REMOTE METHODS IN CLINICAL TRIALS

Quantification of Decentralized Trial Elements in Publicly Available Clinical Trial Protocols, and a Stakeholder's Reflection on Direct-to-Participant Investigational Medicinal Product Supply

Author:	*Renske Grupstra*
Project:	*Drug Innovation Major Internship*
Department:	*Pharmacoepidemiology and Clinical Pharmacology*
Supervisor:	*Dr. H. Gardarsdottir*
Second corrector:	*Dr. Y. Santa Ana Téllez*
Daily Supervisor:	*A. de Jong*

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Abstract

Inclusion of remote trial activities in study designs could potentially reduce some of the recruitment and retention issues currently associated with clinical trial conduct. Little is known about the extent in which remote activities have already been implemented in trial protocols, therefore this study quantified the reporting of remote methods in phase 2, 3 and 4 interventional clinical trial protocols in a cohort of studies with study start in 2019 and 2020. Additionally, an interview series into direct-to-participant investigational medicinal product supply was conducted to gain insights into stakeholders' experiences with implementation of this remote trial activity in the European Union.

Remote methods were found to be reported infrequently, with the exception of remote data collection, and an increase in inclusion of remote methods in 2020 protocols compared to 2019 was observed. Furthermore, this study found that, amongst others, staff training and outreach are often not reported in protocols. In terms of direct-to-participant supply, unharmonized regulations were found to be a big barrier in Europe, as, for instance, the depot-to-participant model can only happen with a pharmacist present. Moreover, interviewees emphasized a need for flexibility in trial designs, and called for more collaboration amongst stakeholders.

Overall, this study shows that remote methods have already been included in study protocols, and that stakeholders are positive towards additional exploration of the opportunities of including remote methods such as direct-to-participant supply in (European) trial designs.

Abbreviations

BBB	Basic building blocks
CDISC	Clinical Data Interchange Standards Consortium
CT	Clinical trial
DCT	Decentralized clinical trial
DtP	Direct-to-participant
EC	Ethics committee
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
HCP	Health care provider
ICD	International classification of diseases
ICF	Informed consent form
ICH	International Conference of Harmonization
IMP	Investigational medicinal product
IRT	Interactive response technology
MRI	Magnetic resonance imaging
NA	Not applicable
NR	Not reported
PI	Principle investigator
PRO	Participant-reported outcome
SOP	Standard operating procedure
UK	United Kingdom
US	United States
WHO	World Health Organization

1. Introduction

1.1 Background

Over the past years, fast advances in technology and digital applications have led to an increased scientific understanding of disease pathogenesis, resulting in many potential therapeutic drug targets (1). Despite this accumulation of fundamental knowledge, the productivity of drug development did not rise at the same pace (2). Clinical trials (CTs) are a cornerstone of the development of new medical treatments, and -given this central role in drug development- inefficiencies within CTs are considered a restricting factor for drug development successes (3). Traditionally, the majority of CT activities is conducted in-person at investigator sites (4). Several bottlenecks of these traditional on-site CTs have been identified including impaired recruitment and retention as time and financial burden is put on participants who need to travel to the clinical site (5)(6). In turn, study populations can be small and not representative, which constrains thorough investigation of novel therapeutics' efficacy and safety (7). Furthermore, prolonged enrollment and extended initiation of the active study phase makes trials inefficient and expensive (6). To circumvent some of these difficulties, interest in the implementation of remote methods in CTs is growing (2). In this, remote methods should be understood as operational trial activities that take place outside the investigator site. An example is the use of technologies such as telemedicine for which participants do not have to visit the investigator's site (NB: 'investigator's site' is used here to explicitly refer to the site where the (sub)investigator resides). One of the opportunities remote methods bring CTs is allowing inclusion of diverse groups of participants from larger geographical areas, resulting in more representative study populations (6). Moreover, this improves the chances of enrolling enough participants to reach statistical power in trials investigating rare diseases (6)(8). Another potential advantage is that remote methods reduce the time and financial burden put on participants during trial conduct as they have to travel less, if at all (9).

Research has demonstrated that remote methods can be used during several stages of CTs, for example during recruitment and retention (e.g., videos, podcasts or social media) (10), and during the data collection phase (e.g., through telemedicine, mobile applications or medical devices)(3). To explore the opportunities of inclusion of remote methods in CTs, a consortium called Trials@Home was established with the aim to reshape clinical trial design, and to develop concrete recommendations supporting widespread acceptance and use of remote methods in trials across Europe. The consortium has described categorization options for trials as either conventional, hybrid or fully remote based on the degree of remoteness (11). Table 1 presents an example of how trials can be placed in these three categories.

Table 1. *Adoption of example provided by Trials@Home consortium to illustrate trial categorization based on degree of remoteness in their design* (11)*.*

Conventional	**Hybrid**	**Fully remote**
- All study visits take place at study site (e.g. hospital)	- Initial and final visit of trial take place at study site - Physical sampling and imaging takes place at study site - Intervention prescribed through usual healthcare provider - Follow-up takes place through online questionnaires and telephone calls	- Participants access all trial activities and support through an online environment (e.g. study specific website) - Intervention is delivered directly to the participants' homes - All trial data is collected remotely - Trial may include telemedicine visits

It is important to note that the 'hybrid' and 'fully remote' categories can be seen as a continuous spectrum on which trials could be placed. An example of a fully remote trial is a CT without physical

sites for face-to-face interactions between research team and the participants (12). For structuring purposes, it is more convenient to compare conventional, on-site CTs with so-called Decentralized Clinical Trials (DCTs), which can either be hybrid or fully remote per the Trials@Home definition: "*Decentralized Clinical Trials make use of digital innovations to make trials more accessible to participants by moving clinical trial activities to more local settings or even the participants home and thus enable participants to visit a clinical trial center less frequently, if at all.*"(12).

To investigate opportunities of DCTs over traditional, site-centered CTs, the Trials@Home consortium has defined high-level basic building blocks (BBB) of CT designs and thereby created a framework of activities found in trial protocols that could (partially) be conducted in a remote manner (11). An schematic overview of this CT basic building block from the consortium can be seen in Figure 1.

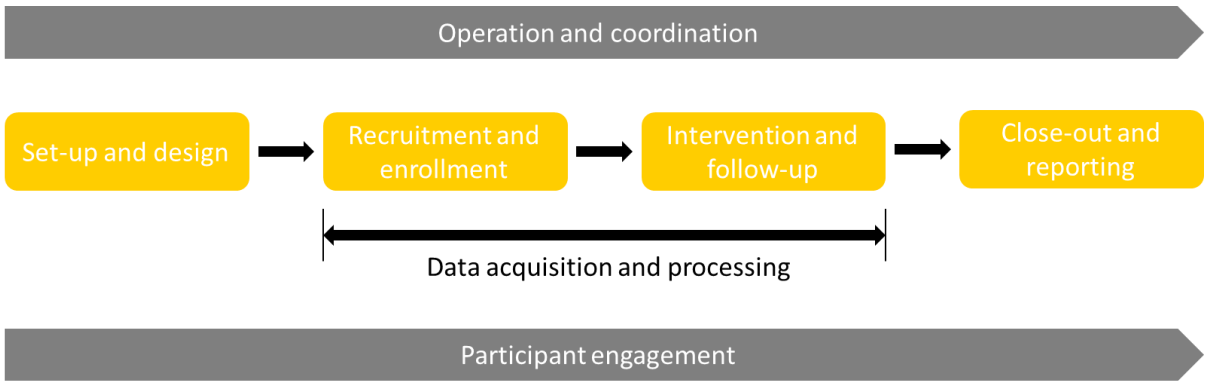

***Figure 1**. Adopted overview of the basic building blocks of clinical trial designs as created by the Trials@Home consortium* (13).

At present, little is known about the extent in which trial activities utilized throughout the lifecycle of a CT have already been conducted remotely. Therefore, in this study, we quantified the inclusion of remote methods in CTs by investigating publicly available CT protocols from 2019 and 2020. Assessing the frequency of remote method inclusion in CT designs contributes to our broader understanding of innovation trends within the field of CTs, and can provide tools for the design of future trials. Moreover, by collecting data from the chosen cohort of trials (i.e. 2019 and 2020), insights into the impact of the COVID-19 pandemic on implementation of remote elements in trial designs can be investigated.

Additionally, this report describes a more in-depth investigation of the use of one remote element: direct-to-participant (DtP) supply of investigational medicinal product (IMP). Multiple models for DtP IMP supply can be distinguished. Namely, IMPs can be sent from a central pharmacy, the manufacturer/sponsor or the investigator site directly to the home of a participant or the participant's own local pharmacy for pick-up. Furthermore, IMPs could be delivered to the participant's home in person by a courier, investigator staff or home nurses (14). A schematic overview of these examples of DtP models compared to traditional on-site IMP supply can be found in Figure 2.

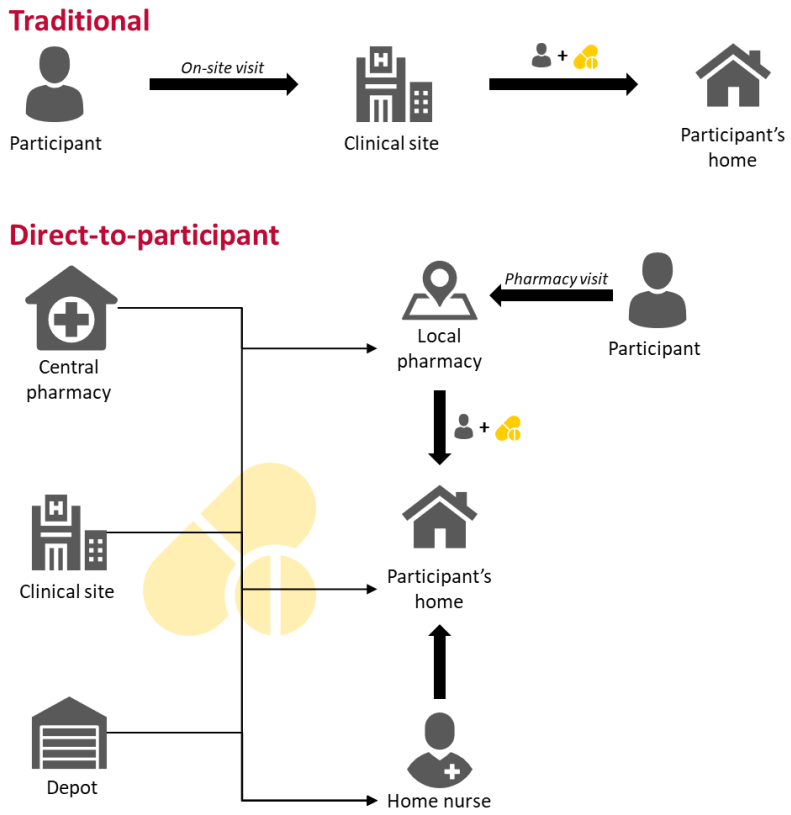

Figure 2. *Schematic overview of examples of DtP IMP supply models compared to traditional on-site IMP supply (14). In the traditional model the participant picks up IMP during an on-site trial visit. In the presented DtP models IMP is supplied from a central pharmacy, clinical site, or depot to a local pharmacy where to participant can pick it up to bring the IMP home, straight to the participant's home, or to a home nurse who delivers the IMP to the home of the participant. Abbreviations: DtP, direct-to-participant; IMP, investigational medicinal product.*

The direct supply of IMP to participants became essential when the COVID-19 pandemic caused for reduction of on-site visits during CTs, hence incentive was created for DtP IMP supply implementation in trials all over the world, including the European Union (EU) (15). As limited information on DtP conduct in the EU is currently available, the researchers were interested to learn which requirements had to be met for the implementation, which barriers and facilitators can be identified, and what experiences stakeholder's already have in the EU. To do so, a qualitative interview series with private and public sponsors, courier services, and pharmacists involved in the supply process was conducted. Findings from the interviews will contribute to understanding the current status of DtP IMP supply in CT conduct, which can be of value for future implementation of DtP models in trial designs.

1.2 Aim, objectives and hypotheses

The overall aim of this project is to elucidate the incorporation of remote methods in trial designs and to highlight one of the investigated remote elements (i.e. DtP IMP supply) by providing case study insights and stakeholder experiences. Specifically, this study consists of two parts: 1) we conducted a quantification of remote methods in a specific cohort of studies to investigate in what extent remote methods are described in trial protocols, 2) we used qualitative interviews to explore how DtP IMP supply has been implemented within trials in the EU based on experiences of (public and private) sponsors and courier services. Both parts taken together, the main research question is constructed as follows:

To what extent are remote methods reported in phase 2, 3 and 4 interventional clinical trial protocols publicly available from ClinicalTrials.gov in a cohort of studies with study start date between 01/01/2019 and 31/12/2020, and what is the experience of stakeholders (i.e. public and private sponsors, courier services, and (central) pharmacists) with the incorporation of the remote element of direct-to-participant investigational medicinal product supply in clinical trials in the European Union?

This main research question can be divided into several sub-questions that were transformed into objectives for each of the two parts of this study. An overview of all study objectives is presented in Table 2.

***Table 2**. Overview of all the objectives of this research, structured according to the division of the quantitative and qualitative part of this study. Abbreviations: CT, clinical trial; DtP, direct-to-participant; EU, European Union; IMP, investigational medicinal product.*

Quantification of remote method
- To identify which trial activities have been conducted remotely more frequently compared to others in a cohort of trials from 2019 and 2020; - To compare the frequency of reporting of on-site only, remote only or a combination of the two for trial activity conduct; - To assess whether the emerged COVID-19 pandemic impacted the use of remote elements as described in the included CT protocols; - To determine whether frequency of remote method use in the cohort of CTs depends on sponsor type (private or public); - To determine whether frequency of remote method use in the cohort of CTs depends on study phase.
Qualitative interviews
- To identify, describe and evaluate case studies of DtP IMP supply in trials conducted within the EU; - To clarify how DtP IMP supply was organized in obtained case studies; - To identify current facilitators and barriers within conduct of DtP IMP supply (in EU-based trials); - To provide recommendations for implementation of and potential future perspectives on DtP IMP supply in CTs.

It is expected that during the quantification, remote methods will be more prevalent in phase 4 trial protocols compared to protocols from other trial phases given the larger study population that is generally included in this type of trial as during this phase of clinical research researchers already have more knowledge of the efficacy and safety of the medicine or therapy of interest (16)(17). Consequently, it is expected that in this trial phase remote methods mainly serve to aid data acquisition, for example by having participants collect data at home through the use of specific devices such as wearables or via mobile applications.

In regards to the effect of sponsor type -either through public or private institutions- on inclusion of remote methods in study protocols, the expectation is that private funding of trials will result in more frequent use of remote methods. Research demonstrates that non-commercial trials which are funded by public institutions often face underfunding (18)(19). Therefore novel and expensive techniques such as those used for remote methods -e.g. use of wearable devices- are less likely to be implemented in publicly funded trials due to financial constraints.

In regards to the impact of the COVID-19 pandemic, the researchers expect to find an increase in remote method use in trials initiated during the pandemic given social distancing regulations that were established during the crisis and their implications for CT conduct.

When it comes to the qualitative interviews series, it is hypothesized that, in general, stakeholders will report less experiences of DtP IMP shipments in the EU compared to the United States (US). The US has demonstrated a more proactive attitude to innovate clinical research, for

example through the establishment of the Clinical Trial Transformation Initiative back in 2012 (20). This organization aims to transform CTs and focused in recent years on inclusion of remote elements, thereby aiding the hypothesis that the US is more ahead when it comes to DtP implementation in trial designs.

Expected barriers for DtP implementation include regulatory hurdles, as the EU has a complex regulatory landscape, e.g. because of decentralization (21). Furthermore, it is believed that specific CT characteristics such as IMP that is not self-administrable, or first-in-human trials will also serve as barriers for DtP implementation, because study staff will probably prefer a clinical setting for these types of trials.

Finally, it is hypothesized that the stakeholders included in the interviews will show a positive attitude towards more DtP implementation in CT designs in the future. DtP is thought to be in line with a general trend towards patient-centricity in CTs, hence the expectation of enthusiasm towards future increased conduct of DtP (4)(22).

2. Methodology

As this study consists of two separate parts, the different methods used for each of these parts of the study are elaborated in separate subchapters. First, methods used for the quantification of trial activity conduct will be presented. Thereafter, the methodology of the qualitative interviews series is elaborated.

2.1 Quantification of remote methods

2.1.1 Quantitative study design

In order to assess the occurrence of remote methods in study protocols, the initial step was to select protocols based on determined eligibility criteria. Thereafter, data of each of the selected studies - including general trial characteristics such as study design, participants, locations and sponsors- was collected in a systematic manner. Next, a matrix framework was created and used to classify remote methods identified within study protocols from the selection of trial protocols.

2.1.2 Protocol eligibility criteria

Study protocols for the analysis of remote methods were collected from a specific cohort of trials. The included trials were downloaded from ClinicalTrials.gov on 23rd and 24th of March 2021, and were selected if in adherence with the eligibility criteria as presented in Table 3. Reasonings behind these criteria are elaborated below the table.

Table 3. *Eligibility criteria for study protocols to be analyzed for presence of remote methods. Sufficiency of information provided within study protocols is based on an initial manual screening of protocol content sections. Abbreviation: IMP, investigational medicinal product.*

Inclusion criteria	**Exclusion criteria**
Interventional Clinical Trials	Non-interventional trials
Trials for which a study protocol is available in ClinicalTrials.gov	Trials without provision of study protocol in ClinicalTrials.gov
Phase 2, 3 and 4 trials	Early phase 1 trials, phase 1 trials, or trials with an unknown study phase
Trials with their study start date between 01/01/2019 and 31/12/2019	Trials with their study start date outside of indicated time intervals
Trials with their study start date between 01/01/2020 and 31/12/2020	Trials of which the protocol contains insufficient information regarding study procedure
Trials using an IMP	Trials used for interventions other than IMP use, e.g. dietary supplements or medical device trials

When it comes to phases of studies, phase 2, phase 3 and phase 4 trials are included here as these represent the part of clinical research that requires the use of larger study populations. (Early) phase 1 trials are excluded as this concerns first-in-human trials that are known to include a limited amount of participants (23).

The specific time frame chosen for trials to be included ranges from the start of 2019 to the end of 2020 as this allows for evaluation of effects of the emerging of the COVID-19 crisis on inclusion of remote methods within study protocols. The World Health Organization (WHO) declared COVID-19 a global pandemic on the 11th of March 2020 (24). Therefore the chosen time frame for trials to be included ranges from roughly one year before and one year after this date. Furthermore, this study aims to elucidate recent (trends in) use of remote methods in CTs, and is less interested in prevalence of remoteness in trial designs from a longer time period ago nor in exploring older, ongoing trends.

Finally, sufficient information provision regarding study procedures is included as a criterium for protocol selection as lack of detailed information within protocols will unable researchers to properly code for remote methods. Filtering for this criterium took place once a trial adhered to all

the other criteria stated in Table 2. A manual scan of the contents of each protocol was carried out, during which inclusion of study procedure headings in the content table of the protocol was screened. In case of absence of sections in the protocol dedicated to study procedure elaboration, eligibility criteria and/or study (visit) schedule information, protocols were excluded.

2.1.3 Data collection: trial characteristics

Basic characteristics of the trials included in the selection for the remoteness analysis were collected in an Excel file. The specific information that was gathered is presented in Table 4 and is based on the by the Clinical Data Interchange Standards Consortium (CDISC) provided protocol toolset v1.0 dating from April 20th, 2012 (25). Definitions of the trial characteristics that are collected can be found in the glossary (Appendix 1).

