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ORIGINAL ARTICLE

Direct-to-participant investigational medicinal product supply in clinical trials in Europe: Exploring the experiences of sponsors, site staff and couriers

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Abstract

Aims: Insights into the current practice of direct-to-participant (DtP) supply of investigational medicinal product (IMP) in the context of clinical trials conducted in Europe are needed, as regulations are unharmonized. This study is set out to explore how DtP IMP supply has been employed in Europe and what the advantages and disadvantages and barriers and facilitators of its implementation are.

Methods: We conducted semi-structured interviews with representatives from sponsor companies, courier services and site study staff involved in the IMP dispensing and delivery process in Europe. Interviews were conducted between May and November 2021, and data were analysed following thematic analysis.

Results: Sixteen respondents participated in one of the 12 interviews. Respondents had experience with different models of DtP IMP supply including shipment from the investigative site, a central pharmacy (a depot under the control of a pharmacist) and a local pharmacy—aiming to reduce trial participation burden. The respondents indicated that investigative site-to-participant shipment is not affected by regulatory barriers, but could burden site staff. Shipment from central locations was considered most efficient, but possible regulatory barriers related to maintaining participants' privacy and investigator oversight were identified. The respondents indicated that the involvement of local pharmacies to dispense IMP can be considered when the IMP is authorized.

Conclusions: Several DtP IMP supply models are implemented in clinical trials conducted in Europe. In this study, three main DtP IMP models were identified, which can be referenced when describing these approaches for regulatory approval.

KEYWORDS
decentralized clinical trial, direct-to-participant, direct-to-patient, DtP, home delivery, patient-centric

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1 | INTRODUCTION

Clinical trials are essential for the development of medicinal products. The increasing availability of digital technologies and the implementation of these technologies into clinical trials offer the possibility of conducting clinical trials in a decentralized fashion. Decentralized clinical trials (DCTs) are trials in which activities are conducted in participants' homes and local settings, rather than at investigative sites,[1] potentially improving accessibility and reducing the burden on participants.[2] One trial activity enabling DCTs is the provision of the investigational medicinal product (IMP, "a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial")[3] directly to the trial participants, thereby reducing the need for travel to the investigative site.

In the European Union (EU), EU laws (Regulation EU 536/2014) and national laws govern the assessment of clinical trials, including the direct-to-participant (DtP) supply of IMPs. While EU laws do not prohibit at-home dispensing or administration of IMPs, the Good Clinical Practice (GCP) Inspectors Working Group of the European Medicines Agency (EMA) has previously highlighted that national legislation may prohibit such practices.[4] Previous research has found that national provisions regarding DtP IMP supply are often lacking and unharmonized,[5,6] necessitating case-by-case decisions by national competent authorities (NCAs) and ethics committees, which ensure that investigator oversight and accountability are maintained per the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 guideline throughout the DtP process.[7] The research by Malone et al found that, pre-Covid-19, DtP IMP supply was not widely accepted by NCAs.[6] During the Covid-19 pandemic, when access to healthcare was limited and travel restrictions were in place, more detailed guidance regarding the shipment of IMPs was provided by international and national regulatory bodies.[8–10] These guidelines state that IMPs normally dispensed at a trial site could be provided from the site, or in certain cases and countries from the sponsor, via a courier service.[8] However, national differences were apparent, and it is unclear whether and how such guidance will be translated into regulation in the future.[10] These factors, taken together, may engender a risk-averse approach to the implementation of DtP solutions.

Given that regulations and NCA perspectives regarding DtP IMP supply are unharmonized, insight into current practice is needed to support the development of harmonized regulatory guidance and the implementation of supply approaches. The current project therefore explores how DtP IMP supply has been employed in trials executed in Europe before and during the Covid-19 pandemic, seeking to identify the advantages and disadvantages of such approaches and to identify the barriers to and facilitators of their implementation in Europe.

