be interpreted differently depending on the geographical location. This could have influenced the geographic distribution of phase 4 labelled studies found in the clinicaltrials.gov database.

Another possible reason for the low number of phase 4 studies using RMTs executed in the EU could be that sponsors of clinical trials struggle with navigating the complex EU's regulatory landscape, which has been mentioned elsewhere in literature. For example, the validity of RMT-based clinical endpoints might be poorly defined, resulting in sponsor hesitancy to invest in using RMTs in clinical trials (Gelis et al., 2023). As a result, sponsors may prefer to use older yet clinically validated endpoints instead of new digital endpoints.

During the clinicaltrials.gov database search we found that 51% of the clinical trials identified were performed in the USA, whereas only 26% were conducted in Europe. This might be explained by the difference in regulatory approval process. In the USA, a single organization (the Food and Drug Administration (FDA)) assesses both medical devices as well as medicinal products. In the EU, this responsibility is more fragmented, and scattered over national and international governmental organizations (national competent authorities and the EMA), and private companies (notified bodies). The USA, with its single point of contact could appeal more to companies to perform studies with innovative technologies (Gelis et al., 2023; Sorenson & Drummond, 2014; Van Norman, 2016).

Relating to pandemic preparedness, this clinical trial search resulted in only one study that met the inclusion criteria relating to infectious diseases. Unfortunately, due to low enrolment numbers this study was terminated.

The clinical trial search that we performed did not result in devices that measured parameters (for example oxygen saturation, respiratory rate and temperature) related to infectious diseases.

Altogether, we can conclude that so far only a small amount of studies labelled as phase 4 studies are making use of RMTs in the EU. A methodological limitation of our study is that a large portion of the studies listed in the clinicaltrial.gov database are not labelled with the study phase. A more extensive study would have to be performed to analyse whether there are studies that apply RMTs in phase 4, but are not labelled as such. Literature provides several potential explanations on why the use of RMTs in phase 4 studies in the EU could be low. However, these explanations would have to be further investigated to validate them and identify “true” hurdles to RMT adoption.

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Deliverable 9: RSNN meeting report - Remote monitoring technologies for regulatory decision making: from technology push to clinical endpoint

Disclaimer: Please note that the information presented in this deliverable consists of responses gathered during a group meeting. The aim of the meeting was to capture knowledge from different organizations regarding the regulatory field. All answers/opinions shared by the meeting participants are of their own and may not reflect the opinions of their organization or that of Lygature.

ZonMw has implemented the program Regulatory Pandemic Preparedness with the goal to evaluate and strengthen the pandemic preparedness of the current regulatory framework in the Netherlands. This program focusses on specific domains in need of regulatory innovation, including the use of remote monitoring technologies (RMTs). Foundation Lygature, the Medicines Evaluation Board (MEB), and RSNN have been granted the opportunity to investigate the regulatory hurdles that impair implementation of RMTs and identify potential solutions to overcome those hurdles. As an integrated part of this assignment, the RSNN organised an expert meeting on the 16th of October 2023, to discuss the topic "Remote Monitoring Technologies for Regulatory Decision Making: From technology push to clinical endpoint." Various national experts from academia, industry and governmental bodies were invited to share their current knowledge and personal views under the Chatham House Rules. The experts were invited to the meeting with the invitation attached in annex 1, and briefed ahead of the meeting on the topics that were discussed during the expert meeting. This report provides a summary of the discussion.

1. **Setting the stage: The Potential of Remote Monitoring Technologies is being underutilized.**

RMTs have the potential to change health care by providing objective, continuous measures of relevant parameters while patients are at home or during their daily activities. RMTs utilization possesses various benefits, including faster data collection and analysis, a reduced research participant burden, and less in-person contact moments. The exploratory adoption of RMTs in both clinical care and biomedical research is increasing (Baldwin Medsker & Skwira-Brown, 2022; Gelis et al., 2023), but RMTs are not widely implemented in drug development programs or regulatory decision making yet (Dekker et al., 2021). Regulatory frameworks and activities are intended to safeguard that RMTs are valid, safe, and effective. European and worldwide policies on innovation friendly legal and regulatory frameworks may thereby directly influence the development and implementations of RMTs (Chronaki & Vardas, n.d.; Diaz-Skeete et al., 2020).