Table 4*. Trial characteristics to be collected from selected cohort of studies.*

Characteristic category	**Specific data to collect**
General	Protocol title
	Protocol identification number (here: ClinicalTrials.gov identifier)
	(Estimated) study start date
	(Estimated) study completion date
	Whether study is pre- or during-COVID
	Disease area and name[a]
	Use of a Data Safety Monitoring Committee (DSMC)
Trial location	Region(s) involved[b]
	All countries involved in the trial
	(Maximum) planned number of sites
	Whether it is a hospitalized trial
Study design	Randomization
	Description of intervention(s) and comparator(s)
	Trial phase
	Primary objective
	Blinding
Trial participants	Target population
	Subject minimum age
	Subject maximum age
	Whether healthy subjects are used
	Number of participants
	Participation duration
	Subject gender
Regulatory trial sponsor	Whether public institution is primary sponsor
	Primary sponsor name

[a] Disease area is based on high-level classifications adopted from the international classification of diseases (ICD) system provided by the WHO (26). Appendix 2 presents an overview of the categories that were used in this study.

[b] The geographical regions used for coding location characteristics of trials are based on the system provided by ClinicalTrials.gov (27). An overview of these regions and the countries they include can be found in Appendix 3.

All mentioned trial characteristics are extracted based on information provided in the study protocol. If needed, information about the trial provided by the ClinicalTrials.gov database was also used for data collection. In case of discrepancies between information provided in the study protocol and information presented by ClinicalTrials.gov, the information from the protocol prevailed. In case trial specifics were not reported in the study protocol nor in the ClinicalTrials.gov database, this was noted as such.

To determine whether a study was pre- or during-COVID, the 11th of March 2020 -the official day on which COVID-19 was declared a pandemic, as mentioned in section 2.3- was taken as a benchmark: in case the by ClinicalTrials.gov presented study start date lies before the 11th of March 2020 the trial is considered as pre-COVID, and any trial with its estimated study start date either on the 11th of March 2020 or on a date later in time is regarded as during-COVID.

2.1.4 Data collection: remoteness filtration and classification

In addition to the specific trial characteristics collection, data regarding specific remote methods used during study conduct were extracted from the included protocols. A classification matrix was used as a framework to guide this coding. The Trials@Home high-level BBB model for the design of a clinical trial (Figure 1) was used as guidance for the creation of this matrix. Compared to the BBB framework, the matrix used in this study focusses primarily on operational trial activity and mainly on patient-facing activities. An expert was consulted during the creating of the matrix, which led to several adjustments such as the removal of synchronous communication and on-site auditing. A summary of the final classification matrix is shown in Figure 3, the complete matrix table can be found in Appendix 4. Important to note that by definition hospital-based trials can only have on-site data collection (see glossary, Appendix 1), meaning that when determining percentages of trials in which remote data collection was reported, hospital-based trials were left out of the denominator.

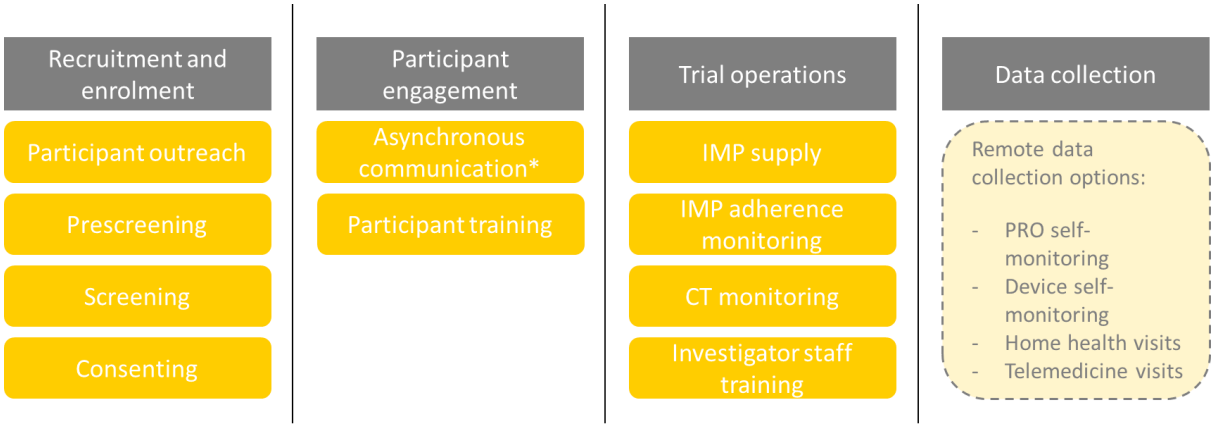

Figure 3. *Summary of the classification matrix. Remote and/or on-site conduct of each of the in the yellow presented trial activities was coded for, with the exception of asynchronous communication as this is remote only (by definition). Four options for remote data collection were used. Abbreviations: CT, clinical trial; IMP, investigational medicinal product; PRO, participant-reported outcome.*

The matrix was used to code and classify trial conduct methods found in the cohort of study protocols extracted from ClinicalTrials.gov. For each study protocol, the methods used for the activities were -based on what was explicitly mentioned in the study protocol- classified as: 'remote', 'on-site', a combination of the two or 'not reported'. This means that remote and on-site conduct of trial activities are not considered to be mutually exclusive in this study. Classifications were tracked in Excel and Nvivo12 software.

In order to try and account for trial activities that were unreported, unclear, or ambiguously reported in trial protocols, implicit coding was used. Rules were created for when implicit coding could be applied, see the following example: '*In case an on-site (pre)screening visit is described and it can be assumed that consenting took place during this visit, consenting is implicitly coded as on-site.*' A full list of all created rules for implicit coding can be found in Appendix 5.

The matrix was revised after coding the first ten protocols to allow for elaborations and additional specifications of matrix elements for optimization purposes. To limit the chance of human error causing failure to find and code descriptions of specific trial activities, data mining was used as verification after a protocol was carefully read and manually coded. To do so, (partial) word

combinations were used for each of the trial activities, for instance 'approach' and 'advertise' for outreach. An overview of all search terms used per trial activity can be found in Appendix 6.

A random selection of fifteen protocols was independently coded in duplicate by another researcher to assure accuracy during the coding process. Finally, for verification purposes and to limit chances of reporter bias, the coding of all protocols was peer-reviewed.

2.2 Qualitative interviews series

2.2.1 Qualitative study design

To explore how DtP IMP supply has been conducted in trials (partially) executed in the EU, case studies have been collected and experienced barriers and facilitators of public and private sponsors, (central) pharmacists, and courier services have been solicited. Data was collected through in-depth semi-structured interviews conducted by the researchers. For the reported methodology of this study, the consolidated criteria for reporting qualitative research (COREQ) were used as reference (see Appendix 7) (28).

2.2.2 Interview sample and recruitment

Participant eligibility was restricted to CT sponsors, representatives of courier services and (hospital) pharmacists with experience in DtP supply, ideally in Europe. Sponsors could either be from the pharmaceutical industry (private sector) or academic institutions (public sector).

For recruitment purposes, purposive sampling within the Trials@Home consortium and amongst external courier services was used. Throughout the outreach period, snowballing was applied by asking approached participants whether they knew other experts who could potentially be included in this study. Outreach as well as scheduling of interviews and provision of additional information was conducted via email. Participants received an invitation letter, a consent form as well as a summary of the interview guide prior to the initiation of the interviews. All accompanying documents can be found in Appendix 8.

2.2.3 Interview guide

Two versions of an interview guide were created for the interview conduct: one for sponsors and one for courier services (see Appendix 8) (N.B.: for the interviews with (hospital) pharmacists the sponsor interview guide was used). The content of the guides was adjusted and validated based on a review discussion with an industry expert in the field of IMP supply. Additionally, a pilot interview was held, after which the interview guide was adjusted as follows: instead of one general interview guide, two versions were made (one focused on sponsors, the other on courier services), and questions were added such as asking stakeholders whether they observed trends towards DtP inclusion prior to the COVID-19 pandemic.

2.2.6 Qualitative data collection

Interviews were audio-recorded and transcribed. In the transcripts, personal identifiers were replaced with pseudonyms in order to protect the privacy of participants (29). As a way to highlight important aspects that were mentioned during the interviews, field notes were also drafted during interview conduct. Furthermore, a summary of the interview was sent to the interviewees, allowing for additional clarification and feedback on their behalf where necessary.

2.2.7 Qualitative data analysis

Transcripts of the interviews were analysed in NVivo 12 software through thematic analysis (30). Thematic analysis was chosen as this induction-based analysis allows for the identification of themes closely linked to the obtained data (31). The iterative analysis process consisted of several phases. In the first phase, two transcripts were coded in detail and the obtained coding was grouped under identified themes, resulting in a coding tree. In the second phase, three additional transcripts were

coded using the created coding tree and the tree was adjusted during this process. Each novel version of the coding tree was discussed and agreed on by the researchers. The final adjusted version of the coding tree was used to code the remaining transcripts. 30% (n=4) of the transcripts was independently coded in duplicate to limit the chances of bias.

2.3 Data management plan

All data from this study is stored in line with the General Data Protection Regulation (GDPR) and Utrecht University policies. Raw data used during study conduct consists of study protocols obtained from ClinicalTrials.gov, audio-recordings of interviews, interview notes, summaries and transcripts. Data processing was conducted in Excel, NVivo12 and online Word files stored in a private OneDrive environment as well as in a private Microsoft Teams environment.

PDF files of the included study protocols for the quantitative analysis were downloaded to a local computer server on 23/03/2021 and 24/03/2021. Each PDF file was named according to the date the study initiated and its ClinicalTrials.gov ID number as follows: [YYMMDD_IDnumber], e.g. 190214_NCT03830281. The protocol files were categorized into two folders based on year of study start: either 2019 or 2020. Per year additional folders based on trial phase were used for further classification of the files. In order to prevent loss of data, the folders were backed-up on an external hard drive as well as uploaded to the private OneDrive environment.

After data analysis of the qualitative interviews was completed, all the qualitative study data was moved to an encrypted database of the Utrecht University (F drive for confidential data).

When it comes to the dissemination of study results, a presentation as well as the final study report will be shared with researchers from the Pharmacoepidemiology and Clinical Pharmacology group from Utrecht University. Moreover, the researchers aim to publish results in an academic journal. Disseminated content will not contain any personal identifiers.

3. Results

3.1 Quantification of remote methods

3.1.1 Protocol cohort

This study included 254 trials of which the protocol was publicly available trials from ClinicalTrials.gov. Figure 4 shows the selection process resulting in the final cohort of protocols. A detailed overview of the year and phase of the excluded studies can be found in Appendix 9.

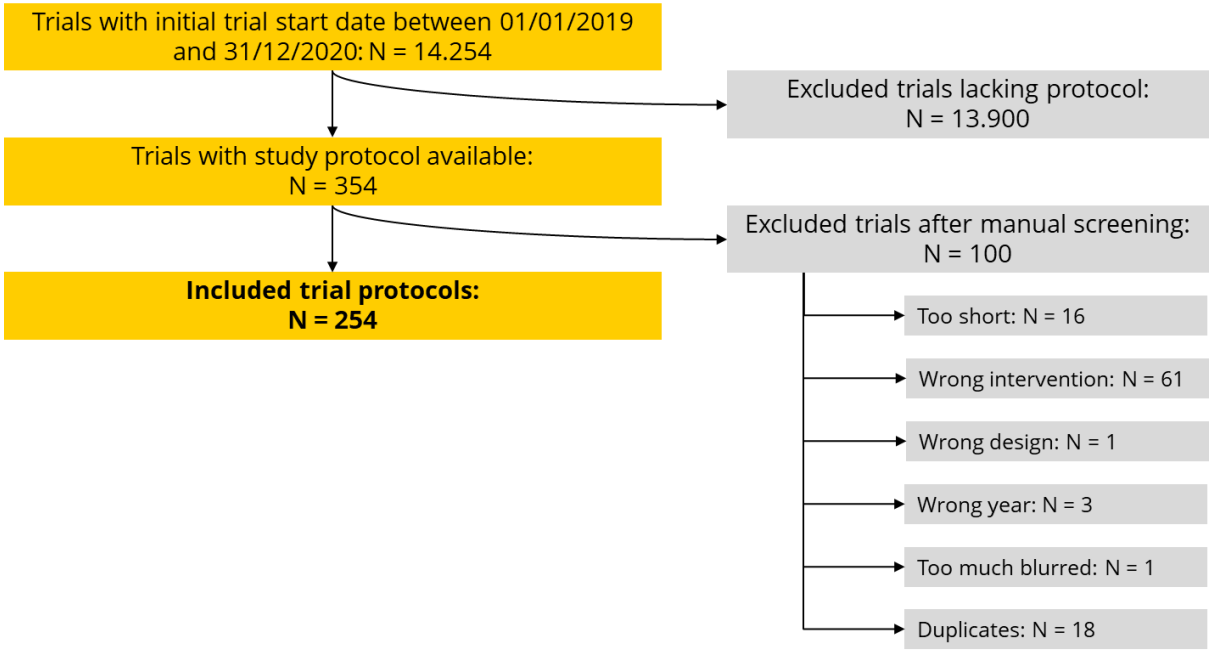

Figure 4. *Flow scheme displaying the protocol inclusion process. All study protocols were downloaded as PDF files from ClinicalTrials.gov on the 23rd and 24th of March, 2021. A detailed overview of the year and study phase of the excluded protocols can be found in Appendix 9.*

The included protocols had their (planned) study start date in 2019 (75%) or 2020 (25%), and the majority of the protocols dates from pre-COVID times (80%). Of the included trials, 46% of the protocols was phase 2, 28% was phase 3, and 26% was phase 4. In terms of sponsor type, 39% of trials had a private sponsor and 61% a public sponsor. The cohort contained studies covering a variety of therapeutic areas, of which infectious diseases (12%), COVID-19 (12%), neoplasms (10%), an endocrine or metabolic diseases (9%) were most common. Of the included trials, 49% was multicentre with a median of 8 sites per multicentre study (23 sites on average). The median number of trial participants was 90, and 11% of the trials was paediatric. In Table 5 a complete overview of the collected characteristics from the cohort of trials is presented.

Table 5. *Frequencies of trial characteristics of the 254 included study protocols.*

CATEGORY	CHARACTERISTICS	FREQUENCY (%)
Timeline		
	Pre-COVID trial	204 (80)
	2019 trial	191 (75)
	2020 trial	63 (25)
	During-COVID trial	50 (20)
Disease are		
	Conditions originating in the perinatal period	1 (0)
	Diseases of the ear or mastoid process	1 (0)
	Extension codes	1 (0)

	Factors influencing health status or contact with health services	1 (0)
	Injury, poisoning or other consequences of external causes	1 (0)
	Development anomalies	2 (1)
	Blood and blood forming organs diseases	4 (2)
	Pregnancy, childbirth or the puerperium	4 (2)
	Diseases of the immune system	5 (2)
	Diseases of the musculoskeletal system or connective tissue	5 (2)
	Diseases of the digestive system	8 (3)
	Diseases of the genitourinary system	9 (3)
	Diseases of the circulatory system	9 (4)
	Diseases of the nervous system	10 (4)
	Diseases of the respiratory system	10 (4)
	Diseases of the visual system	10 (4)
	Mental, behavioural or neurodevelopmental disorders	14 (6)
	Diseases of the skin	16 (6)
	Endocrine, nutritional or metabolic diseases	23 (9)
	Neoplasms	26 (10)
	COVID-19	30 (12)
	Infectious and parasitic diseases	30 (12)
	Symptoms, signs or clinical findings, not elsewhere classified	34 (13)
Trial location		
	Single centre trial	130 (51)
	Multicentre trial	124 (49)
	Hospitalized trial	23 (9)
	North America	151
	Europe	64
	East Asia	23
	Africa	11
	South America	11
	Southeast Asia	9
	Pacifica	5
	South Asia	5
	Middle East	6
	Central America	2
	North Asia	2
IMP		
	Self-administration	141 (56)
	Oral administration	119
	Parenteral administration	112
	Topical administration	21
	Nasal administration	5
	Other type of administration	4
	Sublingual administration	2
Comparator		
	(Active) placebo	101 (40)
	Active comparator	94 (37)
	Comparator not applicable	59 (23)
	Self-administration	103 (53)
	Oral administration	84
	Parenteral administration	70
	Topical administration	20
	Nasal administration	4
	Other type of administration	2
	Rectal administration	1

Study phase		
	2	116 (46)
	3	72 (28)
	4	66 (26)
Design		
	Randomized	190 (75)
	Open label	127 (50)
	Double blind	112 (44)
	Single blind	15 (6)
	Data safety monitoring committee	91 (36)
Participants		
	Health participants used	38 (15)
	Paediatric trial	27 (11)
Sponsor		
	Public	155 (61)
	Private	99 (39)

3.1.3 Trial activity conduct

3.1.3.1. Overall activity conduct

Of the predefined remote elements that was coded for, remote data collection was reported most often as it was explicitly described in 67.7% of the included protocols (NB: hospital-based trials are excluded as by definition their data collection is on-site). Other trial activities with frequent descriptions of remote conduct include participant outreach (25.2%), adherence monitoring (29.5%) and CT monitoring (25.6%). Remote conduct of pre-screening, screening, and participant training was less prevalent as it was found in 7.9%, 4.7% and 4.7% of the protocols, respectively. On-site conduct of trial activities was more frequently coded for compared to remote conduct, as on-site data collection was found in 98.4% of the protocols, on-site consenting in 95.3%, on-site IMP supply in 86.3%, on-site screening in 75.5%, and on-site adherence monitoring in 69.8%. Notably, on-site pre-screening was only described in 26.4% of the protocols and on-site staff training only in 13.4%. Figure 5 shows a complete overview of the trial activity conduct that was reported in the protocols from the included cohort.

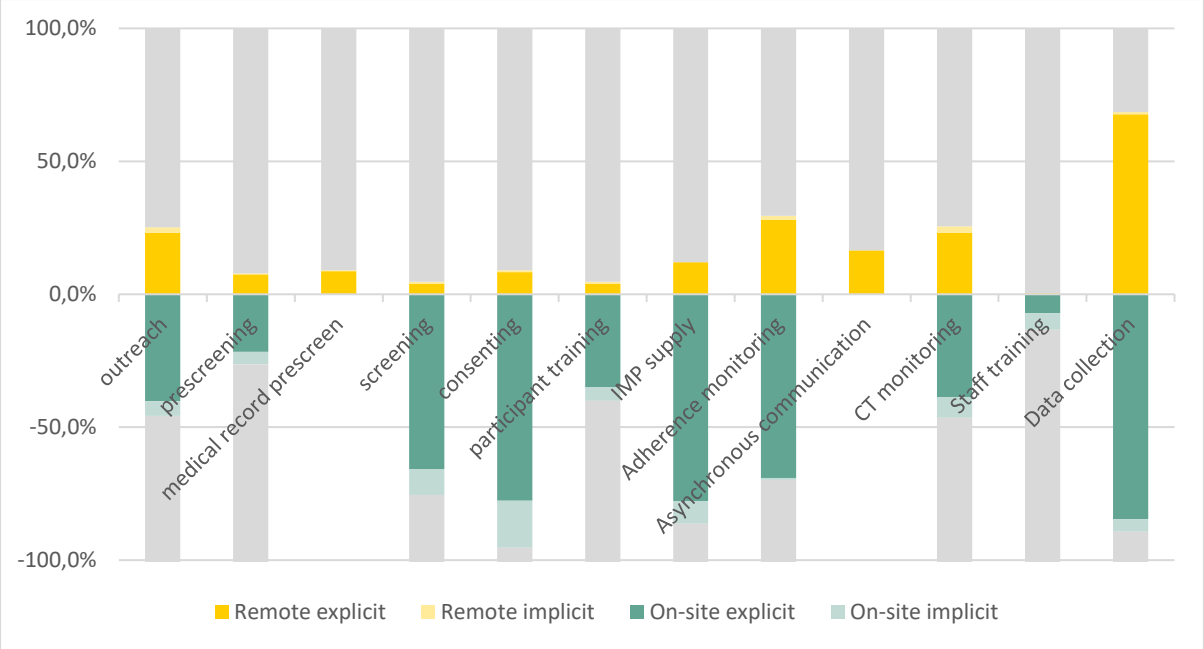

Figure 5. *Overall overview of trial activity conduct that was found in the selected protocols. Remote and on-site conduct of trial activities are not mutually exclusive. Due to definitions, only remote conduct of medical record pre-screening and asynchronous communication is included. Abbreviations: CT, clinical trial; IMP, investigational medicinal product, NA, not applicable; NR, not reported.*

In terms of implicit versus explicit coding, it can be observed from Figure 5 that implicit coding was more common for on-site conduct compared to remote trial activity conduct. For instance, on-site consenting was implicitly coded in 17.7% of the trial protocols and on-site screening in 9.8% of the protocols, whereas percentages of implicit coding for remote trial activity conduct never surpassed 2.4% (remote CT monitoring).