What is already known about this subject

- Regulations regarding clinical trial operations, including the shipment of drugs directly to the trial participants, are not harmonized across Europe.
- Dispensing of investigational medicinal products (IMPs) in clinical trials typically requires on-site visits.
- Direct-to-participant (DtP) supply of IMP could enable decentralization of drug trials.

What this study adds

- DtP IMP supply from the investigative site, central pharmacy and local pharmacy is conducted in Europe.
- The need to lower the burden of trial participants drives the implementation of DtP IMP supply.
- The disease demographic, IMP characteristics, unharmonized regulations and participant privacy should be considered when implementing DtP approaches.

2 | METHODS

2.1 | Study design

This paper explored the experiences of pharmaceutical company representatives, courier-service representatives and investigative site staff operational in Europe. These experiences were collected between May and November 2021 through online, 1-h, semistructured interviews that allowed for tailoring of the discussions to the respondents' expertise, while discussing predefined topics. The consolidated criteria for reporting qualitative research were used to report on the methodology.[11]

2.2 | Eligibility and recruitment

Participant eligibility was restricted to clinical trial sponsor representatives, courier-service representatives and site study staff who were involved in IMP handling and had experience with, or planned to implement, DtP IMP supply in the EU/European Economic Area (EEA) before or during the Covid-19 pandemic. To capture diverse perspectives, maximum variation and snowball sampling were employed,[12] that is, representatives were invited to participate on the basis of the type of sponsor, size of their company and previous (known)

experience with DtP IMP supply. Eight experts were initially approached via the Trials@Home network and asked to identify potential respondents within their networks. Subsequent respondents were identified through snowballing.

2.3 | Interview guide development

Based on the aim of this study and other important concepts from the literature,[6,8,13] four topics for the interview guide were drafted. First, where possible, case study examples of DtP IMP supply put forward by the respondents were discussed. Second, their experiences of barriers to and facilitators of DtP IMP supply were solicited. Third, the advantages and disadvantages of different DtP IMP supply models were discussed. Fourth, recommendations from the respondents were collected. A preliminary interview guide was discussed with an industry expert on DtP IMP solutions. The interview guide was adapted to include questions on (i) sponsors' strategies for supporting hospital pharmacies with the implementation of DtP IMP solutions and (ii) experiences with importing IMP. The interview guide was subsequently piloted, with three interviews. The guide was not adapted based on the findings, and the data were included in the analysis. The concise interview guide can be found in Table 1.

TABLE 1 Concise interview guide.

Topic	Questions
Case study examples	• Can you tell me about a specific trial (conducted in Europe) in which you were involved, where DtP IMP supply was implemented? a. Why was DtP IMP supply chosen to be implemented in this trial? b. What type of DtP IMP supply model was chosen for this trial (eg, from investigative site-to-participant, sponsor-to-participant)?
Experienced facilitators and barriers	• What made the execution of this DtP IMP supply model possible (in terms of ethical, regulatory, practical and legislative matters)? • What barriers did you experience when implementing DtP IMP supply? • Do you know of any clinical trials within your company which were intended to implement DtP IMP supply, but this was ultimately not done? If so, why was this?
Perceived advantages and disadvantages	• What do you consider the (dis)advantages of the different DtP IMP supply approaches you previously described, as compared to on-site supply?
Recommendations and advice	• What advice would you give to sponsors that want to implement DtP IMP solutions?

Abbreviations: DtP, direct-to-participant; IMP, investigational medicinal product.

2.4 | Data collection

Semistructured interviews with one to three interviewees at a time were conducted by R.J.G. and/or A.J.d.J. between May and November 2021 via an online videoconference service (WebEx™). Each interview lasted approximately 1 h. Verbal informed consent was obtained from the trial participants before the interviews. As the research did not include patients, it was exempt from ethics review. Summaries of the interviews were shared with the respondents to ensure correct interpretation and to allow for the provision of additional feedback if deemed necessary.

2.5 | Data analysis

The interviews were audio-recorded, transcribed verbatim and inductively coded following thematic analysis[14] using NVivo 12 Pro, QSR International (Burlington, MA, USA). All the transcripts were coded in duplicate by A.J.d.J. and R.J.G. The identified codes were categorized, discussed and reviewed iteratively within the research team and aggregated into (sub)themes.