RMT can add great value in various ways, for example by providing crucial information to improving patient's care as well as by producing unique data to prove the efficacy of a specific medicine. The various contexts in which RMTs can be used also determine their regulatory opportunities and challenges. Hence, in this report, we distinguish between the use of RMTs for clinical decision-making versus regulatory decision making. We refer to RMT utilization for clinical decision-making when decisions made by a clinical expert regarding the treatment of a patient are (partly) based on data acquired via an RMT. RMT utilization for regulatory decision making refers to the assessment of a medicinal product to obtain a marketing authorisation based on data collected via an RMT.

In the ZonMw Regulatory Pandemic Preparedness project, we have investigated the regulatory players and the existing hurdles that prevent rapid implementation of RMTs necessary for an adequate pandemic response. Some hurdles that prevent their wide and/or rapid implementation relate to regulatory topics. During this expert meeting, we focused solely on RMT utilization for regulatory decision making, while the report describing the findings, conclusions, and recommendation of the overall ZonMw Pandemic Preparedness project also described the possibilities and hurdles underlying RMT utilization for clinical decision-making.

The hurdles limiting RMT utilization for regulatory decision-making have been identified via expert interviews and literature studies. The organizing committee identified four overarching categories of

hurdles which are 1) lack of precedence, limited regulatory guidance and absence of standards, 2) lack of appropriate resources to handle regulatory burden, 3) the difficulty/impossibility to validate an RMT for a future unknown pathogen and 4) complexity of RMT usage in decentralized trials. The solutions corresponding to each hurdle have been suggested by the organising committee which was involved in the RMT Regulatory Pandemic Preparedness program. **Table 1** summarizes the identified hurdles and their proposed solutions. The goal of this expert meeting was to have a multidisciplinary expert discussion on the identified regulatory hurdles and suggested solutions for RMT utilization for regulatory decision making in a non-pandemic and pandemic situation.

***Table 1**: Summary of the discussed hurdles and corresponding associated solutions regarding RMT utilization for regulatory decision-making organised in four categories.*

Hurdle	Solution
1 Lack of precedence, limited and fragmented regulatory guidance, and absence of standards and established approaches to validation and implementation	
1.1 Changed legislation: From MDD to MDR and IVDR, and from CTD to CTR	Evaluate impact of changes in a structured way; pre-empt potential hurdles
1.2 Fragmentated feedback and assessment of each step of the development process; high costs, resource (knowledge and funding) heavy process	"one-stop-shop" for integrated feedback and advice, potentially building on already available knowledge and infrastructures
1.3 Lack of knowledge of innovators on regulatory routes and regulations	Take the topic of regulatory affairs up in the curriculum of relevant studies; Netherlands well-positioned to become a knowledge hub; Engage consultants;
2 Lack of appropriate resources (knowledge and funding) to manage product validation and handle regulatory burden	
2.1 Lack of appropriate resources (knowledge and funding) to manage product validation and handle regulatory burden.	Increase interaction between regulators and innovators to explore and validate RMTs and develop digital endpoints in a precompetitive space, for example via projects funded by the Innovative Medicines Initiative
2.2 Assessment of software and devices under the MDR and IVDR takes a long time due to shortages at the notified bodies. Requirements are not always clear and processes to ask for feedback are not present at the NBs	Exemptions could be applied during a pandemic. Invest in education and training of assessors at NBs. Set up a system for feedback on devices, similar to QA and SA at the European Medical Agency (EMA)
3 Not knowing the next pandemic pathogen complicates the process of validating devices in the correct context of use and in a timely manner	
3.1 Lack of time and information to assess the safety and validity of a RMT in the pandemic context	Pandemic-specific exemptions: - Allow for the use of validated RMTs to be used outside of their context of use (different disease context) - Allow for the use of validated RMTs to be used outside of their context of use (from hospital- to home-setting) - Fast-tracking of RMT review - Align upfront (before a pandemic) on regional, national and international mandates, tasks and responsibilities
4. Increased use of decentralised clinical trial elements facilitated by RMTs is highly complex.	
4.1 Complexity of switching from traditional to decentralised clinical trial	Prepare protocols, lines of responsibility, guidelines, etc. upfront; discuss regulatory acceptability of collected data

2. Identified hurdles and proposed solutions underlying RMT utilization for regulatory decision making

The following chapters describe in more detail the hurdles that limit widespread RMT utilization for regulatory decision making in general and consequently even more during a (pre)pandemic phase, identified during the ZonMw program through expert interviews and literature studies. For each identified hurdle, potential solutions have been proposed and discussed to explore their potential, validity, feasibility, and application from multistakeholder perspective during the expert meeting.