When looking at remote data collection specifically, telemedicine visits (i.e., telephone and teleconference visits) were reported in 57.5% of the protocols, remote data collection through participant-reported outcomes (PROs) was reported in 45.4% of the protocols, the use of devices for remote data collection was described in 17.3% of protocols, and use of home health visits was described in 8.6% of the protocols. A visualization of these numbers is presented in Figure 6.

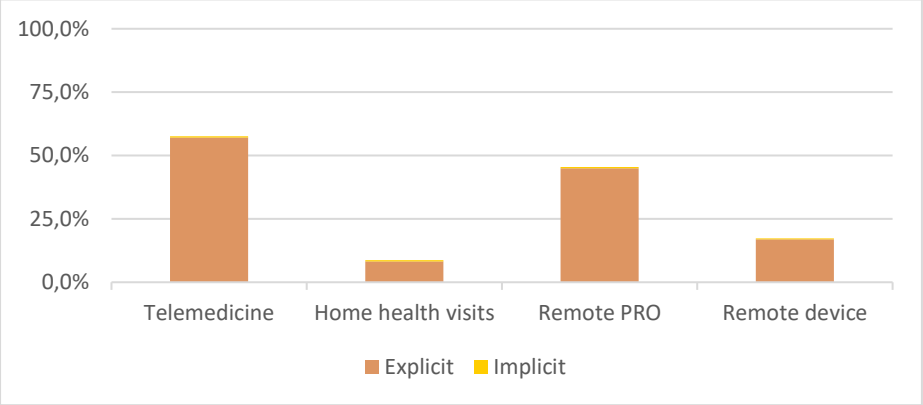

Figure 6. *Distribution of remote data collection methods found in the included protocols (excluding hospitalized trials). Abbreviation: PRO, participant-reported outcome.*

For the majority of trial activities, reporting of only on-site conduct is the most common, as can be seen in Figure 7. In those trials that do report remote activities, this is usually in combination with on-site conduct of the same activity. Noticeably, for data collection the combination of remote and on-site reporting is reported more than on-site data collection only: 67,3% versus 31,1%

respectively. The only exception to this is pre-screening, for which 12,2% of protocols reported only remote conduct compared to 3,9% of protocols describing the combination of remote and on-site pre-screening. Furthermore, the combination of remote and on-site staff training has not been reported in any of the protocols from the included cohort.

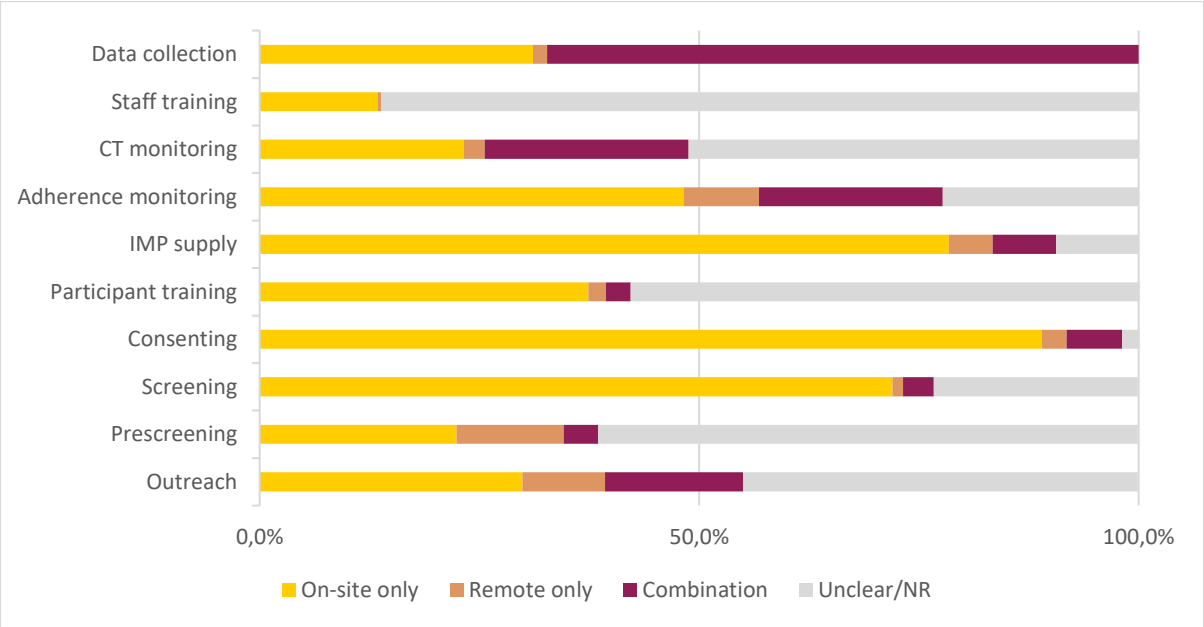

***Figure 7**. Overall overview of mutually exclusive trial activity conduct options as found in the included cohort of trial protocols. Abbreviations: CT, clinical trial; IMP, investigational medicinal product, NR, not reported.*

3.1.3.2 Study start stratification

When stratifying the data per year of study initiation (i.e., 2019 or 2020), only small differences were observed in on-site reporting of the predefined activities, as can be seen in Figure 8. In terms of remote conduct of trial activities, protocols from 2020 report more remoteness for all except remote CT monitoring, remote staff training and remote data collection. The largest differences in remote reporting between 2019 and 2020 were observed for remote IMP supply, as this was described in 8.3% of 2019 protocols compared to 26.7% of 2020 protocols, and for remote consenting, which was described in 1.0% of 2019 protocols compared to 17.5% of 2020 protocols.

In terms of explicit versus implicit coding, implicit coding is typically observed more for on-site elements in both 2019 and 2020 trial protocols. This is in the line with the general finding as described in section 3.1.3.1.

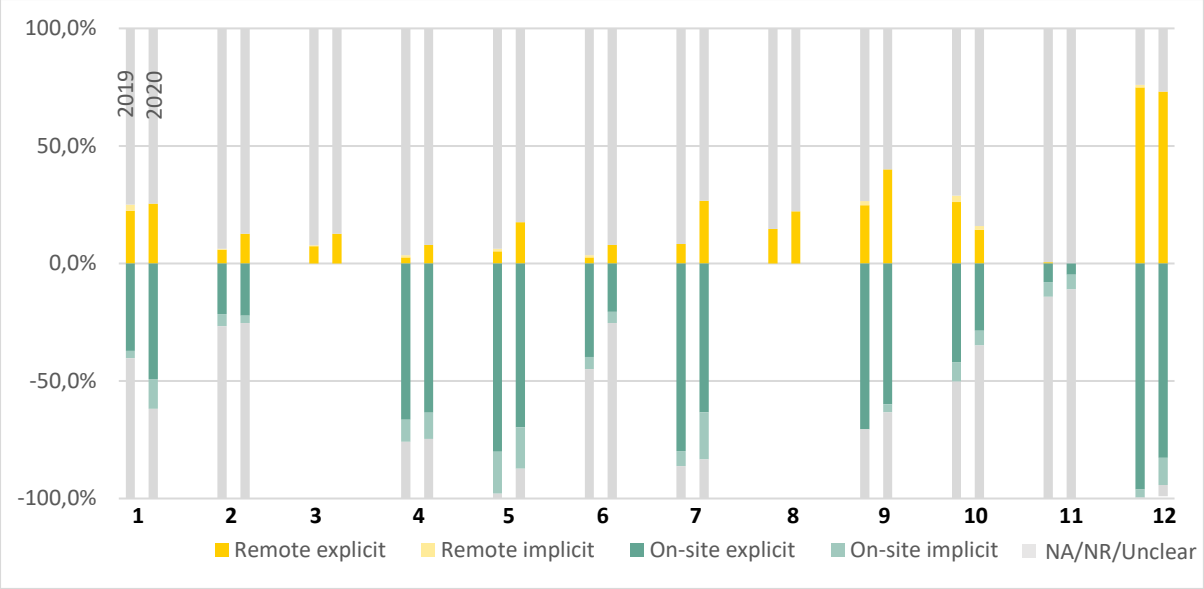

Figure 8. *Stratification of trial element conduct per year of study initiation (per activity: left bar 2019, right bar 2020).* ***1****, Participant outreach;* ***2****, Pre-screening;* ***3****, Medical record pre-screening;* ***4****, Screening;* ***5****, Consenting;* ***6****, Participant training;* ***7,*** *IMP supply;* ***8****, Asynchronous communication ;* ***9****, Adherence monitoring;* ***10****, CT monitoring;* ***11****, Staff training;* ***12,*** *Data collection. Abbreviations: CT, clinical trial; IMP, investigational medicinal product, NA, not applicable; NR, not reported.*

When looking at the four predefined options for remote data collection, only small differences between 2019 and 2020 protocols can be observed (see Figure 9), in line with the observation of remote data collection in Figure 8. The general trend of mainly reporting of telemedicine and PRO self-monitoring -as visualized in Figure 6- holds for this stratification.

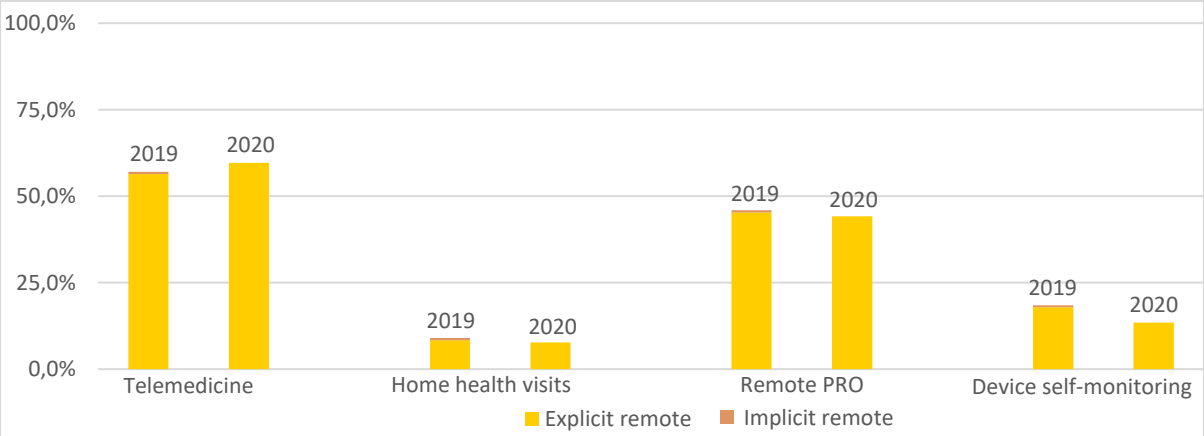

Figure 9. *Distribution of remote data collection methods found in the included protocols stratified per year of study initiation (excluding hospital-based trials). Abbreviation: PRO, participant-reported outcome.*

Obtained data has also been stratified based on whether a study was pre-COVID or during-COVID, and results were comparable to what was found when stratifying for 2019 and 2020 protocols. The only exception is data collection, as protocols from during-COVID reported more remote data collection compared to pre-COVID protocols (79,5% versus 73,4%), where 2019 protocols were found to report more remote data collected compared to 2020 protocols (74,9% versus 73,1%), but these differences are only marginal. Figures of the COVID-related stratification can be found in Appendix 10.

3.1.3.3 Sponsor stratification

Trial activity conduct was stratified per sponsor type (i.e., private or public), and results are visualized in Figure 10. When comparing public and private sponsors, it can be observed that public sponsors described more remote outreach in their protocols (30.3% versus 17.1%), more remote consenting (12.9% versus 3.0%), more DtP IMP supply (15.0% versus 8.5%), and more asynchronous communication (19.4% versus 12.1%). In contrast, private sponsors were found to report more remote CT monitoring (49.5% versus 10.3%) and remote data collection (93.8% versus 61.9%).

Looking at reporting of on-site trial element conduct, the trends between public and private sponsors compare to the reporting or remote conduct, with the exception of screening (public sponsor 63.3% and private sponsor 95.0% for on-site conduct, compared to 5.1% and 4.0% for remote conduct), consenting (on-site public 92.9% and private 99.0% compared to 12.9% and 3.0% for remote), participant training (on-site public 30.3% and private 55.6% versus 5.2% and 4.0% remote) and adherence monitoring (on-site public 57.6% and private 84.7% versus 30.0% and 28.8% remote).

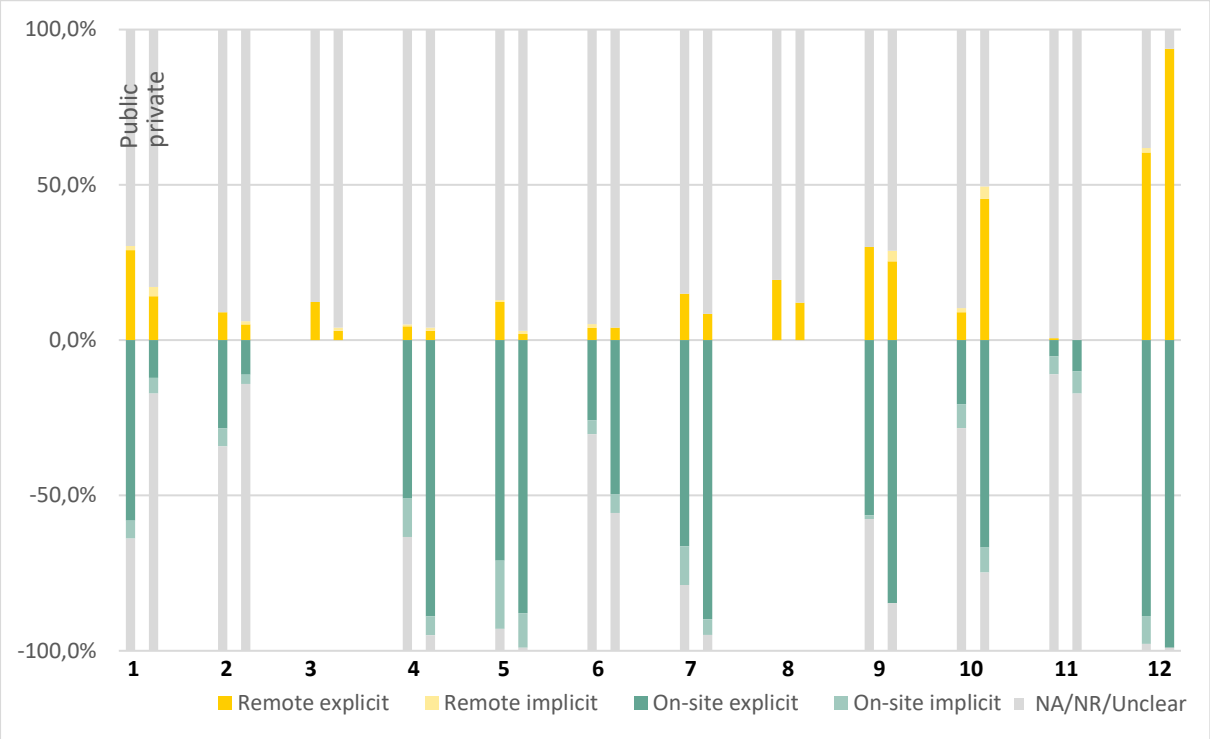

Figure 10. *Stratification of trial element conduct per sponsor type (per activity: left bar public sponsor, right bar private sponsor).* ***1****, Participant outreach;* ***2****, Pre-screening;* ***3****, Medical record pre-screening;* ***4****, Screening;* ***5****, Consenting;* ***6****, Participant training;* ***7,*** *IMP supply;* ***8****, Asynchronous communication ;* ***9****, Adherence monitoring;* ***10****, CT monitoring;* ***11****, Staff training;* ***12,*** *Data collection. Abbreviations: CT, clinical trial; IMP, investigational medicinal product, NA, not applicable; NR, not reported.*

When it comes to explicit versus implicit coding, Figure 10 shows that trends observed in the stratification per sponsor type are comparable to what was observed in the overall cohort, i.e. more use of implicit coding for on-site trial activity conduct compared to remote trial activity conduct.

Comparable to the observation in Figure 10 (of more remote data collection reported in protocols from private sponsors), Figure 11 shows how private sponsors described almost each of the predefined remote data collection methods more compared to public sponsors, albeit with small differences.

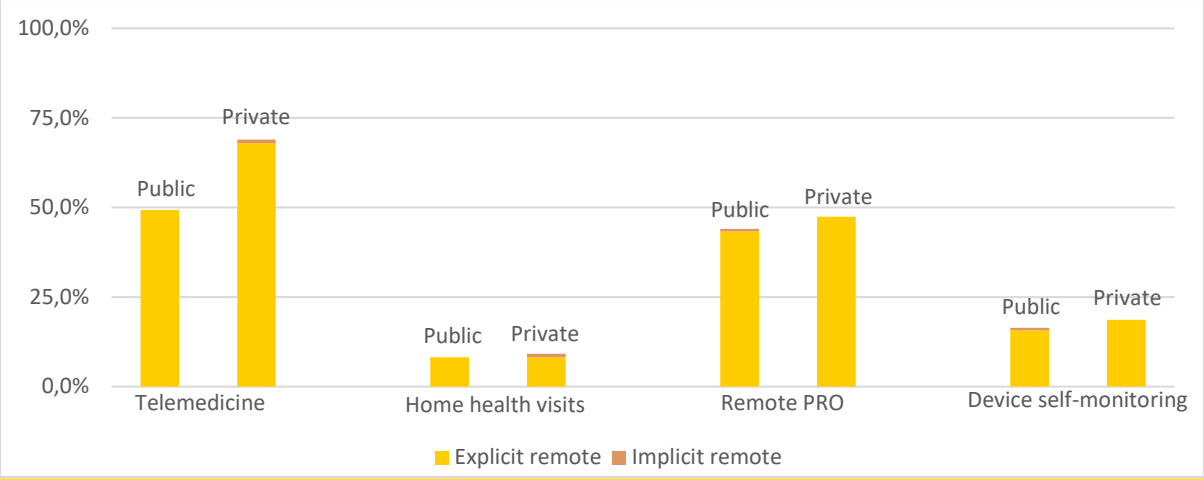

Figure 11. *Distribution of remote data collection methods found in the included protocols stratified per sponsor type (excluding hospitalized trials). Abbreviation: PRO, participant-reported outcome.*

When sub-stratifying the effect of sponsor type on conduct of trial activities per year (i.e., 2019 or 2020), the differences were comparable to the observed trends in Figure 10, with the exception of the reporting of remote adherence monitoring. In the overall stratification per sponsor type, the difference in reporting of remote adherence monitoring between public and private sponsors is small (30.0% versus 28.8%, respectively). A similar small difference is observed when sub-stratifying the data for 2019 (23.2% for public sponsors versus 30.2% for private sponsors). However, when sub-stratifying for 2020, 45.8% of the protocols from public sponsors (n=52) report remote adherence monitoring, whereas only 16.7% of private sponsors (n= 11) reported remote adherence monitoring. Important to Figures of these sub-stratifications can be found in Appendix 11.

3.1.3.4 Phase stratification

Upon stratification per study phase, it can be observed in Figure 12.A that phase 3 protocols described more remote data collection (92.1%) compared to phase 2 and phase 4 protocols (48.6% and 52.6%, respectively). Specifically, all predefined remote data collection methods (i.e., telemedicine, home health visits, PROs, and use of devices) were most frequently reported in phase 3 protocols as can be seen in Figure 12.B.