Hurdle 1: Lack of precedence, limited and fragmented regulatory guidance, and absence of standards and established approaches for validation and implementation.

Hurdle 1.1. Changed legislation: From MDD to MDR/ and IVDR, from CTD to CTR

Expert discussion summary:

In 2017 the European Commission announced that the Medical Device Directive (MDD) and In-vitro Diagnostic Directive (IVDD) would transition into the Medical Device Regulation (MDR) and In Vitro Diagnostic Regulation (IVDR). The new regulation is more stringent and requires innovators to present more evidence of safety and efficacy to receive the CE-marking. Assessment of the intended purpose of the device by the notified bodies is the first step in the regulatory process. RMT that have been positively assessed by the notified bodies receive CE-marking which allows it to be used commercially in the EU. When aiming to utilize certified RMTs in a clinical trial, the European Medicines Agency (EMA) has the responsibility to assess if the quality of the data collected by the RMT is sufficient for the scientific evaluation for centralised marketing authorisation applications. This changed legislation (from MDD and IVDD to MDR and IVDR has had significant consequences for the involved regulatory authorities. As a consequence of this transition, the notified bodies are currently dealing with a limited capacity to perform the assessments, having led to an extensive backlog of filed assessments, and a long waiting list for new assessments. The regulators noted that recent regulatory adaptations (such as extending the transition period) have helped to handle the resource problem of the notified bodies and diminishing the existing waiting lists. However, the present SMEs indicated that they have yet to experience a swifter response in the assessment procedure.

During this transition, devices under the IVDR that are placed on the market or put into service after 26 May 2022 (i.e., the IVDR's date of application) are considered 'legacy devices' until the end of the respective transition period. These legacy devices cannot be subject to further developments or adaptations until these are compliant with the new legislation. The implemented increased duration of the transition period to MDR and IVDR forms a welcomed possibility for the notified bodies to handle the large backlog of assessments. From industry- and SME-perspective, this is a preferable adaptation but results in a halt on innovation of legacy devices until the MDR certificate has been granted. To further complicate RMT utilization, the COVID-19 pandemic struck while we were in the midst of the transition from MDD and IVDD to MDR and IVDR, respectively. Since then, the implementation of the MDR and IVDR has progressed and improved understanding of the requirements of the adapting regulatory framework exists. It is therefore expected that, by the time the next pandemic emerges, the implementation of the changed legislation will be finalised and improved understanding of the established regulatory framework will allow for improved RMT utilization.

Similarly, a transition has been initiated from the Clinical Trials Directive (CTD) to the Clinical Trials Regulation (CTR). This regulatory transition will, amongst others, task the Central Committee on Research Involving Human Subjects (CCMO) with the responsibility to assess clinical studies on certain medical devices (depending on their risk class). It was proposed by the experts present that it would be beneficial for RMT utilization if a regulatory authority with a central role, like CCMO, would provide scientific guidance and advice on request. One of the experts expressed their concerns that interpretation of clinical trial applications with RMTs varies between member states, which complicates international clinical trial execution. The questions arises if it would be possible to further harmonize RMT utilization in clinical trials on an international level, for example by appointing a dedicated, multinational task force.

As a potential solution for the lack of precedence, limited and fragmented regulatory guidance, absence of standards and established approaches for validation and implementation is to systematically evaluate the impact of the changed legislation and potential future hurdles. The current regulatory transition from MDD and IVDD to MDR and IVDR is almost finalised. Further

research towards the existing knowledge gap is required. In the Netherlands, CCMO monitors the hurdles in the CTD to CTR transition process on a national level. On a European level, the European Commission has established the COMBINE project to study the interface between IVDR, MDR and CTR, which will initiate its activities this period. The EMA's medical device coordination group and the clinical trials expert group have published guidance documents on combined trials (simultaneous investigation of a medicinal product (clinical trial authorised under the CTR) and an IVD (clinical performance study)) to help investigators (*MDCG 2022-10 Q&A on the Interface between Regulation (EU) 536/2014 on Clinical Trials for Medicinal Products for Human Use (CTR) and Regulation (EU) 2017/746 on in Vitro Diagnostic Medical Devices (IVDR)*, 2022).

Hurdle 1.2. Fragmentated feedback/assessment to each step of development process; high costs, resource (knowledge and funding) heavy process

Expert discussion summary:

The assessment process of MDs and IVDs is verified by notified bodies which review the technical documentation from the manufacturer on the safety and performance of devices, depending on their classification. However, the notified bodies do not give feedback and advice on the product assessed. Furthermore, the assessment process is a resource intensive process. From industry perspective, it would be beneficial to establish a centralised body in the position to provide advice on RMTs and on valid, safe, and swift RMT implementation in clinical trials. Real-life examples of partnerships between academic and industry partners indicate that the search for expert advice on adaptation of specific elements of a clinical study towards a decentralised approach exceeds a year. Establishment of a 'one-stop-shop' for integrated feedback, advice, and practical implementation, building on already available knowledge and infrastructures, on a European level, would help to overcome the fragmented landscape especially during a (pre) pandemic phase. Currently, integration of the patient's perspective in RMT implementation or development is limited. Including patient engagement as a regulatory requirement could improve acceptability of the patient.

The EMA currently interacts with the various notified bodies regarding the assessment procedures. The EMA has established and coordinates on a European level, 12 disease domains-specific panels and 2 screening panels. Pilots have been initiated in which these panels of medical experts are being consulted for clinical evaluation of high-risk devices (*EMA Pilots Scientific Advice for Certain High-Risk Medical Devices | European Medicines Agency*, n.d.). Similarly, a focus group has been established with involvement of the notified bodies, European Commission, and the EMA as 'one-stop shop'-pilot to provide scientific advice on drug and medicine combinations. This pilot has been terminated for unknown reasons. Publishing the lessons learned from this pilot may aid similar future initiatives.

As an example outside of the European context, the Digital Medicine Society (DiMe) initiative helps to navigate digital health regulations to optimize product development, strategy, and decision-making in the US. They do so by providing guidance to navigate and identify regulatory pathways, assist in the creation and integration of a fit-for-purpose regulatory strategy, and provide insight into the possibilities to interact with regulatory authorities. The proposed one-stop-shop would form a centralised initiative aware of previous efforts and as well as current and future developments in the field. Importantly, this initiative may play a fundamental role in providing the required information to respond to future pandemics swiftly and adequately through RMT utilization.

Hurdle 1.3. Lack of knowledge of innovators on regulatory routes and regulations

Expert discussion summary:

Currently, innovators affiliated to academia and SMEs lack both the necessary basic regulatory knowledge and the expert knowledge on the existing regulatory routes and associated requirements to bring RMTs from concept to validation for regulatory decision making. Increasing basic knowledge concerning the regulatory framework through education in university curriculum will help to increase the general level of regulatory knowledge. Especially in the 'cold phase' – the situation in which the

immediate threat of a pandemic is absent- it is important to make optimal use of this situation to increase the understanding of the regulatory landscape to prepare for RMT utilization during a pandemic. In a pandemic situation the possibilities to not only explore routes, requirements and implementation but also exemptions and tools for a healthcare/public crisis are limited given the time pressure and the burden on the regulatory framework. For example, increasing insight into the RMTs that are validated to monitor specific vital signs that are likely to play a role in future pandemics, like fever, oxygen saturation, and heart rate, will help to respond swiftly to a future urgent pandemic threat. Numerous actions are being taken in collaborations between universities and regulators in the Netherlands to increase the regulatory knowledge and awareness in various educational curricula. In general, these educational initiatives are challenged by a limited sustainability and intense efforts to keep the content up to date with the latest regulatory and technological developments. The solution is suggested to establish a centralised point for access to past and current educational materials on the regulatory framework and specifically regarding RMTs. Also here, the risk exists that published materials will become outdated on a short notice. Appointing an initiative or organisation (for example Innovative Medicine Initiative/Innovative Health Initiative) responsible for the management of all education resources, including identification, and compiling of the available materials, providing transparency on their publication date, and widespread communication, may help to centralize efforts federated in a fragmented landscape. It is important to also educate the persons involved in the utilization of the RMTs in the clinics, such as the clinicians and the legal and privacy departments of the hospitals. With the current location of the EMA in Amsterdam, the Netherlands are well-positioned to become a regulatory knowledge hub.

Hurdle 2: Lack of appropriate resources (knowledge and funding) to manage product validation and handle regulatory burden.