Phase 4 protocols reported more remote pre-screening compared to phase 2 and phase 3 protocols (21.2% versus 10.4% and 6.9%), and phase 2 protocols reported more remote outreach with 31.0% describing it versus 19.4% in phase 3 and 21.2% in phase 4. When comparing these trends to the description of on-site trial activity conduct, observations for on-site pre-screening, on-site adherence monitoring and on-site CT monitoring were comparable to the extent of remote conduct reporting of these activities per study phase. Other observations, however, differed as for on-site conduct of consenting and data collection only small distinctions in reporting between protocols from phase 2, 3 and 4 were found. Furthermore, on-site conduct of participant outreach was reported most often in phase 4 protocols (57.5% versus 38.8% in phase 2 and 45.8% in phase 3) whereas remote outreach was described most frequently in phase 2 protocols.

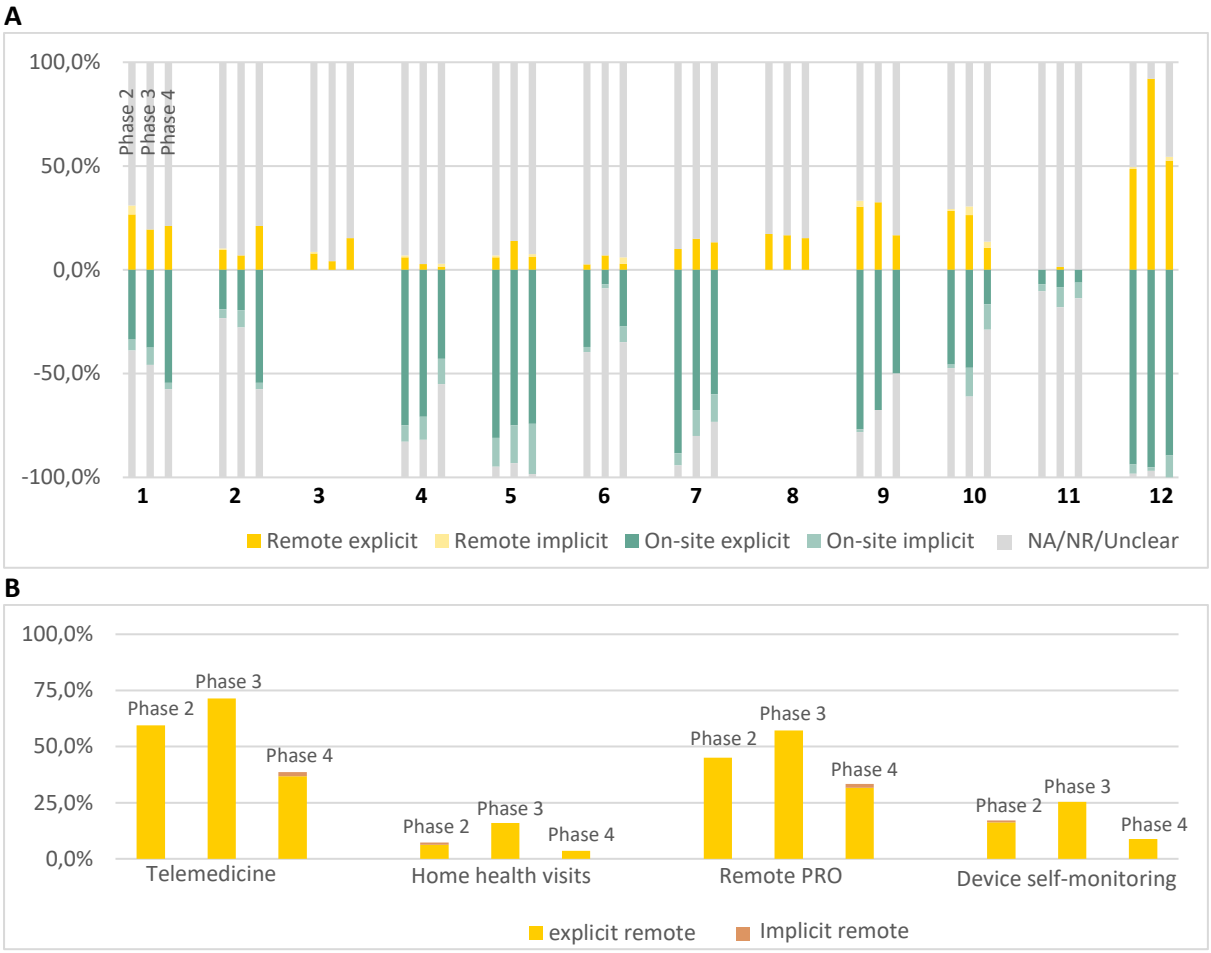

Figure 12. **A)** *Stratification of trial element conduct per study phase (per activity: left bar phase 2, middle bar phase 3, right bar phase 4).* ***1****, Participant outreach;* ***2****, Pre-screening;* ***3****, Medical record pre-screening;* ***4****, Screening;* ***5****, Consenting;* ***6****, Participant training;* ***7,*** *IMP supply;* ***8****, Asynchronous communication ;* ***9****, Adherence monitoring;* ***10****, CT monitoring;* ***11****, Staff training;* ***12,*** *Data collection.* **B)** *Distribution of remote data collection methods as reported in protocols per study phase (excluding hospitalized trials). Abbreviations: CT, clinical trial; IMP, investigational medicinal product, NA, not applicable; NR, not reported; PRO, participant-reported outcome.*

Like with the stratification per sponsor type, the stratification per study phase also shows a similar trend in the use of implicit versus explicit coding as found in the entire cohort of protocols: implicit coding is more frequently used for the indication of on-site trial activity conduct.

Upon sub-stratification of the effect of study phase per study start year (i.e., 2019 and 2020), a notable difference in conduct of pre-screening using medical records can be observed: 38.5% of phase 4 protocols from 2020 (n=13) report medical record screening compared to 7.4% of phase 2 protocols from 2020 (n=27) and 4.3% of phase 3 protocols (n=23). In contrast, smaller differences between phase 2 (n=89), 3 (n=49) and 4 (n=53) protocols from 2019 are observed (9.0%, 4.1%, and 9.4%, respectively).

Similarly, in protocols from 2020, adherence monitoring was reported more in phase 3 (63.6%) compared to phase 2 (38.5%) and phase 4 (7.7%), whereas protocols from 2019 show smaller differences between the phase 2, 3 and 4 (32.2%, 20.7%, and 20.8%, respectively). Trends in conduct of the other trial activities per phase for 2019 and 2020 were more comparable with the trends per phase as observed in Figure 12.A. Visualizations of the sub-stratification can be found in Appendix 12.

3.2 Qualitative interviews series

3.2.1 Interviewees and their experiences

After reaching out to 27 different parties, 21 responded and 16 agreed to participate in 12 online videoconference interviews (using WebEx and MS Teams), which were conducted between the 8th of September and the 5th of November 2021. Each interview lasted approximately 60 minutes and was conducted in either English (n=11) or Dutch (n=1), whichever had the preference of the interviewee. The Dutch transcript was only partly translated to English for quotation purposes. During the interviews, DtP IMP supply was discussed with industry sponsors (n=5), an academic sponsor (n=1), hospital pharmacists (n=2) and employees from courier services (n=8). N.B.: the hospital pharmacists in some trials may provide services for either public or private sponsors. Characteristics of the interviewees (n=16) are summarized in Table 6. Furthermore, their experiences with DtP conduct in Europe have been listed.

Table 6. *Overview of stakeholder groups that were included in the interview series and their experiences with direct-to-participant supply. Abbreviations: DtP, direct-to-participant; EU, European Union; US, United States.*

CHARACTERISTIC	SUB-GROUP	NUMBER OF INTERVIEWEES, N (%)
STAKEHOLDER GROUP	Industry sponsor	5 (32)
	Academic sponsor	1 (6)
	Hospital pharmacist	2 (12)
	Courier service	8 (50)
YEARS OF EXPERIENCE*	0-4 years	4 (25)
	5-10 years	5 (31)
	>10 years	7 (44)
TYPE OF DTP EXPERIENCE	Depot/central pharmacy-to-participant	
	• US experience	10 (63)
	• EU experience	7 (44)
	Site-to-participant	
	• US experience	11 (69)
	• EU experience	13 (81)
	DtP in combination with home nursing	
	• US experience	10 (63)
	• EU experience	8 (50)
	Local pharmacy-to-participant	
	• US experience	0 (0)
	• EU experience	2 (13)

** Experience with DtP in clinical trials based on what was shared by the interviewees during the interviews or by their work experience as shown on LinkedIn pages of interviewees.*

Based on what was shared by stakeholders in the qualitative interviews series, case study examples (n=5) of EU trials including DtP IMP supply have been collected. Table 7 presents an overview of characteristics of the obtained case studies. More detailed information about each of the examples can be found in Appendix 13.

Table 7. *Overview of characteristics of the during interviews collected case study examples of EU trials including DtP IMP supply. Abbreviations: DtP, direct-to-participant; IMP, investigational medicinal product; NR, not reported.*

Trial characteristic	Number of case examples (%)
Therapeutic area	
• Neoplasms	2 (40)
• Diseases of the skin	1 (20)

• Endocrine, nutritional or metabolic diseases	1 (20)
• NR	1 (20)
Cross-border trial	4 (80)
DtP IMP supply model[a]	
• Central pharmacy-to-participant	1 (20)
• Local pharmacy pick-up by participant	1 (20)
• Site-to-participant[b]	3 (60)
• Inclusion of home nursing[c]	2 (40)

[a] One of the case examples included two DtP models (site-to-participant and central pharmacy-to-participant): one was default, the other a back-up because of specific regulations in one of the participating countries: only the default model counted here.
[b] The DtP of one of the case examples was not explicitly mentioned, but implicitly assumed to be a site-to-participant model based on context of the interview.
[c] Home nursing inclusion refers to having a nurse present in the participants' home to aid with e.g. administration of IMP.

3.2.2 Identified themes

During the analysis of the interview data, four main themes emerged: the need for DtP approaches, experiences with different DtP models, determinants for DtP implementation, and stakeholders' perspectives on DtP conduct in the EU. An overview of the identified themes can be found in table 8. An overall coding tree including themes and subthemes can be found in Appendix 14. In the following sections each of the themes will be discussed. In the following sections, main findings per theme are presented. A complete overview of all during the interviews identified facilitators and barriers per theme can be found in Appendix 15.

Table 8. *Overview of the themes and sub-themes identified based on the conducted interviews. Abbreviations: CT, clinical trial; DtP, direct-to-participant.*

Theme	Sub-theme	Description
Need for DtP approaches	- COVID-19 impact on CT conduct - Participant-centricity	CT challenges DtP (potentially) addresses, which cause it to be implemented in CT designs
Considerations of different DtP models	- Site-to-participant model - Depot/central pharmacy-to-participant model - Local pharmacy-to-participant model - DtP with home nurses - Courier services' role in DtP	Considerations stakeholders have of each of the different DtP models based on their experiences in the EU, including their view on home nursing and the role of courier services in the different models
Determinants for DtP implementation	- Ideal CT setting for DtP - Operational aspects of DtP	Characteristics of CT settings suitable for DtP, and practicalities associated with its implementation
Reflection of stakeholders on DtP conduct in the EU	- Stakeholders' role and perception - Conservatism and risk-aversiveness - Hopes and future perspectives	Perception of stakeholders on their role in DtP conduct in Europe, as well as their perspective on and hopes for the future of DtP in CTs

3.2.2.1 Need for DtP approaches

When asked about reasons and drivers for the inclusion of DtP approaches, many of the interviewees referred to the COVID-19 pandemic impacting clinical trial conduct as it caused a need for DCTs,

providing stakeholders with the opportunity to explore different DtP IMP supply models. In the words of one of the respondents:

> *"The situation that the COVID pandemic put us in has kind of forced us –in a good way- to re-evaluate the way we run conductance for clinical studies. Thinking about the patients, thinking about our sites. How can we make it easier for them, better for them, more convenient for them to participate in one of our clinical studies?"* (Interview 2, industry sponsor)

Even though some DtP IMP supply was already conducted prior to the COVID-19 pandemic, the majority of interviewed stakeholders mentioned that the pandemic was the main driver for more DtP implementation in clinical trials. One interviewee reported how this was a matter of costs for sponsors, complementing the established desire to lower costs of CTs:

> *"Patient visits to a mortar and brick site are so extremely expensive that the capability to have something sent to the patient at home [during COVID-19] is just aligned with the rest of where the pharma industry is going."* (Interview 1, industry sponsor)

Apart from costs, multiple stakeholders also mentioned how they started to think more about patients and how to make trial participation more convenient for them. This is in line with a general trend towards patient-centricity within the field of clinical trials as stated by the majority of interviewees. For example, one respondent mentioned the following:

> *"There has been a lot of focus in recent years on patient-centricity in clinical trials. Previously, sites preferred a medical model, where the patient attends the sites for every visit. That is not patient friendly, especially for studies that are long and that require frequent visits, in those cases it is an encumbrance on the patients. Sponsors now are much more attuned to, you know, the voice of the patient, and what patients prefer or do not prefer."* (Interview 1, industry sponsor)

Moreover, several stakeholders acknowledged that DtP is not a solution for all participants as, for example, some will struggle when having to deal with thermal packaging or when using smart devices at home. Therefore they stressed the need for optionality in trial designs when it comes to DtP and on-site trial conduct.

Apart from incorporation of the participant's voice, several other advantages of a participant-centric approach were presented during the interview series. Primarily, it will lower the burden for participants, which in turn could improve recruitment and retention. Furthermore, an interviewee shared how it aids the acquisition of more diverse participant populations

3.2.2.2 Considerations of and experiences with different DtP models

As shown in Figure 2, several models for DtP conduct exist: site-to-participant, depot-to-participant, central pharmacy-to-participant, local pharmacy-to-participant. Furthermore, for each of these models there is the option to include home nursing, where a nurse is present in the participants' home to aid with, amongst others, IMP administration. When asked about EU experiences with the different DtP models, the majority of stakeholders shared during the interviews how they consider the site-to-participant model relatively easy to implement:

> *"I would say that the site-to-patient paradigm thus far has been OK. I mean, you can almost think of it as the extended arm of a study nurse. There is no change in any of the processes, and therefore there is truly little or no barriers really"* (Interview 1, industry sponsor)

Other DtP models, however, do have their interest, as shared by one interviewee:

> *"The best [DtP model] would be the depot-to-patient, because that would give us the most possibilities with the drug as we would not have to send it to the site. But there are challenges (…) especially with the regulatory piece of it."* (Interview 2, industry sponsor)

In terms of challenges associated with the depot-to-participant model, several of the stakeholders described how in Europe it requires a central pharmacy to be used, whereas in the US this is not the case:

> *"In the US we are shipping from our depot, so both models exist: central pharmacy to patient or depot to patient. In Europe the regulation is clear that a central pharmacy is required, so we work with a central pharmacy in Germany and ship to various patients in Europe."* (Interview 13, courier service)

Notably, an interviewee shared how some courier service companies' depots have a pharmacist present, thereby making shipments from that location to participants' homes possible, as the depot can then be considered a central pharmacy. As reported by the courier service representative:

> *"We have a global network of 23/25 depots for clinical trials, for IMP. Some of them (…) would have a pharmacist present (…). Not in all countries is there a pharmacist present in the depot, so if that is a country with the requirement of a pharmacist present to release the IMP product, we run into certain regulatory and legal issues."* (Interview 6, courier service)

Furthermore, several interviewees shared how a central European pharmacy is only able to ship from cross-border from one EU-country to another; shipments to countries outside of EU are not possible. In the words of a courier service representative:

> *"Outside of the EU you really require an in-country pharmacy, so for example in the UK, you need to have a UK-based pharmacy to be able to provide IMP or comparator directly to the patient."*(Interview 10, courier service)

In terms of the local pharmacy-to-participant model, only one interviewee reported a case study in which this DtP model was used. It concerned an already marketed antibiotic drug, and took place in the Netherlands only. The COVID-19 pandemic was the sole reason for the using DtP IMP supply in this study, and the interviewee shared how after some pandemic restrictions were lifted, the supply returned to a traditional, on-site model.

When it comes to experiences with home nursing in the EU, the interviewed stakeholders are divided, with some of them having experience with it and other did not. The interviewees with home nursing experience stressed the logistical challenges that arise when implementing home nursing services within a DtP model, stating:

> *"If you are adding nursing visits on top, where a nurse is already there waiting to start the infusion for example, and you get an [temperature] excursion there, then it gets even more complicated."* (Interview 13, courier service)

Additionally, it was mentioned by a stakeholder that home nursing is not ideal for any trial, and that instead it should be considered as an optional concept depending on participant's preferences. According to the stakeholder, this flexibility can be hard for mobile nursing companies, as it complicates their staffing and budgeting. But even without implementing home nursing, using courier services for DtP deliveries results in added challenges for trials compared to using postal shipments. A pharmacist described this as follows:

> *"It is incredibly expensive to use a courier, there is a great increase in costs compared to posting something through a mailbox. Ringing someone's doorbell and asking them to sign for a parcel is a lot more expensive."* (Interview 5, hospital pharmacist)

Several interviewed courier service representatives described the role of couriers as consulting towards sponsors in regards to DtP options:

> *"We would not be involved to set it [DtP IMP supply] up, but we would let them know what we need from a courier's perspective, so at what time do we need the address, or what type of information do we need, how far in advance do we need to receive it, what is the best way to get access to this information, what is the safest way for us to provide input"* (Interview 13, courier service)

Furthermore, couriers shared how they have a lot of logistical expertise that might be of great value for future DtP implementations. One of them mentioned, for instance, how their in-house technology and procedures could easily be transferred to aid coordination of IMP arrival at a participant's home, making the CT industry benefit from their existing work flows. Moreover, several stakeholders shared that using a courier for IMP deliveries at the participants home allows for more control during the shipment -e.g. through temperature monitoring- compared to when participants come to sites to pick up drug and bring it to their homes themselves. This was therefore presented as an argument pro the use of DtP models.

3.2.2.3 Determinants for DtP implementation

When talking about factors to determine whether and how DtP could be implemented, stakeholders first of all discussed characteristics of the ideal DtP setting, thereafter they went into several operational aspects that should be considered when implementing DtP.

In terms of the ideal DtP setting, stakeholders mentioned that clinical trial characteristics such as the therapeutic aim as well as geographical location of the target population are important to consider when deciding whether a DtP model could be implemented. In addition, trial phase has an influence, as several stakeholders acknowledged how late-phase studies allow for DtP models more easily than early-phase studies as more safety data is already available. The type of measurements that ought to be conducted during study visits should also be considered, as an interviewee stated that, for instance, MRI or CT scans require on-site presence, meaning that IMP might as well be provided on-site too. Furthermore, the type of study population is mentioned to have an influence as DtP is said to be easier if, for example, participants are adults that are able to take care of themselves compared to paediatric trials. As put by one of the respondents:

> *"If you have adult patients who are entirely responsible for their own health and care, then that is easier than patients who are dependent on others. But that does not mean that it is impossible, and I know that people have been using remote methods in paediatric trials or in trials with people who are unable to travel to sites because of their health conditions. I think it is a model that probably should be considered in any therapeutic area, and until you can find a reason not to do it, I think it is worth considering, because there are advantages to the participant."* (Interview 3, academic sponsor)

Apart from CT characteristics that need to be considered, multiple stakeholders mentioned that the type of IMP also plays a role when deciding to implement DtP. Stated by one interviewee:

> *"There is a lot that goes into making that decision. One of them is the type of IMP for the study. Does it need to be prepared? That carries a risk, we would take that off the table. If an IMP has*

short stability, if it must be kept at certain temperatures, that might preclude DtP, at least today, from being used. We do not want to add too many risks into an evolving process." (Interview 2, industry sponsor)

Many of the stakeholders stated that the current scope of their DtP solution tends to be limited to products that can be self-administrated, such as tablets and sometimes sub-cutaneous (s.c.) injections. Only a few of them have experience with intravenous (i.v.) injections being conducted in an at-home setting, but this would require a home nurse to aid the administration. One illustrative European case study was presented concerning a monoclonal antibody therapy trial (phase 2 and 3) for which participants with the help of home nurses received continuous i.v. infusions of IMP at their home.