Hurdle 2.1. Lack of knowledge of innovators on regulatory routes and regulations, and the interpretation of these

Expert discussion input:

In addition to the lack of regulatory knowledge in academia and SMEs, expert knowledge on the details of the regulatory possibilities and requirements and the interpretation of these, for example, specifically applying in the field of RMTs, requires further improvement amongst all type of developers. Having and maintaining the required expert regulatory knowledge in house is labour and cost intensive, favouring the larger private developers. Increased expert knowledge requires the involvement of the leading regulatory authorities. Increasing the transparency of the existing possibilities for interaction and expert advice may help developers. While doing so, efforts should not only focus on increasing interaction but also on ensuring early regulatory advice to maximize the possibilities for redirecting RMT development. The present experts affiliated to regulatory authorities and industry also indicate that also they would like to stay on top of the latest technological and regulatory developments.

Furthermore, a precompetitive space offers a safe environment to explore the existing possibilities to validate RMTs through development of digital endpoints and may help to increase the expert knowledge regarding the boundaries of the current regulatory framework. Various projects funded by the Innovative Medicines Initiative and Innovative Health Initiative prove that international public private collaborations form an effective and safe sandbox in the precompetitive space. More specifically, IMI RADAR-AD is an example of validation of digital endpoints in a precompetitive space, stimulating regulatory awareness of involved partners (e.g., SMEs and academia) and providing educational materials relevant to parties inside and outside of the consortium. Moreover, the Digital Evidence Ecosystem and Protocols (DEEP) initiative has been ideated to cover gaps in the current digital endpoint development ecosystem. This solution is supported by EFPIA and addresses these gaps with three key components: 1) catalogue component that enables re-use of (parts of) digital measures; 2) collaboration ecosystem that enables pre-competitive and multistakeholder

collaboration on digital measure development, and 3) and ecosystem of services to connect the relevant stakeholders and facilitate the connections (*ISPOR - The Digital Endpoints Ecosystem and Protocols (DEEP) Initiative*, n.d.).

Hurdle 2.2 The requirements for the assessment of software and devices under the MDR and IVDR are not always clear.

Expert discussion summary:

Given the ongoing transition period of the MDD and IVDD towards the MDR and IVDR, limited understanding exists amongst the developers regarding the regulatory requirements associated. Especially in the context of a future pandemic, where well-informed decisions need to be made in a short period of time, direct interaction with the regulatory experts at the notified bodies regarding requirements including pandemic-specific exemptions could overcome this hurdle. For example, the medicinal product field with a leading role for the EMA allows for a direct feedback system by means of scientific and regulatory advice prior to assessment. Implementation of a comparable system at the various notified bodies in which developers can request tailored advice on medical devices, software, and the requirements of the MDR and IVDR may help to developers by tailored, RMT-specific advice.

Hurdle 3: Not knowing the next pandemic pathogen complicates the process of validating devices in the correct context of use and in a timely manner.

Hurdle 3.1 Lack of time and information to assess the safety and validity of a RMT in the pandemic context.

Expert discussion summary:

As the next pandemic pathogen is unknown, validating RMTs for the context of use of the next pandemic pathogen will be impossible. Given the unpredictable character of a potential future pandemic, it is suggested to plan RMT utilization for different scenarios. A solution that was agreed upon is that the mandates of the different authorities need to be clear, accessible, and aligned during the 'cold phase' in preparation for the next pandemic. A guideline needs to be written that adequately describes the route for validating different types of RMTs in the pandemic context. One of the experts suggested having anonymized RMT dossiers as a possible tool to help with the validation of new RMTs during a pandemic. This way, once another pandemic emerges, the mandates enforced, and the lessons learned for previous RMTs validated during a pandemic can be used. With the mandates aligned upfront, CCMO or METC would be better prepared in reviewing clinical trial applications.

From a legal perspective, it was also recommended that a central ethical advisory board should be setup ahead of time to ensure that during a pandemic the health and interest of a populations' needs are weighed against the health and interest of a single patient. According to Dutch law, *wet medisch-wetenschappelijke onderzoek*, the interest of the patient is at the centre of clinical research. This central ethical advisory board can help advise on balancing the patient's interests against the populations' interest.

Another solution agreed upon was to already develop upfront, before a pandemic, as many validated RMTs for endpoints that are caused by a viral infection such as fever or respiratory symptoms. This could also include disseminating knowledge and insights of already developed and validated RMTs. This way a "toolbox" of RMTs could be rapidly tested and implemented for monitoring patients during a pandemic. This use of RMTs could potentially also be used to gather endpoints during a clinical trial for a medicinal product or vaccine against the pandemic pathogen.

Importantly, an often-overlooked aspect mentioned by several experts is the communication around data collection and the accompanying data protection laws to the general public regarding RMTs. It is essential to communicate during a non-pandemic time, the benefits of additional data collection and remote monitoring for disease as well as the GDPR rules around RMTs. As such, during a pandemic,

the foundation of the general populations' trust in data collection has already been built, making it easier to use RMTs.
It is crucial to learn from other countries how regulations have been adapted or exemptions were used during the pandemic. For example, from an industry and regulator's perspective, mirroring the Food and Drug Administration (FDA)'s premarket authorization 30-day notice for a change to a medical device might be a solution (*30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes Guidance for Industry and Food and Drug Administration Staff*, n.d.). This effectively means that after 30 days, and no comment from the FDA, the RMT developer would be allowed to proceed with the clinical trial, including with digital endpoint(s), for market approval. This would potentially speed up the process as in the EU the RMT developer needs to wait for a formal letter of approval before commencing with the clinical trial. The present regulators note that the EMA's approval is generally slower and more complex as more parties are involved in the approval while the FDA's approval is coordinated by only one or two parties. However, the industry and regulator also note that the EMA's input on digital health endpoints are generally experienced from a higher quality than that of the FDA. From a legal perspective it was noted that the FDA has a unique role, in which is acts as an approver as well as a compliance body.
During a public health crisis such as a pandemic a fast-track approval process for RMTs was suggested as a possible solution. The regulators note that this was done during the COVID-19 pandemic for other materials, out of necessity since no adequate alternative was available. The Health and Youth Care Inspectorate (in Dutch "*inspectie gezondheidszorg en jeugd*") allowed self-tests on the market before the product was fully validated and approved. It was suggested that, in the situation of a future pandemic in which no approved method is available to measure relevant diagnostic or prognostic health outcomes, unapproved RMT can be used at risk but ensuring all the data would be collected. Using the unapproved RMT (with increased monitoring process to facilitate the possibility of halting the use), one accepts more uncertainty in the beginning without increased risk in the end. By collecting all the data, the data robustness and quality can be ensured for the official CE approval.
The correct context of use remains one of the biggest discussion topics. The FDA defines the context of use as the best biomarker specific to the biomarker's intended use in drug development. Representatives from the SMEs, industry and regulators suggested that fast-tracking the assessment of a previously validated RMT for a different disease domain would be a possible solution as the majority of a dossier has already been approved. The proposed repurposing of RMTs would require a couple of changes to the dossier and require all the data to be collected to ensure data robustness and quality. Important to note is that during a pandemic, data robustness and quality are still essential when fast-track approving previously validated RMT for a different intended use. As such, if an RMT is developed during a pandemic for a disease different to the pandemic pathogen, the fast-track approval might be more stringent. However, when developing a medicine against the pandemic disease such as for example, a vaccine, the rules for robustness of the data of the fast-track approval RMT would be less stringent.

Hurdle 4: Increased use of decentralised clinical trial elements facilitated by RMTs is highly complex.

<u>Hurdle 4.1. Complexity of switching from traditional to decentralised clinical trial</u>

Expert discussion summary

Academic experts noted that it is expected that future clinical trials are not fully remote, but include both remote and on-site elements, which is also known as "hybrid" trials. The academic experts added that based on the Trials@Home consortium research, only ~1% of trials are fully decentralized. From an industry perspective, it was noted that specific elements are more suited for a decentralized approach, such as collection of informed consent or trial onboarding which could be completed at home. However, changing the endpoints of a running clinical trial during a pandemic

would most likely not be accepted by the regulators as this would result in a different methodological approach for a fraction of the ongoing data collection, negatively affecting the robustness of the data. The industry notes that only in case of a last resort would a trial have an endpoint measured digitally for a part of the patient population and the remaining part on site. Furthermore, it was again suggested to repurpose an existing validated RMT for a different intended use. While doing so, it is important to ensure data robustness and compliance are met to prevent compromising data quality. From SME perspective, it was noted that digitalization of endpoints can be achieved by either developing newly existing endpoints or by digitalizing existing endpoints. As an example of the latter approach, it has been shown that performing a walking tests with a validated app is a valid alternative for the walking test traditionally performed in the clinic.
From a regulatory perspective, the transition from MDD to MDR during a pandemic was unfortunate timing. However, guidance documents on the implementations of the MDR and IVDR are being worked on. As a result, during the next pandemic, with better understanding and experience of the regulatory requirements, it will be easier for RMT developers and innovators to adhere to the MDR and IVDR.
The attending experts recognize the listed overview of hurdles and confirm that these include the major obstacles to RMT utilization. No additional hurdles were proposed.