When it comes to operational aspects of DtP implementation, several of the stakeholders stated that regulatory guidance for DtP implementation only came about through specific COVID-19 regulations and pandemic related flexibilities. One stakeholder put it as follows:

"With COVID-19 guidance to deal with the situation, this was the first time that many countries (e.g., FDA, AMA, Japan, China) issued guidance mentioning direct-to-participant, explaining how it could be managed to treat a patient at home. This was the first time that we really saw guidance and that this possibility was mentioned in guidance and regulations." (Interview 7, courier service)

Other stakeholders confirmed this view and stated that dialogue between stakeholders and regulators has now been created, for example through the TransCelerate initiative.

Interviewees stressed the need for sponsors and couriers to assure data privacy and confidentiality for participants. Doing so in Europe could require stakeholders to provide country-specific solutions as regulations differ:

"Data privacy is a big topic. Sometimes you have –on top of the GDPR- in European countries specific regulations like in France that are clearly saying, for example, that a driver must, or we must not know the protocol number of a trial, because we could go into Google and just find out which treatment this patient is receiving, and we are not allowed to know that. Our only purpose is to deliver something to a patient, we should not know which treatment, which trial, unless we are involved in home nursing, but not for pure DtP." (Interview 13, courier service)

When comparing European regulations with United States' (US) regulations, it was stated that:

"It is easier in the US than in Europe to include DtP as the regulation is different in the US: more things are allowed; it is less complicated. That is why in general the US is the first country where we started studies in which new models are implemented, because the registration is different and less complicated." (Interview 9, industry sponsor)

Additionally, stakeholders stated the importance of privacy, for instance by stressing the need to assure that vendors throughout the entire chain of custody comply with data privacy regulations, and that the informed consent form (ICF) should properly inform participant about how DtP will be carried out. Furthermore, some of the interviewees elaborated how they have encountered the use of IRT systems to ensure data privacy by providing limited access. It was also mentioned that thorough staff training -specifically courier driver training- is important:

"We ensure that the driver is trained in patient confidentiality, that they are trained in following specific processes, that they never enter a patient's home, that they are not allowed

to talk to the patient about their disease, that they will not touch the product, […] to ensure patient safety" (Interview 13, courier service)

Apart from regulatory aspects, internal organizational considerations where also presented during the interviews as determinants for DtP implementation. Stakeholders referred to standard operating procedures (SOPs) and how they often were not yet in place for DtP prior to the COVID-19 pandemic, meaning that companies had to swiftly create them. Furthermore, interviewees mentioned the need for companies to adapt to changes in the regulatory landscape, which brings about high costs, as one respondent stated:

"We interpret the regulatory in the strictest way possible. So, if they recommend something, we do it. If they say we have to assess, we assess. If they say record, we basically record it in stone. You can imagine the cost of this." (Interview 1, industry sponsor)

A private sponsor stated that having flexibility in the design of a trial is a convenient way of dealing with differences between country-specific regulations:

"We are doing that assessment up front, but building in flexibility as my colleague said. We have and situations where we were hoping that we could do some sort of home health model in a country and we found out that the regulations did not allow it, so we used a traditional model in that country. No hard, no foul, just because that option was already in the plan." (Interview 2, industry sponsor)

An European case study example was shared in which this flexibility in terms of DtP model implementation is illustrated: it concerns a phase 4 Gout trial with a central pharmacy in the UK shipping oral tablets of IMP to participants in the UK and in Denmark, but with a local pharmacy in Sweden to ship IMP to Swedish participants as regulations did not allow the UK central pharmacy to ship drug to those participants.

Another mentioned aspect to consider when implementing DtP is how to deal with adherence and drug accountability checks. The interviewed pharmacists stated that this is not part of their responsibilities, but that this falls under the obligations of the investigator staff. A clinical service provider described how adherence could be checked in a DtP model, for example through pill counts by mobile clinicians, or through the use of patient-facing technology.

3.2.2.4 Reflection of stakeholders on DtP conduct in the EU

The perception of a few other parties involved with DtP conduct was discussed during the interviews. When it comes to health care providers (HCPs) and investigator staff, some interviewees mentioned that remaining oversight during DtP conduct is paramount for them, as one respondent indicated:

"I think that you might see that physicians are concerned about delegating authority on the use of an IMP to someone that they do not know, even if it is a trained mobile nurse from a well-respected mobile nursing company. They may prefer to have someone from their own staff go and administer that in the patient's home." (Interview 8, courier service)

Moreover, in regards to the site-to-participant model, it was suggested that this could introduce additional burden for investigator staff:

"What we are also seeing is that when we have the clinical site with the responsibility of organizing shipments, booking shipments, sending over data, quite often these sites make complaints that they are overloaded […] and said that they did not want to continue with DtP

because it was too much workload for them, so they went back to the traditional model." (Interview 7, courier service)

Others, however, described that investigator staff is starting to realize that they must accept DtP as a more default model in trial designs. This is in line with what participant's feedback has been according to one of the interviewed private sponsors. An important side note is that stakeholders should always evaluate whether DtP fits the patient's needs, as sometimes they might not be interested in it:

"Most patients are saying, yeah, it is great that I can limit my visits, and if I live 3 hours from the site, I do not have to drive all that way and wait all day just to pick up a drug and drive back home, but I still want a little personal touch, so I would like to be able and go into the doctor's office every once in a while as part of this trial." (Interview 12, industry sponsor)

When it comes to the perception of pharmacists, one the interviewees mentioned how they were concerned that within the depot-to-participant model there will not be good information provision services in place for participants. Nonetheless, pharmacists also pointed out how they believe DtP will be the delivery model of the future. Other future perspectives and hopes presented by the interviewed stakeholders included the wish for proper regulatory DtP guidance, the need for inclusion of vendors early on in the design process of CTs, and the pressing notion that DtP should be considered for the majority of trials but that it will not be suitable for all of them. Overall all respondents stated that DtP will become more common within the world of clinical trials. One respondent indicated for example:

"I think it will be more and more requested, it will become a standard model for maybe trials where patients can self-administer the drugs. And we will also stay in and increase home health care, and this is based on the further development of additional technologies like types of devices that really allow communication virtually. We just think that DtP makes trial participation more convenient for the patients, and that is something that they can support in their private life." (Interview 13, courier service)

4. Discussion

4.1 Quantification of remote methods

This study aimed to quantify the extent in which remote elements have been reported in a specific cohort of study protocols. When interpreting the overall results, it is noticeable that several trial activities (e.g., staff training, pre-screening, participant training and CT monitoring) were only reported in a small percentage of the included protocols, regardless of it being described as remote or on-site. These findings suggest that, even though guidelines for Good Clinical Practice (GCP) by the International Conference of Harmonization (ICH) describing minimal requirements for study protocol content exist (32), insufficient information provision of trial activities is still common in protocols. This issue has also been addressed in literature, and makes it hard to determine whether investigators adequately handled trial conduct (33). In addition, the unclear description of trial activity conduct served as a reason for the use of implicit coding in this study: in case a mandatory trial activity was not clearly described in a protocol, it could sometimes be coded for in an implicit manner. For the majority of cases where we used implicit coding, it was used for on-site trial activity conduct. The fact that remote conduct of trial activities -particularly trial activities other than data collection- is relatively new in the field of CTs might explain this difference in use of implicit coding between on-site and remote conduct (34).

Moreover, it can be argued that the novelty of remote methods also translates in the general observation that only a small fraction of the included protocols reported remote conduct of any of the predefined trial activities. It is important to take into consideration that remote and on-site conduct are not mutually exclusive, and that the results show that most of the protocols reporting remote conduct of a specific activity also describe on-site conduct of that same activity. Data collection is a good example of this, with 67% of the included trials describing both on-site and remote data collection. This finding aligns with the emerging trend in CTs towards participant-centricity, where CT designs move away from on-site models by default and instead adjust to specific needs of participants (22)(4).

Focussing on remote conduct findings specifically, remote data collection was most often reported in the included protocols. In particular, telemedicine and remote patient-reported outcomes (PROs) were most frequently described. This is in line with what was hypothesized in this study, and could be explained by an in literature described continued interest in the use of telehealth solutions (e.g. telephone contact, mobile applications, videoconferencing) in health care (35). Furthermore, literature shows that amongst stakeholders there is an increased interest in application of telemedicine solutions for trial activities other than data collection, for example consenting, but recognizes a need for further research and development of these telemedicine opportunities (36). This might explain why a shift towards remoteness through the use of telemedicine in activities other than data collection has not widely been observed in the protocols included in this study.

When comparing findings from 2019 and 2020, results are in line with what was expected, i.e. protocols from 2020 describe more remote methods, and these results are comparable with observed differences between pre- and during-COVID protocols. The extent of the observed differences, however, was smaller than expected. No clear explanation to this can be found in the literature, but this could be explained by the fact that the majority of 2020 trials was COVID-related and took place in a hospital setting, reducing the opportunity to include remoteness.

Additionally, the hypothesis that private sponsors would include the most remote methods in their protocols only holds for data collection and CT monitoring. For the other trial activities, publicly sponsored trials reported -albeit marginally- remote methods more frequently, or differences between the two sponsor types were small. On top of that, on-site conduct of trial activities was less coded for in publicly sponsored protocols compared to privately sponsored protocols, meaning that relatively speaking there was also more remoteness reported in protocols with public sponsors. This observation could be related to a risk-aversive attitude of private sponsors (37), making them reluctant to include remote activities in their trial protocols.

In terms of the effect of trial phase, it was hypothesized that phase 4 trial protocols would report the most remote conduct of trial activities as more data on safety and efficacy is available at that stage of drug development. The results, however, revealed that this only holds for remote pre-screening (either with active participation by trial subjects or via medical records). With the exception of remote data collection -which was reported in 92,1% of phase 3 trials compared to only 48,6% in phase 2 and 52,5% in phase 4-, no large differences in reporting of the other predefined trial activities were observed. The rejection of the phase-related hypothesis could be due to the fact that trials from the included phases (i.e., 2, 3, 4) all take place after phase 1 trials, in which crucial safety data is collected (16). As was shared by stakeholders during the interview series, availability of safety data obtained in phase 1 can for them be a determinant for implementation of remote activities, which could explain why little differences between the phases later on in drug development are found. Interestingly, however, it could also be argued how remote activities can also be implemented in phase 1 trials under certain conditions, for instance through using telemedicine solutions during follow-up, as was shared by other stakeholders.

4.2 Qualitative interview series

When asking stakeholders about DtP IMP supply conduct, interviewees reported limited experiences with DtP IMP supply in Europe, and in contrast, US experiences were more frequently described. This is in line with what was hypothesized, and in accordance with observations from literature of more CT innovation initiation (e.g. through the use of digital tools for data collection) in the US compared to Europe (20). In the interviews, stakeholders mentioned unharmonized regulations and lack of guidance as main causes of this difference.

Concerning different DtP models, interviewees stated that the site-to-participant model is easiest to implement as -in contrast to the depot-to-participant model- it requires limited changes in protocol. Interestingly, very few stakeholders were able to provide specific case study examples of this model in Europe, nor can case studies be identified from existing literature. Therefore, little evidence to validate the statement for EU trial conduct was collected.

Furthermore, throughout the interviews series, it became apparent that stakeholders may refer to different DtP models when talking about their DtP experiences, stressing the need to properly define which model is talked about. Specifically, when discussing the depot-to-participant model, stakeholders shared that in Europe this 'depot' refers to a central pharmacy, as regulations prohibit shipments without the involvement of a pharmacy. An example of this is in guidance provided by the European Medicines Agency (EMA) for CT during COVID-19 as they -when referring to DtP solutions in CTs- stated: *"The delivery should be done from trial sites (hospital pharmacies as applicable) to trial participants"* (15). In contrast, some of the interviewees shared how in the US a depot may refer to a location without a pharmacy license that is able to ship IMP to participants, as their regulations do allow those shipments. This is a valuable insight, as it discloses the need for stakeholders to be meticulous with wording, or perhaps may serve as incentive to adjust DtP jargon.

In terms of facilitators and barriers, stakeholders presented the COVID-19 pandemic as one of the main causes for increased implementation of DtP solutions in CTs. This comes as no surprise, given social distancing regulations (38). On top of that, a few of the stakeholders deemed CT and IMP characteristics of influence when determining whether or not to implement DtP. They mentioned, for example, how they prefer to implement DtP in late-phase trials because of more safety data being available already, which is in line with what was hypothesized. In contrast, however, the majority of interviewees emphasized that ideally all trials should individually be assessed on all their aspects to decide if DtP can be included, regardless of CT and IMP characteristics, because there is no 'default' type of study for which DtP solutions are best suited. This personalized approach per trial can be seen as another argument towards flexibility in study designs, which in return creates the opportunity to consider including a participant-centric vision, for which the need has also been underlined by several stakeholders.

Where some stakeholders described how site staff might be reluctant to implement DtP -as it creates additional burden for them in terms of trying to remain oversight-, the majority of interviewees, highlighted that stakeholders are prone to further explore the opportunities DtP has to offer. Specifically, courier service representatives emphasized how couriers have experiences from other complex deliveries outside of the field of clinical logistics (e.g. dangerous chemicals), that might benefit the development of DtP in the clinical setting, thereby pointing out a desire to share experiences amongst stakeholders. Luckily, several platforms for stakeholders to learn from each other and for research into DtP (and other remote trial elements) have already been established, for instance the TransCelerate Initiative (39) and the Clinical Trials Transformation Initiative (20). Nonetheless, multiple stakeholders agreed on the relevance of additional research, for example like the pilot study that the Trials@Home consortium is planning, comparing an on-site, a flexible, and a fully remote study arm (40). This could create incentive for future research into DtP supply options in CTs, and emphasizes the relevance of the current study.

4.3 Strengths and limitations

One of the main strengths of this research is how manual coding was used to allow for holistic data capture, whilst -through the use of constant peer-review- assuring validation of collected data. Specifically, the coding matrix was created based on expert meetings and continuous feedback sessions, and was adjusted during the coding process to best fit the aim of this research. These efforts resulted in the acquisition of a large dataset, allowing for many insightful analyses.

Furthermore, by adding an interview series in this study, gained observations were deepened with qualitative insights. By including interviewees from several different stakeholder groups, the interviews allowed for the collection of a diverse set of perspectives on DtP IMP supply.

However, the methodology of this study had some limitations. Despite the Food and Drug Administration Amendment Act of 2007 requiring all interventional clinical trials of which the studied product is to be approved, licenced, or cleared by the FDA to be publicly available on ClinicalTrials.gov (41)(42)(43), the chosen database was limiting as only a small number of study protocols (n=254) was available from all registered interventional phase 2, 3 and 4 trials from 2019 and 2020 (n=14.254). This low public availability of protocols was also described by Lucey et al. in 2017 (44), and results in the possibility of collected study data not representing trial activity conduct for the majority of trials registered at ClinicalTrials.gov.

Another limitation of this study is the finding that -in general- several trial activities were not frequently described in CT protocols, as this lack of information availability in protocols could have resulted in distorted data interpretation.

When it comes to the coding of remote and on-site conduct of predefined trial activities, the use of implicit coding results in less robust data collection as -despite thorough peer-reviewing- the risk for bias increases when applying coding rules created by the researchers during the protocol coding process.

In terms of interview conduct, only limited details about case studies in Europe were obtained as stakeholders did not readily have this information available. For this reason, only a small selection of illustrative case study examples for the different themes was collected.

Moreover, difficulties were encountered when reaching out to stakeholders to include in the interviews series. This resulted in an uneven representation of the different stakeholder groups in the final selection of interviewees, meaning that not all perspectives were equally represented, and thereby potentially affecting saturation of the themes (e.g. perspectives of stakeholders on their roles in DtP not equally represented).

The interviews did, however, elucidate which DtP models are used in Europe, and provide insights into facilitators and barriers that stakeholders encountered, which makes them a valuable addition to this study.

4.4 Outlook

Future research could focus on investigating the extent in which CT protocols are readily available in public databases, as in this study the availability was found to be limited. Furthermore, it could be valuable to determine whether trial activities that were infrequently reported in the protocols included in this study, are also underreported in larger datasets. Doing so may provide insights for guidance on writing CT protocols.

Furthermore, because the data collection phase was quite extensive in this study, multiple additional analyses using the created dataset could be conducted. For instance, assessing the impact of trial characteristics other than study phase, year and sponsor type on the inclusion of remote methods in protocols. In this regard, the amount and nature of study visits could also be accounted for.

When it comes to future research into DtP IMP supply, a systematic review of study protocols or literature to collect EU case study examples might be valuable to compliment findings from this interview series. Moreover, obtaining insights from additional stakeholder groups -such as participants, regulators or ethics committees- might be an insightful way to learn what they consider to be pain points for implementation of DtP models in trials.

Finally, apart from gaining additional insights into stakeholders' perspectives on DtP models, learning about their perception of the other remote methods that were quantified is also a valuable new research topic. The quantification of this study showed that most of the trial activities have only limitedly been reported in a remote manner. Therefore, it can be insightful for the design of future trials to learn -for instance through more qualitative research- reasons for this limited inclusion of remoteness in trial designs.

5. Conclusion

Overall, remoteness of the majority of the predefined trial activities was found to be described in the cohort of protocols, albeit infrequently. Specifically, remote data collection through telemedicine visits or PROs was most often reported. Public sponsors marginally reported more remote methods in their protocols compared to private sponsors. Furthermore, the results show an increase in remote method inclusion during the COVID-19 pandemic, a trend that was also described by CT stakeholders during the qualitative interview series. Amongst others, stakeholders described lack of (harmonized) regulations as barrier, and IMP characteristics like self-administrability as facilitator for DtP conduct in the EU. A central pharmacy-to-participant model was found to be more suitable in the EU compared to the depot-to-participant model, as European regulations typically require a pharmacist dispensing the IMP. Respondents stated that flexibility -in terms of whether and how DtP is implemented- in trial designs is favourable, and that they are open to explore possibilities for DtP inclusion on a case-by-case basis, as DtP is believed to become a more default option in future trial designs.

In conclusion, this research shows that remote methods have been reported in publicly available phase 2, 3 and 4 protocols from 2019 and 2020, and that stakeholders are positive towards additional exploration of the opportunities of including remote methods such as DtP IMP supply in (European) trial designs.

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8. Appendices

Appendix 1: Glossary

Term	Definition	Source
Active comparator	An investigational or marketed medicinal product used as a reference in a Clinical Trial	EMA
Administration by participant	Participants administrates medicine themselves without help or intervention by researcher(s) or medical practitioner	Current study
All countries involved	All countries listed where trial sites are present.	Current study
ATC code	WHO ATC-DDD code used to indicate specific drug/medicine/active comparator	Current study
Blinding	A clinical trial design strategy in which one or more parties involved in the trial, such as the investigator or participants, do not know which participants have been assigned which interventions. Types of masking include: open label, single blind masking, and double-blind masking. Double-blind masking also includes higher levels of blinding such as triple blinding.	ClinicalTrials.gov
Data Safety Monitoring Committee (DSMC)	A group of experts external to a study that reviews accumulating data from an ongoing clinical trial	EMA
Drug (medicinal product)	A substance or combination of substances that is intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action	EMA
Electronic case report form (eCRF)	An electronic document designed to record information to be reported to the sponsor on each trial subject created via laptop/desktop, mobile device based programs or web based tools (e.g. REDcap), which may contain source data directly entered, transcribed data by rekeying from other sources, or both	EMA
Female participants	Participants of the female sex based on biological characteristics are included in the trial	Current study
Healthy participants	All participants included in the study are healthy volunteers	Current study
Hospitalized trial	Trial for which the entire data collection phase takes place whilst participants are hospitalized	Current study
Investigational medicinal product	Pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form	EMA
Male participants	Participants of the male sex based on biological characteristics are included in the trial	Current study
Maximum participation duration	Maximum total length of time (in days) that a subject is expected to participate in the trial [benchmark: 1 year = 365 days, so 1 month is 365/12 days. 1 week = 7 days]	Current study
Nasal administration	Administration via the nose (e.g. nose spray)	Current study
Number of trial visits	Total number of trial visits that are conducted by participants, these can be on-site, home health visits or can be conducted through electronic means (e.g. telemedicine)	Current study
Oral administration	Administration via the mouth (e.g. pill, liquid, vapor inhalation)	Current study

Other route of administration	Drug administration routes applied in studies that cannot be categorized as oral, nasal, sublingual, topical or parenteral according the definitions used in this study (e.g. radiotherapy)	Current study
Parenteral administration	Administration via injection, which refers to intradermal (i.d.), intramuscular (i.m.), intravenous (i.v.), intraperitoneal (i.p.) or another type of injection (e.g. intravesical, intrafilamentary, intravitreal, perineural)	Current study
Paediatric clinical trial	All participants included in the study are younger than or exactly 18 years old	Current study
Phase 2	A phase of research to describe clinical trials that gather preliminary data on whether a drug works in people who have a certain condition/disease (that is, the drug's effectiveness). For example, participants receiving the drug may be compared to similar participants receiving a different treatment, usually an inactive substance (called a placebo) or a different drug. Safety continues to be evaluated, and short-term adverse events are studied.	ClinicalTrials.gov
Phase 3	A phase of research to describe clinical trials that gather more information about a drug's safety and effectiveness by studying different populations and different dosages and by using the drug in combination with other drugs. These studies typically involve more participants.	ClinicalTrials.gov
Phase 4	A phase of research to describe clinical trials occurring after FDA has approved a drug for marketing. They include post-market requirement and commitment studies that are required of or agreed to by the study sponsor. These trials gather additional information about a drug's safety, efficacy, or optimal use.	ClinicalTrials.gov
Placebo (active)	A control product that does not have a therapeutic effect on the condition being treated, but that may (in case of an active placebo) produce side effects similar to those caused by the substance whose effectiveness is being tested	Current study
Planned (maximum) number of sites	Maximum number of clinical sites where study activities are performed	Current study
Pre-COVID study	In case the by ClinicalTrials.gov presented study start date lies before the 11th of March 2020, the trial will be considered as pre-COVID. Studies initiated on or after this date are considered during-COVID	Current study
Primary endpoint	The outcome variable(s) of interest in the trial. Differences between groups in the outcome variable(s) are believed to be the result of the differing interventions.	CDISC
Primary objective	The primary objective(s) is the main question to be answered and drives any statistical planning for the trial (e.g. calculation of the sample size to provide the appropriate power for statistical testing)	CDISC
Private sponsor(s) only	An private individual, company, institution, or organization that takes responsibility for the initiation and management of a clinical trial, although may or may not be the main funding organization	CDISC
Public sponsor(s) only	An public institution, or organization that takes responsibility for the initiation and management of a clinical trial, although may or may not be the main funding organization	CDISC
Randomization	The process of assignment of the subjects to groups (treatment or control) in a clinical trial	Trials@Home
Rectal administration	Administration via the anus	Current study

Region(s) included	Regions as presented by Clinicaltrials.gov of which countries are included in execution of the trial. The regions are as follows: Africa, Central America, East Asia, Europe, Middle East, North America, North Asia, Pacifica, South America, South Asia, Southeast Asia. A list of which countries are part of each of these regions can be found in a table below this glossary.	ClinicalTrials.gov
Secondary endpoints	These are outcome variables other than the primary endpoint. Data on secondary endpoint are used to evaluate effects of the intervention.	CIDSC
Secondary objectives	Secondary objectives are goals of a trial that will provide further information to support the primary objective	CDISC
Study completion date (estimated)	(Estimated) date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and adverse events (that is, the last participant's last visit).	ClinicalTrials.gov
Study start date	The actual date on which the first patient was enrolled in the clinical study	ClinicalTrials.gov
Study visit	Study visits are defined as remote or on-site study related (follow-up) visits during which study related data is obtained. Therefore, visits should not be understood as data collection points. As an example, if a clinical trial is conducted with hospitalized participants and all data is collected during the hospitalized period, this is classified as 1 'visit'. However, if an additional follow-up visit is required, this is classified as 2 study visits, as participants have to travel to the site twice. If data is obtained during a telemedicine visit, this will also contribute to the total number of study visits.	Current study
Subject maximum age	Maximum age of subjects (in years), which should align with specific inclusion/exclusion criteria as applicable. In case no age limited is presented in the protocol, this is presented as ‘no maximum’.	Current study
Subject minimum age	Minimum age of subjects (in years), which should align with specific inclusion/exclusion criteria as applicable	Current study
Sublingual administration	Administration through placement under the tongue	Current study
Topical administration	Administration through application to specific part of the body (e.g. skin surface, eye drops)	Current study
Total (maximum) number of (planned) participants	(Estimated) total (maximum) amount of subjects (to be) consented for study participation (in case several trial phases are included in one study: total amount of participants taking part of all these phases presented here)	Current study

Appendix 2: List of disease area classes adapted from WHO ICD-11

Therapeutic area	**Elaboration according to WHO ICD-11**
Blood and blood forming organs diseases	NA
Codes for special purposes	NA
Conditions originating in the perinatal period	This chapter includes conditions that have their origin in the perinatal period even though death or morbidity occurs later
Developmental anomalies	This chapter includes conditions caused by failure of a particular body site or body system to develop correctly during the antenatal period
Diseases of the circulatory system	This refers to diseases of the organ system that passes nutrients (such as amino acids, electrolytes and lymph), gases, hormones, blood cells, etc. to and from cells in the body to help fight diseases, stabilize body temperature and pH, and to maintain homeostasis
Diseases of the digestive system	NA
Diseases of the ear or mastoid process	NA
Diseases of the genitourinary system	Any disease characterised by pathological changes to the genitourinary system
Diseases of the immune system	NA
Diseases of the musculoskeletal system or connective tissue	NA
Diseases of the nervous system	Conditions characterised as being in or associated with the nervous system
Diseases of the respiratory system	NA
Diseases of the skin	Diseases of the skin incorporate conditions affecting the epidermis, its appendages (hair, hair follicle, sebaceous glands, apocrine sweat gland apparatus, eccrine sweat gland apparatus and nails) and associated mucous membranes (conjunctival, oral and genital), the dermis, the cutaneous vasculature and the subcutaneous tissue (subcutis)
Diseases of the visual system	This refers to any diseases of the visual system, which includes the eyes and adnexa, the visual pathways and brain areas, which initiate and control visual perception and visually guided behaviour
Endocrine, nutritional or metabolic diseases	NA
Extension codes	NA
Factors influencing health status or contact with health services	NA
Infectious and parasitic diseases	Includes certain conditions caused by pathogenic organisms or microorganisms, such as bacteria, viruses, parasites or fungi
Injury, poisoning or other consequences of external causes	In the ICD, injury means physical or physiological bodily harm resulting from interaction of the body with energy (mechanical, thermal, electrical, chemical or radiant, or due to extreme pressure) in an amount, or at a rate of transfer, that exceeds physical or physiological tolerance. Injury can also result from lack of vital elements, such as oxygen. Poisoning by and toxic effects of substances are included, as is damage of or due to implanted devices. Maltreatment syndromes are included even if physical or physiological bodily harm has not been reported. Otherwise, psychological effects are not included (e.g. injured feelings).
Mental, behavioural or neurodevelopmental disorders	Mental, behavioural and neurodevelopmental disorders are syndromes characterised by clinically significant disturbance in an individual's cognition, emotional regulation, or behaviour that reflects a dysfunction in the psychological, biological, or developmental processes that underlie mental and behavioural functioning. These disturbances are usually

	associated with distress or impairment in personal, family, social, educational, occupational, or other important areas of functioning.
Neoplasms	An abnormal or uncontrolled cellular proliferation which is not coordinated with an organism's requirements for normal tissue growth, replacement or repair
Pregnancy, childbirth or the puerperium	A group of conditions characterized as occurring during the period of time from conception to delivery (pregnancy), during labour and delivery (childbirth) or during the approximately six weeks after delivery during which the uterus returns to the original size (puerperium)
Symptoms, signs or clinical findings, not elsewhere classified	Diseases can manifest in many ways and in different body systems. Such specific manifestations may be a reason for treatment or encounter, with or without identifying or addressing the underlying condition. Categories in this chapter include the less well-defined conditions and symptoms that, without the necessary study of the case to establish a final diagnosis, could be designated 'not otherwise specified', 'unknown aetiology' or 'transient'. Clinical findings include those found using physical, laboratory and imaging techniques.

Appendix 3: Geographical regions

Region	**Included countries according to ClinicalTrials.gov**
Africa	Algeria; Angola; Benin; Botswana; Burkina Faso; Burundi; Cameroon; Central African Republic; Chad; Congo; The Democratic Republic of Congo; Côte D'Ivoire; Djibouti; Egypt; Equatorial Guinea; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Guinea; Guinea-Bissau; Kenya; Lesotho; Liberia; Libyan Arab Jamahiriya; Madagascar; Malawi; Mali; Mauritania; Morocco; Mozambique; Namibia; Niger; Nigeria; Rwanda; Senegal; Sierra Leone; Somalia; South Africa; Sudan; Swaziland; Tanzania; Togo; Tunisia; Uganda; Zambia; Zimbabwe
Central America	Bahamas; Belize; Costa Rica; Cuba; Dominican Republic; El Salvador; Guatemala; Haiti; Honduras; Jamaica; Nicaragua; Panama; Puerto Rico; Trinidad and Tobago
East Asia	China; Hong Kong; Democratic' s People's Republic of Korea; Republic of Korea; Mongolia; Taiwan; Japan
Europe	Albania; Austria; Belgium; Bosnia and Herzegovina; Bulgaria; Croatia; Czech Republic; Denmark; Estonia; Finland; France; Germany; Greece; Hungary; Iceland; Ireland; Italy; Latvia; Lithuania; Luxembourg; The Former Yugoslav Republic of Macedonia; Montenegro; Netherlands; Norway; Poland; Portugal; Romania; Serbia; Slovakia; Slovenia; Spain; Sweden; Switzerland; United Kingdom
Middle East	Cyprus; Islamic Republic of Iran, Iraq; Israel; Jordan; Kuwait; Lebanon; Oman; Qatar; Saudi Arabia; Syrian Arab Republic; Turkey; United Arab Emirates; Yemen
North America	Canada, Greenland, Mexico, United States
North Asia	Armenia; Azerbaijan; Belarus; Georgia; Kazakhstan; Kyrgyzstan; Republic of Moldovia; Russian Federation; Tajikistan; Ukraine; Uzbekistan
Pacifica	Australia; Fiji; New Caledonia; New Zealand; Papua New Guinea; Solomon Islands; Vanuatu
South America	Argentina; Bolivia; Brazil; Chile; Colombia; Ecuador; French Guiana; Guyana; Paraguay; Peru; Suriname; Uruguay; Venezuela
South Asia	Afghanistan; Bangladesh; Bhutan; India; Nepal; Pakistan; Sri Lanka
Southeast Asia	Brunei Darussalam; Cambodia; Indonesia; Lao Peoples Democratic Republic; Malaysia; Myanmar; Philippines; Singapore; Thailand; Vietnam

Appendix 4: classification matrix

Category	Specific activity	Activity definition	Questions for remoteness ascertainment	Examples from protocols
1. Recruitment and enrolment	1.1 Participant outreach	Outreach to potential participants to increase the awareness of participation options to clinical trials	Are potential participants informed of trial participation opportunities through the use of online platforms or other forms of digital or remote contact (e.g., radio advertisements, telephone calls, e-mail)?	On-site: *Patients will be recruited from the practice of <doctor> in the Division of Urology, Department of Surgery.* Remote: *Patients will be recruited […] through printed and digital advertising media.*
	1.2 Participant prescreening	Trial element to describe participant identification activities before informed consent is obtained, for which participants' active involvement is required or through the screening of electronic medical records	Were participant identification activities performed in a remote fashion requiring participants' active involvement, e.g., through telephone questionnaires, teleconference, or online surveys?	On-site (active participant involvement): *Once obtaining weight and size, we identify overweight or obese patients and risk factors for DM2, they will be invited to continue the counting (i.e., glucose) phase.* Remote (active participant involvement): *The research assistant will obtain verbal consent from patient in order to conduct a preliminary phone screen. Phone screening will be conducted as part of the Anxiety Disorders Clinic's pre-existing screening protocol.* Through medical records: *Potential subjects will be identified from the scheduled surgical list.*
	1.3 Participant screening	Trial element to describe activities performed to ensure participant eligibility after informed consent is obtained	Is screening performed in a remote fashion through for example telephone, teleconference, or via at home visits?	On-site: *After obtaining informed consent, the investigator or sub-investigator will perform a screening examination.* Remote: *Screening […] will be conducted through a web-based screening tool, HIPAA-compliant video conference (Telehealth), telephone, or text messaging.*
	1.4 Consenting process	Subject's free and voluntary expression of his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the	Is the participant consented and/or educated on the clinical trial whilst participant and researcher were not physically at the same location, for	On-site: *Subject must be 40 years to ≤80 years of age inclusive, at the time of signing the informed consent form at Visit 1.*

		clinical trial that are relevant to the subject's decision to participate or, in case of minors and of incapacitated subjects, an authorization or agreement from their legally designated representative to include them in the clinical trial	example through the use of telephone contact or online means?	Remote: *The informed consent form may be mailed, emailed or faxed to the participant. The consent discussion may then be conducted by phone, conference phone call or in person so that the participant can read the consent form during the discussion.*
2. Participant engagement	2.1 Remote synchronous investigator-participant interaction	Remote, real-time interactions between participants and investigator staff to provide study updates and to engage participants throughout the clinical trial (i.e., after enrolment)	Are telemedicine (i.e., teleconference, telephone) interactions implemented to conduct trial activities and thereby engaging participants in a remote synchronous manner? Are participants updated or reminded of trial activities through the use of telemedicine tools?	*Study day 2: the study site will contact the subject by phone around the time that study treatment is supposed to be started*
	2.1 Remote asynchronous investigator-participant interaction	Remote, asynchronous interactions between participants and investigator to provide study updates and to engage participants throughout the clinical trial (i.e., after enrolment)	Are participants updated or reminded of trial activities through the use of asynchronous interactions, including text messages, e-mail, mobile applications?	*To maintain updated contact details, participants will be contacted every two months by SMS […].*
	2.3 Participant training	Trial element to describe training of the trial participant by the investigator staff on study-related materials and/or procedures. This element includes any participant education that is conducted after consenting has taken place	Are participants trained on study-related materials and/or procedures in a remote manner, for example through a telemedicine visits, home nursing, or mobile applications?	On-site: *Subjects randomized to <intervention> will be trained in intravenous technique by study nurses.* Remote: *[…] study team member calls the participant and reviews use of the study drug, establishes best contact information for response monitoring, and asks the patient to connect/wear the cardiac telemetry monitoring device. […] A video will be sent to the participant's email address and texted to them providing visual instructions on use.*
3. Trial operations	3.1 IMP supply	Dispensing investigational medicinal products/devices/other study intervention, as detailed in the protocol	Is IMP delivered direct-to-participants, for example from the investigator site or central depot to the participants' homes,	On-site: *IMP will be distributed to the patient during each visit it is expected drug dispensation.*

		to the participant so they will be able to use it according to the clinical trial protocol. IMP supply was considered 'not applicable' in case IMP was administered by site study staff during on-site visits or administrated to hospitalized patients.	a local pharmacy, or through the use of home nurses?	Remote: *Drug dispensation will occur in-clinic but may be delivered to subjects by other means (e.g., traceable courier) if warranted due to extenuating circumstances (e.g., coronavirus disease 2019 [COVID-19] restrictions), which will be determined individually for each site and/or subject.*
	3.2 IMP adherence monitoring	Monitor and/or investigator staff monitoring participant compliance with IMP self-administration and dosing according to the protocol. In case (e)Diaries were verified during an on-site visit by site study staff, this was considered 'on-site' IMP adherence monitoring. IMP adherence monitoring was considered 'not applicable' in case IMP was administrated by site study staff during on-site visits or administrated to hospitalized patients.	Is IMP adherence evaluated in a remote manner, for example through the use of smart caps, ingestible sensors, photographing, or eDiary verification by site study staff? Were eDiaries used as a means to monitor IMP adherence, and were these eDiaries reviewed independent of on-site visits?	On-site: *Compliance will be assessed by weekly pill count.* Remote: *The investigators (or appropriately qualified designees) are required to review the e-diary data online at frequent intervals to evaluate subject compliance and reported events as part of the ongoing safety review.*
	3.3 CT monitoring	Quality control process to ensure participant safety and data integrity. Important activities include verification of documentation, protocol and regulation adherence, and source data	Are clinical trial monitoring activities performed remotely/centrally, for example through telephone interactions with site staff, and/or remote access to study data?	On-site: *<Company> or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and GCPs are being followed.* Remote: *The sponsor's monitors will […] communicate frequently via telephone, e-mail, and written communications.*
	3.4 Remote auditing[a]	Quality control activities performed by the trial sponsor to verify proper clinical trial conduct in an exclusive remote manner. This includes auditing master files, audit trail logs, and record access.	Are quality control activities executed in a manner where evaluators are not physically present at the investigation site or other research related locations, for example through the use of teleconferences or virtual audit trials?	*Prior to each remote visit, company will issue a letter notifying the investigator of the scheduled remote audit.*
	3.5 Investigator staff training	Activity that describes the training of investigator staff by the sponsor or	Is investigational staff trained on how to use study-related materials in a remote	On-site: *All training and reads will be conducted by an imaging*

		contact research organization (CRO). This encompasses training on the trial design, trial equipment, IMP, and investigator responsibilities.	fashion, for example through a telephone initiation visit, a teleconference call or online means?	*contract research organization (CRO) as described in the imaging review charter (IRC). Five readers will be trained in-person.* Remote: *The company coordinator will conduct the initial web-based system training sessions for study teams via online teleconferences.*
4. Data collection	4.1 On-site data collection	In-person study visits at the investigator site by clinical trial participants, whereby activities such as image, sample, clinical and safety data acquisition are conducted	NA	*Subjects will return to clinic for Visit 4, for history, physical exam, quality of life (QoL), Satisfaction, and Cost Effectiveness questionnaires, and AE assessment.*
	4.2 Remote self-monitoring (participant reported outcome (PRO), wearable device, biomarker kits)	Patients perform activities to remotely collect data themselves. Data is collected by filling out (e-)PROs, wearable devises and sensors, or biomarker kits.	NA	*Subjects will perform home pregnancy testing on day 1 of Cycle 1 and Cycle 2.* *Provide subject with an e-diary, thermometer, and measuring device and instruct them how to collect prompted local reactions, systemic events, and use of pain/antipyretic medication.*
	4.3 Home health visits	Study visits are performed at the participant's home. Data is collected by health care professionals, including image acquisition, sample acquisition, clinical and safety data acquisition. IMP interventions may also be performed by health care professionals during home health visits.	NA	*Blood and urine sample collection may be performed by a mobile nurse professional.*
	4.4 Telemedicine visits	Remote study (follow-up) visits through teleconference or telephone calls during which data may be collected by health care professionals (e.g., AEs, verbal questionnaires)	NA	*Telephone contacts will occur at Weeks 56, 64, 68, 76, 80, 88, 92, and 100.* *If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.*

	4.5 Central laboratory	In case several sites are used during the trial and specimens for laboratory analysis are send to one (or several) central laboratories instead of anaysis conduct at each study site. In case only one site was used for study conduct, the central verus local laboratory determination is not applicable.	NA	*All laboratory samples will be collected using kit supplies provided by the central laboratory, which will also analyze all samples.*
	4.6 Local laboratory	In case several sites are used during the trial and specimens for laboratory analysis are analyzed at each of the participating trials instead of at one central laboratory. In case only one site was used for study conduct, the central verus local laboratory determination is not applicable.	NA	*Local laboratory will be used for the analysis of hematology and biochemistry.*

[a] Only the definition of remote auditing is presented here as auditing was only coded in case remote conduct was explicitly mentioned in the protocol.