Key messages and conclusions

From this meeting, we can conclude the following:

- All experts present during the meeting were in agreement with the identified hurdles underlying RMT utilization for regulatory decision making, deriving from the ZonMw Regulatory Pandemic Preparedness program (see table 1 for a summary).
- All experts present during the meeting agreed with the proposed solutions for each of the hurdles (see table 1 for a summary). All experts provided valuable feedback that helped to further detail the proposed solutions.
- The transitions from MDD and IVDD to MDR and IVDR, as well as the from CTD to CTR, was set forth to harmonize across EU member states which is a welcomed development better suited for novel technologies, including RMTs. However, knowledge regarding the changed legislation, regulatory requirements, and the roles and responsibilities need to be further improved and communicated amongst all stakeholders. Furthermore, the changed legislation has resulted in a significant delay of RMT assessment which is expected by some experts to be solved on relatively short notice. However, other experts still experience delays at the notified bodies.
- Early, and low threshold interaction between regulators and RMT developers should be improved to facilitate tailored regulatory advice. Various initiatives and pilots exist to explore the possibilities for interaction. Successful outcomes of these initiatives and pilots will also help to raise regulatory awareness and aids with education of MDR, IVDR and the CTR.
- A precompetitive space is crucial to bring together the various stakeholders with each their own expertise and knowledge to achieve digitalization of endpoints by RMT utilization, through the development of novel endpoints or via digitalization of existing endpoints.
- Improved pandemic preparedness is crucial since scientific, regulatory, and clinical ecosystems are under severe strain during a pandemic. The non-pandemic, “cold phase” needs to be utilized to increase the pandemic preparedness by:
    - Taking the lessons learned from the Netherland’s response to the COVID-19 pandemic but also learning how other countries responded.
    - Increasing understanding of the existing regulatory routes and requirements amongst all stakeholders that could potentially play a role during the next pandemic. This can be

achieved by preparing (pandemic-specific) protocols and guidelines, as well as increased transparency of the regulatory authorities and the lines of responsibility.
- Steps should be taken to ensure early interactions with citizens to inform them about data collection methods and data protection laws. During a pandemic, with the citizen's trust in data collection already fostered, could make the adoption of RMTs easier.
- By planning RMT utilization for different pandemic scenarios based on the characteristics of the pandemic pathogen. Amongst others, a RMT "toolbox" providing an international overview of RMTs that have received certification and/or have been validated for use in a specific context of use could help to quickly respond to a novel pandemic by testing and validating RMTs previously validated in a different context.
- Allow for pandemic-specific exemptions that facilitate the needed regulatory adaptation while safeguarding the risk for the general population. For example, flexible fast-track approval processes and repurposing processes for RMTs, including feedback rounds at notified bodies and other relevant regulatory authorities, could be considered to facilitate RMT utilization.

Follow-up activities / Future research and actions

The findings and points of concern discussed during this meeting will be integrated into the report of the RMT subprogram within the current ZonMw-subprogram Regulatory Pandemic Preparedness. This report provides the hurdles that impair implementation of RMTs and proposes potential, tangible solutions to overcome the identified regulatory hurdles in the RMT-landscape.
For future research, it is important to investigate the RMT-assessment procedures and all regulatory authorities involved. While doing so, it could be considered to study 1) the impact of the transition from MDD to MDR and IVDR and potentially existing knowledge gaps or problems in implementation, and 2) the feasibility of a 'one stop shop' for guidance and advice on RMT utilization for regulatory decision making. Another important topic (although not fully related to regulatory) is to engage with citizens and facilitate an ongoing discussion on novel technologies, data collection and data protection laws, which will contribute to a bidirectional understanding of advantages and concerns. Furthermore, the findings of this meeting will be taken on by our RSNN partners and will be included in future research agendas where possible.

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