Appendix 5: rules for implicit coding use

Remote element	On-site analogue	Rule of implicit use
Remote participant outreach	On-site participant outreach	*When hospitalized patients are used as a study population, outreach is implicitly coded as on-site as it is assumed to be conducted during the hospital stay of the potential participants, unless explicitly mentioned to be conducted prior to hospitalization* *In case the protocol states that during outreach participants will be invited to attend the clinic, assumed that during this outreach the participants are not yet present on-site, hence implicitly coded as remote outreach*
Remote (pre)screening	On-site (pre)screening	*If complex tests for (pre)screening requiring biological samples (e.g. hematology testing, uranology or serum pregnancy tests) or larger medical measuring devices (e.g. ECG, CT or MRI) are performed and remote conduct is not explicitly mentioned, (pre)screening assumed to be conducted on-site* *In case hospitalized patients are used as a study population, (pre)screening is implicitly coded ass on-site, unless explicitly mentioned that prescreening is conducted remote prior to hospitalization*
Obtaining remote (electronic) informed consent	Obtaining on-site (electronic) informed consent	*In case study population consists of hospitalized patients and outreach as well as (pre)screening is conducted on-site, consenting is assumed to be conducted on-site during (pre)screening visit* *In case an on-site (pre)screening visit is described and it can be assumed that consenting took place during this visit, implicitly coded as on-site consenting* *In case protocol states that 'A copy of the informed consent form, including patient's signature, will be provided by the investigator to the patient', consenting is assumed to be conducted in-person on-site unless explicitly mentioned that it was conducted remotely (e.g. home health visit, electronic means)*
Remote participant training	On-site participant training	*If participants were supplied with study materials on-site (e.g. self-monitoring devices, (N)IMP) and the need for training on use of these materials is apparent based on protocol (e.g. use of study materials by participants is checked during follow-up on-site visits), but training method is not explicitly mentioned to be conducted remotely (e.g. through videos on a website), this activity is implicitly coded as on-site*
DtP IMP supply	On-site IMP dispensing	*In case an initial dose of IMP is given to the participant during an on-site visit, assumed that IMP for at-home self-administration is also provided during this on-site visit, unless explicitly mentioned that additional supply takes place via direct-to-patient deliveries* *In case participants are trained on how to self-administrate the IMP during an on-site visit and no direct-to-participant IMP supply explicitly mentioned in the protocol, IMP supply implicitly coded to be conducted on-site*
Remote IMP adherence monitoring	On-site IMP adherence monitoring	*Pill counts implicitly coded as on-site unless explicitly mentioned to be conducted via electronic means*

Remote, central CT monitoring	On-site CT monitoring	*If protocol states that 'continuous CT monitoring/central monitoring' was conducted, this is assumed to be remote (data) monitoring and therefore implicitly coded as remote CT monitoring* *In case it is stated that source data is monitored at specific time points during the trial and source data includes hardcopy paper data that is only available on-site, CT monitoring is implicitly coded as being conducted on-site*
Remote training investigator staff	On-site training investigator staff	*In case staff training is mentioned, all trial activities that require training are conducted on-site (e.g. data collection, IMP supply, adherence monitoring) and remote investigator staff training is not explicitly mentioned, then this activity is implicitly coded as being conducted on-site* *In case the protocol mentions an on-site initiation visit, this can be assumed to be a training session for investigator staff, which is then implicitly coded as on-site investigator staff training* *Implicitly coded as on-site investigator staff training in case type of training requires on-site presence, e.g. technique training for taking respiratory swaps or training on how to use larger medical machinery*
Remote data collection (self-monitoring, home health visits, telemedicine visits)	On-site data collection	*If remote data collection method were not explicitly mentioned, and on-site visits were performed and/or complex data collection tools were utilized (e.g. MRI scan), it was assumed that data collection was performed on-site* *In case participants are hospitalized patient or are undergoing on-site procedures (e.g. surgery), assumed that all data collection takes place on-site, unless remote follow-up data collection (e.g. follow-up via telemedicine after hospital discharge) is explicitly mentioned* *In case of cancer treatment with chemo- and/or radiation therapy, this is assumed to be conducted on-site unless explicitly mentioned to be conducted remotely (e.g. via home health visit)*
Local laboratory	Central laboratory	*In case only one laboratory is mentioned, assumed that this is the only lab used, hence coded as a central laboratory*

Appendix 6: text mining word combinations

Trial activity	Data mining terms
Participant outreach	'outreach', 'approach', 'advert-'
Participant education on trial specifics	'educate', 'explain'
(Pre)screening	'screen'
Consenting	'consent'
Asynchronous communication with participants	'letter', 'email', 'SMS', 'mail'
Participant training	'training', 'educat..'(-ing, -e)
IMP supply	'supply', 'provide', 'dispens.' (-ing, -e), 'administer'
IMP adherence and trial compliance	'adherence', 'compliance'
CT monitoring	'monitor' (-ing)
Auditing	'audit' (-ing)
Investigator staff training	'training' 'educat..' (-ing; -e)
Data collection: laboratory use	'laboratory', 'central laboratory', 'local laboratory', 'lab'

Appendix 7: Filled out COREQ Checklist for Qualitative Research

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	13
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	0
Occupation	3	What was their occupation at the time of the study?	0
Gender	4	Was the researcher male or female?	N/A
Experience and training	5	What experience or training did the researcher have?	N/A
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	13
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	N/A
Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	N/A
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	N/A
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	13
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	13
Sample size	12	How many participants were in the study?	25
Non-participation	13	How many people refused to participate or dropped out? Reasons?	25
Setting			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	25
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	N/A
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	25
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	13
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	N/A
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	13
Field notes	20	Were field notes made during and/or after the inter view or focus group?	13
Duration	21	What was the duration of the inter views or focus group?	25
Data saturation	22	Was data saturation discussed?	N/A
Transcripts returned	23	Were transcripts returned to participants for comment and/or	13
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	26
Description of the coding tree	25	Did authors provide a description of the coding tree?	26
Derivation of themes	26	Were themes identified in advance or derived from the data?	26
Software	27	What software, if applicable, was used to manage the data?	14
Participant checking	28	Did participants provide feedback on the findings?	N/A
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	27
Data and findings consistent	30	Was there consistency between the data presented and the findings?	38
Clarity of major themes	31	Were major themes clearly presented in the findings?	26
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	25/26

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Appendix 8: Accompanying documents used for the interview series

8.1 Interview invitation letter

Universiteit Utrecht

UMC Utrecht

Faculty of Science
Department of Pharmaceutical Sciences

Pharmacoepidemiology & Clinical Pharmacology

Visiting address
Universiteitsweg 99
3584 CG Utrecht, the Netherlands

Invitation to participate in a Trials@Home research project

Dear Sir, Madam,

On behalf of the IMI Trials@Home consortium, we cordially invite you to participate in a study on direct- to-participant (DtP) investigational medicinal product (IMP) supply in clinical trials, led by Utrecht University and University Medical Center Utrecht. In this study we aim to describe the requirements for DtP IMP supply in the European Union by reviewing the clinical trial regulations and guidelines, besides corroborating these findings with case studies from clinical trial sponsors and courier/central pharmacy services. To collect data on case studies and experiences from sponsors and courier services, we will conduct in-depth semi-structured interviews.

We aim to interview representatives from clinical trial sponsors -from private as well as public institutions-, courier services, and (central) pharmacies that have experience with DtP IMP supply in the European Union. The findings of this research will contribute to understand the current status of DtP IMP supply, which can be of value for future implementation of DtP IMP supply models in trial designs. We are attaching, below this letter, the topics that we will discuss during the interview, including example questions.

The interviews will be conducted via videoconference and will approximately take one hour. If you are interested in participating in this study, please confirm your interest by sending an e-mail to Renske Grupstra (r.j.grupstra@students.uu.nl). Your participation is very much appreciated.

Confidentiality

It is of the highest importance that obtained data are correctly handled. The interviews will be audio- recorded, for which the participants are asked to give verbal consent. The audio recordings and pseudonymized transcripts will be managed as confidential information, and access to the data will be limited to the Utrecht University and University Medical Center Utrecht research team. The researchers aim to disseminate the results of this study in peer-reviewed scientific publications. Disseminated results and quotes will never contain personal information that could reasonably identify respondents.

Yours faithfully,

Renske Grupstra (Utrecht University) Amos de Jong (Utrecht University)
Yared Santa-Ana-Tellez (Utrecht University)
Mira Zuidgeest (University Medical Center Utrecht) Helga Gardarsdottir (Utrecht University)
Anthonius de Boer (Utrecht University, Dutch Medicines Evaluation Board)

8.2 Informed consent form

Informed consent form

Direct-to-patient medicinal investigational product experiences in the European Union

Dear participant,

Purpose of the research

You have been invited to take part in an interview about direct-to-patient investigational medicinal product supply conducted by researchers from the Utrecht University. It is important that you understand why we conduct this research and what it entails. Please carefully read the information outlined in this document and ask questions in case something is unclear or if you would like to receive additional information.

The current project aims to explore how direct-to-patient (DtP) investigational medicinal product (IMP) supply has been conducted in trials (partially) executed in the European Union based on experiences of sponsors and courier services. Findings from the interviews will contribute to a better understanding of the current status of DtP IMP supply in clinical trial conduct in Europe. Insights can -amongst others- be of value for future clinical trial designs. The researchers aim to disseminate results through the Trials@Home consortium[1] and potentially in scientific publication(s).

Procedure and data protection

The interview will take approximately one hour and takes place via teleconference (or telephone, if preferred) using WebEx or MS Teams. The interview will be audio-recorded and the recording will be stored at an encrypted server of the Utrecht University. The audio-file will be transcribed verbatim and pseudonymized after transcription. The pseudonymized file will not contain direct personal identifiers (e.g., name, organisations), and will only be available to the Utrecht University research team. Other genuine researchers may request access to de-identified data excerpts in the future. Access will only be granted if they agree to preserve the confidentiality of the information as requested in this form. Their access will also require approval from the Utrecht University research team. Dissemination of research findings through publicly available scientific articles or website items will be anonymized (i.e., these files will not include company names, personal names, product names, or information that could reasonably identify organizations or individuals). Note, however, that quotations may be used to contextualize findings. However, these quotations will not be traceable to individual participants. Furthermore, case study descriptions can be included in the research output. Only high-level trial characteristics (e.g. therapeutic area, study phase, and/or administration type) will be used for this purpose.

Voluntary participation

Your participation in this study is highly appreciated. Participation is voluntary and you are free to withdraw at all times, also after consenting to participate. If you withdraw from the study, you do not have to state why. Please do inform the researcher about your decision. Data analysed by that time may not be affected by the withdrawal of the informed consent.

Consent

I understand the information outlined in this form and agree that my participation in this research is voluntary.

Verbal consent

8.3 Summaries of the used interview guides

Interview guide summary - sponsors

Experiences: case study clarification

1. Can you tell me about a specific study/studies you were involved in where direct-to-participant (DtP) investigational medicinal product (IMP) supply was implemented?
    a. Why was DtP IMP supply chosen to be implemented in the design of this trial?
    b. What type of DtP IMP supply was chosen in this trial? (e.g. from central pharmacy to home of participant, or from sponsor to local pharmacy, etc)
    c. Do you have experience with home nurse administration for complex IMP?
    d. Can you provide study characteristics of these trials in which DtP IMP supply was used?

Experienced facilitators and barriers

2. What made execution of this DtP IMP supply in [case example] possible (in terms of ethical, regulatory, practical, legislation clearance etc)?
3. What barriers did you experience when implementing DtP IMP supply in [case example]?
4. Do you know of any clinical trials within your company where you wanted to implement DtP IMP supply, but where this was eventually not implemented? If so, why was this?

Perceived advantages and disadvantages

5. What do you consider (dis)advantages of DtP IMP supply in clinical trials compared to on-site supply? And why?

Recommendations and advice

6. Do you see a future with more DtP IMP supply in trial designs? Why (not)?
7. Do you have any other advice regarding DtP IMP supply you'd like to share?

Interview guide summary – courier services

Experiences: DtP IMP supply models

1. Can you tell me about a specific study/studies you were involved in where direct-to-participant (DtP) investigational medicinal product (IMP) supply was implemented?
    a. What was your role and how does this compare to the role of other stakeholders (e.g. sponsors, investigator staff)?
    b. What type of DtP IMP supply model was applied in these trials? (e.g. from central pharmacy to home of participant, or from site to home of participant, or to local pharmacy, etc)
    c. Did you need special containers for transportation? (e.g. for temperature control).
    d. Which countries were shipments of IMP sent to in these examples?
    e. In case you are aware of any, could you provide trial characteristics of these case study(s)? (e.g. study timeline, what type of IMP was used, private or public sponsor, therapeutic aim, trial phase, etc)

Experienced facilitators and barriers

2. What made execution of the DtP IMP supply in [case example] possible (in terms of ethical, regulatory, practical, legislation clearance etc)?
3. What other types of DtP IMP supply are you familiar with/do you have experience with? Any preferences for specific models?
4. Do you know of any CTs where investigators/sponsors wanted to implement DtP IMP supply, but where this was eventually not implemented? If so, why was this?

Perceived advantages and disadvantages

5. What do you consider (dis)advantages of DtP IMP supply in clinical trials compared to on-site supply? And why?

Recommendations and advice

6. Do you see a future with more DtP IMP supply in trial designs? Why (not)?
7. Do you have any other advice regarding DtP IMP supply you'd like to share?

*complete interview guides can be provided upon request.

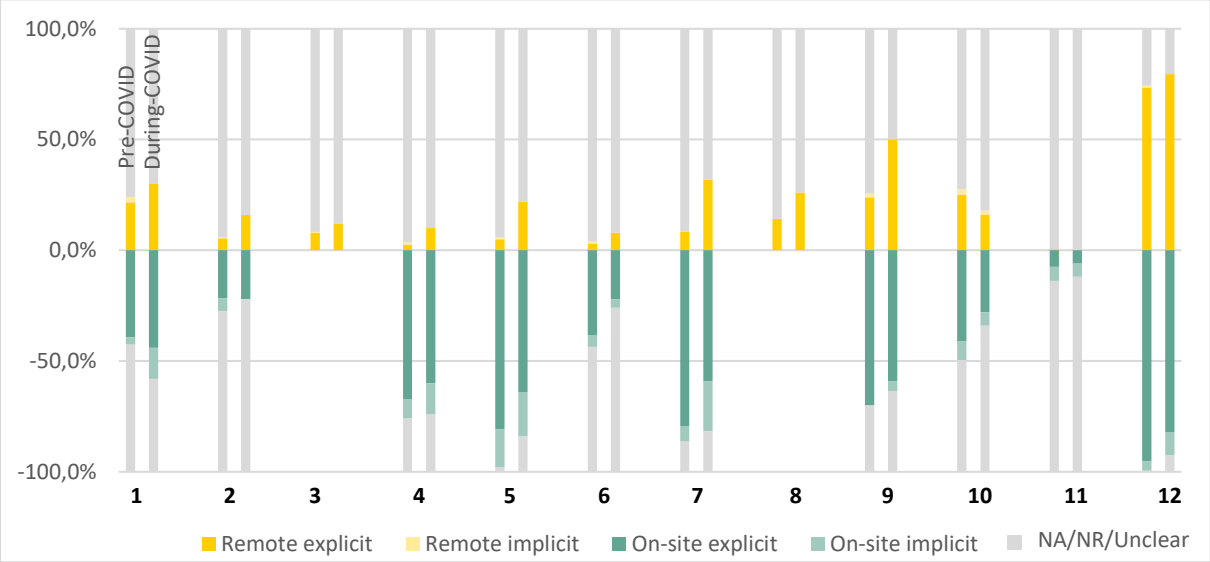
Appendix 9: Overview of reasons for protocol exclusion per phase and year

Reason for exclusion	**Number of excluded protocols**
Duplicates	18
Protocol too short	16
Too short _phase 2_2019	*0*
Too short _phase 2_2020	*6*
Too short _phase 3_2019	*2*
Too short _phase 3_2020	*3*
Too short _phase 4_2019	*2*
Too short _phase 4_2020	*3*
Wrong design	1
Wrong design _phase 2_2019	*0*
Wrong design _phase 2_2020	*0*
Wrong design _phase 3_2019	*0*
Wrong design _phase 3_2020	*1*
Wrong design _phase 4_2019	*0*
Wrong design _phase 4_2020	*0*
Wrong intervention	61
Wrong intervention _phase 2_2019	*23*
Wrong intervention _phase 2_2020	*6*
Wrong intervention _phase 3_2019	*11*
Wrong intervention _phase 3_2020	*8*
Wrong intervention _phase 4_2019	*10*
Wrong intervention _phase 4_2020	*3*
Wrong year	3
Too much blurred text	1
TOTAL	**100**

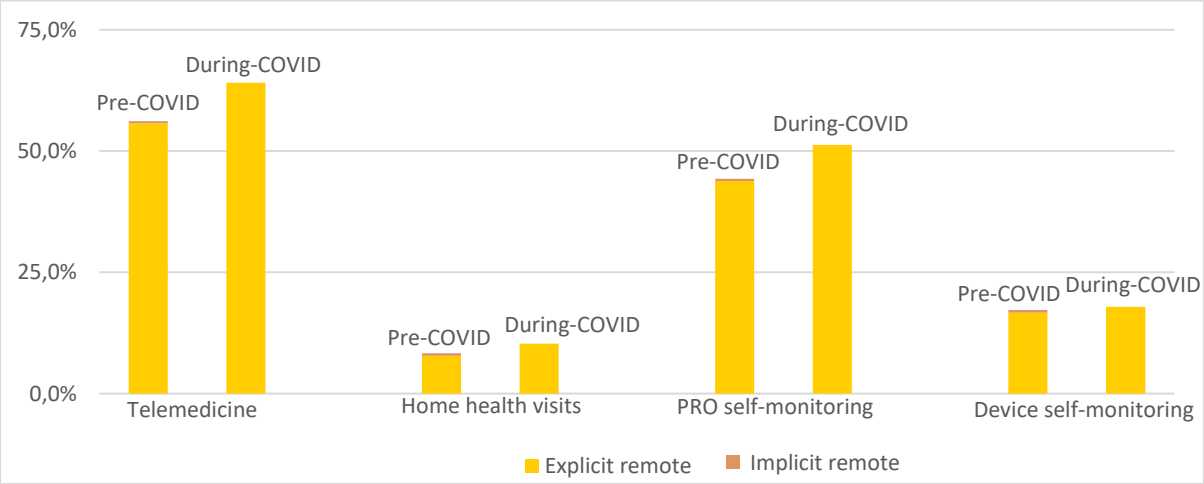
Appendix 10: pre- and during-COVID stratification

10.1 Stratification of trial activity conduct comparing pre-COVID and during-COVID trials

1, Participant outreach; **2**, Pre-screening; **3**, Medical record pre-screening; **4**, Screening; **5**, Consenting; **6**, Participant training; **7,** IMP supply; **8**, Asynchronous communication ; **9**, Adherence monitoring; **10**, CT monitoring; **11**, Staff training; **12,** Data collection

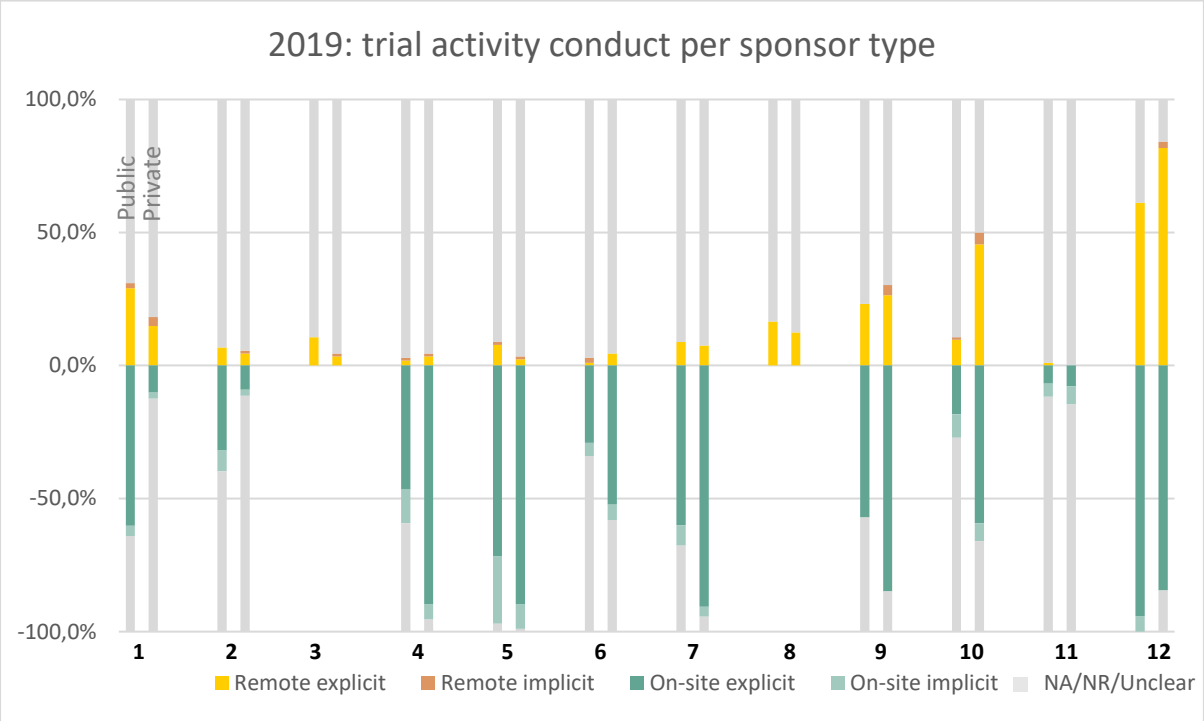


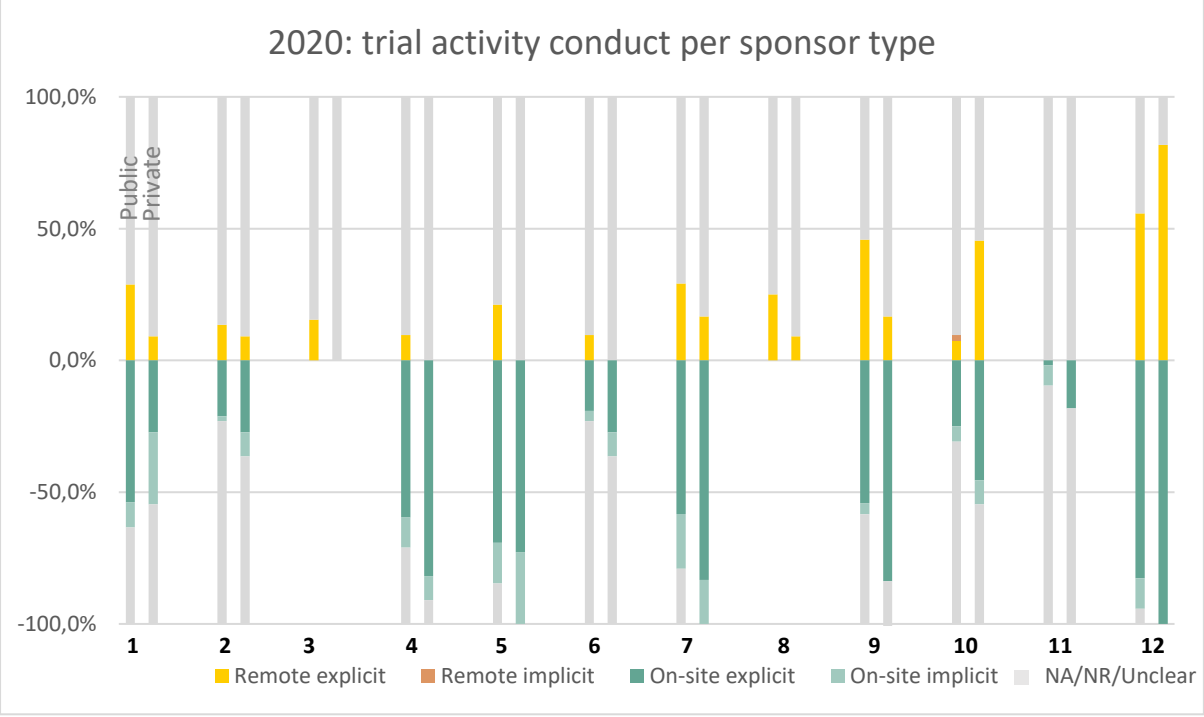
10.2 Distribution of remote data collection methods comparing pre-COVID and during-COVID protocols



Appendix 11: Sub-stratification of trial activity conduct per sponsor type and year of study initiation

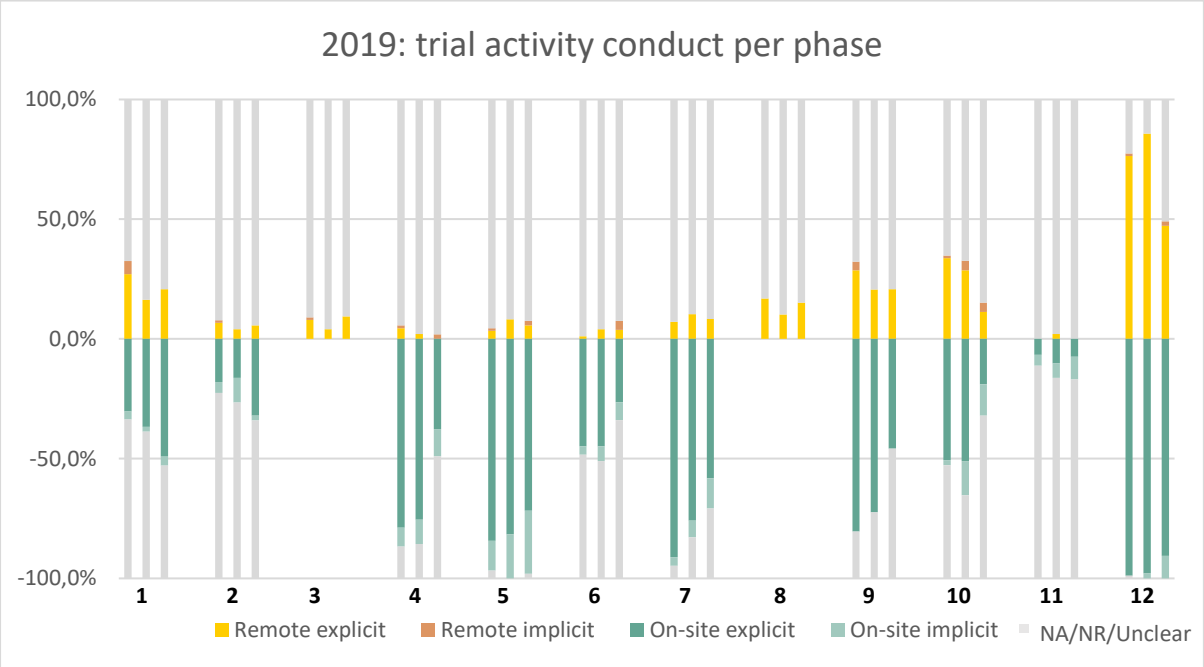
1, Participant outreach; **2**, Pre-screening; **3**, Medical record pre-screening; **4**, Screening; **5**, Consenting; **6**, Participant training; **7**, IMP supply; **8**, Asynchronous communication; **9**, Adherence monitoring; **10**, CT monitoring; **11**, Staff training; **12**, Data collection. Per activity: left bar public, right bar private sponsor. NB: hospitalized trials are included in the remote data collection percentage of trial protocols.

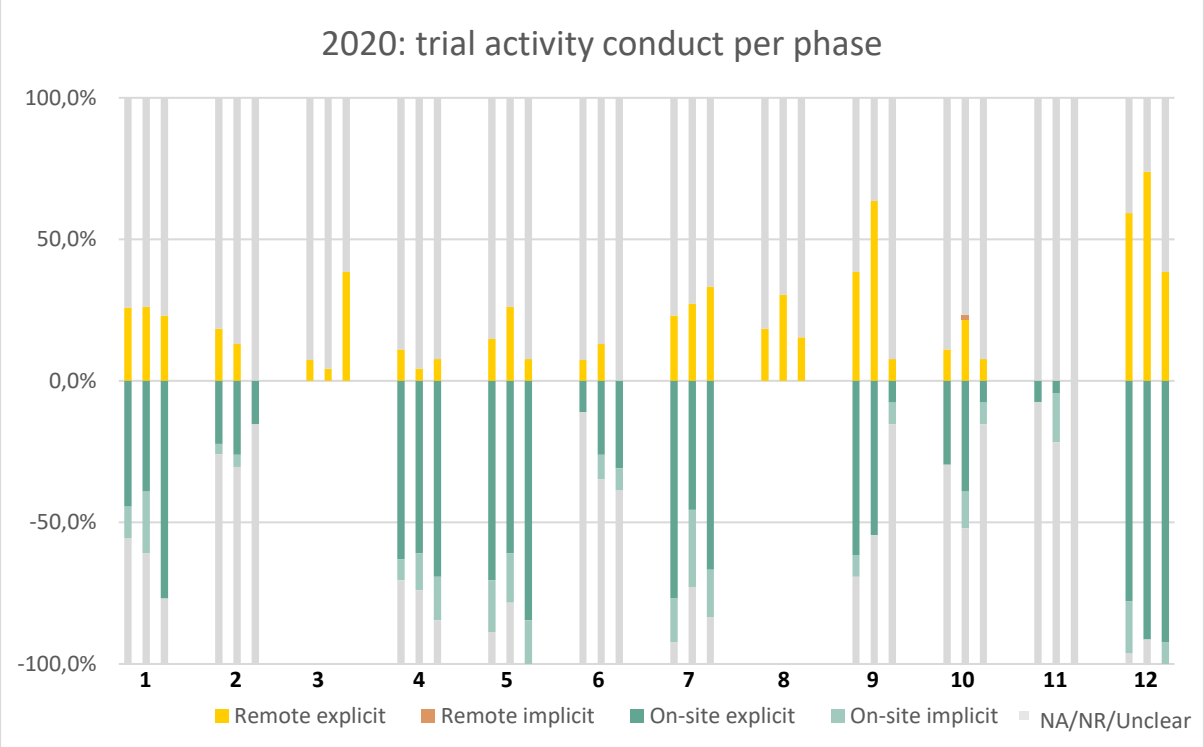




Appendix 12: Sub-stratification of trial activity conduct per study phase and year of study initiation

1, Participant outreach; **2**, Pre-screening; **3**, Medical record pre-screening; **4**, Screening; **5**, Consenting; **6**, Participant training; **7**, IMP supply; **8**, Asynchronous communication; **9**, Adherence monitoring; **10**, CT monitoring; **11**, Staff training; **12**, Data collection. Per activity: left bar phase 2, middle bar phase 3, right bar phase 4 protocols. NB: hospitalized trials are included in the remote data collection percentage of trial protocols.





Appendix 13: DtP case study examples from the EU

Case study example characteristics	Source
- Metabolic disease (gout) trial - Oral tablets IMP - Phase 2/3 - Central pharmacy-to-participant model (and site-to-participant in specific country) using postal service - Across borders in Europe	210913_I1_RG
- Psoriasis trial - Oral tablets IMP - Phase 2 - Site-to-participant model - Different European countries involved (including France, Germany, Poland, Spain, UK)	211018_I12_RG
- Metabolic disease trial - i.v. infusion IMP - Phase 2/3 - DtP with home nursing model - Several European countries	211105_I13_RG
- Monoclonal antibody therapy - Continuous i.v. infusion IMP - Phase 2/3 - Site-to-participant model with use of home nursing - EU and North-America based	211008_I10_RG
- Unclear therapeutic aim - Registered antibiotic drug as IMP - local pharmacy-to-participant model - Only in the Netherlands	211014_I11_RG

Appendix 14: Interview coding tree

Need for DtP approaches

a) COVID-19 impact on CT conduct
    a. Trends prior to COVID-19
b) Participant-centricity
    a. Recruitment benefit
    b. Retention benefit
    c. Lower participant burden
    d. Higher diversity in study population
    e. Incorporation of patient's voice
    f. Allowing participants to choose

Considerations of and experiences with different DtP models (in the EU)

a) Site-to-participant
b) Depot/central pharmacy-to-participant
c) Local pharmacy-to-participant
d) DtP with home nursing
    a. Home supply options
e) Courier services in DtP
    a. Couriers' role in DtP
    b. Advantages of courier service use
    c. Disadvantages of courier service use

Determinants for DtP implementation

a) Ideal DtP setting
    a. CT characteristics
        i. Study phase
        ii. Therapeutic area
    b. IMP characteristics
        i. Shelf-life
        ii. Cold chain
        iii. Administration type
b) Operational aspects
    a. Regulatory aspects
        i. (country) specific regulations
        ii. COVID-19 regulations/flexibilities
        iii. Ethics assessments
        iv. Data safety and privacy
    b. Internal organization for DtP
        i. SOPs
        ii. Dealing with regulations
        iii. Discussion within pharma/collaborations
    c. Conducting adherence checks
        i. Participant training options
    d. Drug accountability
    e. Staff training
    f. Home nursing considerations
    g. Resources and financial aspects
    h. Logistical aspects
    i. Flexible approach in design to allow for last minute changes

Reflection of stakeholders on DtP in the EU

a) Stakeholder's role and perception
    a. (industry) sponsors
    b. Investigators
    c. Participants
    d. ECs
    e. Home nurses
    f. Pharmacists
    g. Couriers/mobile clinical services
    h. Local GPs/HCPs
    i. CROs
b) Conservatism/risk-aversiveness
c) Stakeholders' predictions and hopes for the future

Appendix 15: During the interviews identified facilitators and barriers per theme

Need for DtP approaches	
Facilitators	**Barriers**
- Benefits retention in times with travel restrictions (e.g. strict COVID-19 regulations) as DtP models allow IMP to still be distributed; - Ability to include participants from larger geographical area benefits recruitment; - Ability to include immobile or severely ill participants benefits recruitment; - Lowers participant burden (e.g., less to zero travel time), which benefits retention; - Reduction of costs caused by reduction in on-site visits; - Reduction of costs as no unnecessary stocking in site pharmacies is needed - Ridden chance of participants forgetting drug pick-up on-site; - More control (e.g. temperature monitoring) of IMP during transport to participant's home compared to on-site drug pick-up by participant.	- DtP implementation increases costs, for example when conducting multiple shipments or if using an expensive courier to deliver inexpensive drug; - DtP not suitable for all participants (e.g. some difficulties with using technologies or home-devices); - Currently everything is orientated around on-site visits, so would require 'culture' change; - For many trials COVID-19 restrictions were the trigger for DtP implementation, when they are lifted the main reason for DtP inclusion in CT designs is lost, meaning that it makes sense to return to the 'traditional' on-site model.
Determinants for DtP implementation	
Facilitators	**Barriers**
- As more safety data is already available and close monitoring is less needed, late-phase trials are more suitable for DtP than early phase trials; - Self-administrable IMP (e.g. oral product) is suitable for DtP; - Flexibility in CT designs is favourable; - Stakeholders benefit from streamlined communication (e.g. between vendors, home nurses, participants regarding shipment timing); - Oversight can be enhanced by sufficiently training participants in IMP handling; - Up-front assurance of participant confidentiality (e.g. by presenting it in the ICF) eases DtP conduct (particularly in Europe where regulatory bodies put emphasis on data privacy); - Novel digital technologies (e.g. mobile applications) can aid adherence monitoring; - By involving vendors and providers of mobile clinical services early on in the design of a CT, stakeholders can benefit from their delivery experiences.	- Protein-based treatments with complex administration routes are becoming more prevalent in medicine, which does not fit the ideal setting for DtP as it requires a nurse (and close monitoring) for the administration; - Regulations are unharmonized and succumb to change, hence they need to be assessed on case-by-case basis; - Strictly trying to adhere to (changing) regulations adds financial burden to sponsors; - When complex measurements (e.g. MRI scans) are required at same time as drug delivery, DtP is not a logical model to implement; - High quantity of required ECs' assessments may cause a timeline disconnect during CT set-up (e.g. each aspect of patient-facing technology must be approved); - DtP is often not yet included in company's SOPs, resulting in interpretation difficulties; - Additional practical complications (e.g. organizing deliveries, training drivers, etc.) associated with DtP conduct likely to result in higher financial burden for sponsors;

	- Realizing temperature logging for cold chain product complicates the DtP process; - Additional hurdles for DtP conduct may arise when participants cross borders during their enrolment (e.g. cross-border shipment or cross-border payment issues); - Conflicting requirements from the GDPR and trial regulators regarding data retention after shipments complicate DtP conduct; - Maintaining data privacy and patient confidentiality is more complex during DtP conduct as a larger variety of parties is involved compared to the on-site model; - Preparing DtP packages can cause a practical constraint as it is a timely activity; - Oversight responsibilities are increased and remain with the PI in DtP models, meaning that PIs might not be eager to include and execute DtP in their trials.
Considerations of the different DtP models	
Facilitators	**Barriers**
Site-to-participant model: - Site-to-participant model is very similar to the traditional on-site model of drug supply, therefore few barriers arise; Home nurse involvement in DtP: - For home nurses (and other stakeholders) a clear, easy-understandable interface system facilitates smooth DtP conduct; - In order to check adherence, nurses could use telemedicine (e.g. regularly phoning participants); - Stakeholders benefit from having one company arrange home nurses as well as DtP delivery conduct; Depot-to-participant model: - An IRT system enabling restricted access to specific participant's information is particularly useful when implementing a depot-to-participant model; - In case of a depot-to-participant model, the clinical site is released of some tasks; Courier services' role in DtP: - Driver training will ensure patient data safety, aiding DtP implementation (e.g. training on how to deal with address information, training on how to use temperature loggers);	- When using IMP deliveries, travel times are precarious (e.g. risk of delays because of weather conditions); - Availability of transportation systems determines success of DtP shipments (e.g. shipments complicated for remote areas); Home nurse involvement in DtP: - Required credentials for home nurses differ per country; - Home nurse inclusion in a trial is costly; - Not all participants will accept having strangers come in their home to administer drug or conduct medical tests; - Home nursing is time consuming for nurses, and there already is a shortage of nurses (in the Netherlands specifically); Depot-to-participant model: - In Europe specifically, strict regulations state you need a pharmacist at a depot in order to deliver IMP; - When no nurse or pharmacists is involved in a depot-to-participant model, this means lack of service towards participants compared to the 'traditional' on-site model; Courier services' role in DtP: - Role of courier difficult to define as regulations are vague (e.g. what are they and

- As a courier it helps to set-up detailed process with driver in terms of how the delivery will take place (e.g. communicate specific delivery window, specific delivery place, with participants in the loop too).	what are they not allowed to do upon delivery at the door of a participant); - With drug shipments there is a theoretical lack of control, e.g. when it comes to package arrival confirmation; - White glove courier services can be very expensive; - When using a courier, working with an IMP that requires daily delivery and dosage each day can be complicated.
Reflection of stakeholders	
Facilitators	**Barriers**
- If HCPs can maintain proper oversight, they are positive about inclusion of DtP models in CT designs; - Participants are enthusiastic about DtP if it is able to lower the burden for their CT participation; - Couriers are willing to take on the additional tasks (e.g. taking out temperature loggers) associated with their role in DtP; - Since the emergence of COVID-19, there is a (novel) dialogue between stakeholders and regulators, which creates more opportunities for DtP to be implemented now compared to earlier days; - It would benefit all stakeholders to work together more, for example by sharing best practices; - In general regulators are supportive of DtP, provided that PIs and site staff can show how they ensure quality and data safety.	- Cultural biases, cultural backgrounds, and different life-styles affect participant's perception on DtP; - The clinical trial community is quite conservative and risk-aversive, but industry sponsors in particular; - PIs are still responsible for patient-safety, if they are not comfortable with DtP, then it will not be implemented in the trial design (in the experience of a courier, the PI can be a barrier); - Study staff might be reluctant to implement DtP because they might get paid based on time participants are present at clinical site; - Study staff might be reluctant to delegate tasks to home nurses who they do not know (even if these nurses are properly trained); - Patients sometimes prefer to see a doctor in a physical clinic over having drug be send to their home as this might make them feel more safe.