3 | RESULTS

3.1 | Respondents' characteristics

In total, 27 potential respondents were approached, of whom 16 (59%) participated in one of the 12 interviews. Eleven invitees did not reply or confirm their participation. The participants were representatives from courier-service providers (n = 8), pharmaceutical companies (n = 5), hospital pharmacists (n = 2) and one academic researcher. The characteristics of the respondents, including their experiences with DtP IMP in Europe, are displayed in Table 2.

3.2 | Themes identified from the data

Three main themes were identified from the transcript data: (i) DtP models employed in Europe, (ii) drivers of DtP supply implementation and (iii) impact of regulations.

3.2.1 | Direct-to-participant models employed in Europe

Experience

Several DtP IMP supply models were identified from the respondents' experiences (Figure 1). The respondents indicated that they had predominantly implemented the investigative site-to-participant model in Europe, as there are few barriers to its implementation, as one respondent explained:

> You can almost think of the site-to-patient paradigm as the extended arm of a study nurse. There is no change in any of the processes, and therefore there are little or no barriers really.
>
> (Pharmaceutical company representative)

In addition, the respondents had experience with delivering IMPs from local and central pharmacies to participants, although this was less common. We observed a lack of standardized terminology to distinguish DtP models from one another, with the terms "central pharmacies", "sponsor depots" and "courier depots" all used. The respondents indicated that, in Europe, the dispensing of an IMP to a participant is performed by a pharmacist following a single or consecutive prescription, without the sponsor having access to personally identifiable information. Therefore, references to "central pharmacy to participant" or "pharmacy depot to participant" denote those models in which IMP is dispensed from a pharmacy depot under the control of a pharmacist who is then able to distribute to other locations away from the clinical setting (Table 3). The respondents did not have any experience with the sponsor-to-participant model, in which IMP is shipped from a private company sponsor or distributor depot, in Europe, whereas some had implemented this model in trials conducted elsewhere.

Additionally, the respondents had implemented several means of delivery, including the delivery and potentially the administration of IMPs to the participant by home nurses (Box 1), the shipment of IMPs via postal mail (Box 2), delivery by courier services (Box 3) and collection at a local pharmacy (Box 4).

TABLE 2 Respondents' characteristics (n = 16).

Characteristic		Number of interviewees (%)
Stakeholder group	Industry sponsor	5 (31)
	Site study staff[a]	3 (19)
	Courier-service providers	8 (50)
Years of experience[b]	0-5 years	3 (19)
	6-10 years	4 (25)
	≥10 years	9 (56)
Experience with DtP IMP supply in Europe[c]	Investigative site-to-participant	13 (81)
	Central pharmacy-to-participant	7 (44)
	Local pharmacy-to-participant	2 (13)

Abbreviations: DtP, direct-to-participant; IMP, investigational medicinal product.
[a]Research staff, hospital pharmacists.
[b]Experience with clinical trial logistics based on information shared during the interview or online curricula vitae.
[c]As discussed during the interviews (unprompted).

Advantages and disadvantages of the different models

Despite the investigative site-to-participant supply model being reported as relatively easy to implement, it was indicated that the logistics associated with the shipment may be burdensome for sites and that easy-to-use interfaces and processes may facilitate this model. Furthermore, industry and site study staff representatives mentioned that shipment from a central location is most efficient, in other words, only interactive response technology (IRT)-ordered IMP is dispensed, provided this can be accommodated by the central location and no excess IMP is dispensed due to inflexibility in quantity contents, thereby reducing IMP spillage and saving costs associated with setting up the sites' pharmacies. Additionally, one respondent indicated that shipment from central pharmacies facilitates DtP supply for IMP with stringent stability requirements. However, when IMPs are shipped from a central location, the services provided by a nurse or pharmacist (eg, answering participants' questions) were expected to be limited.

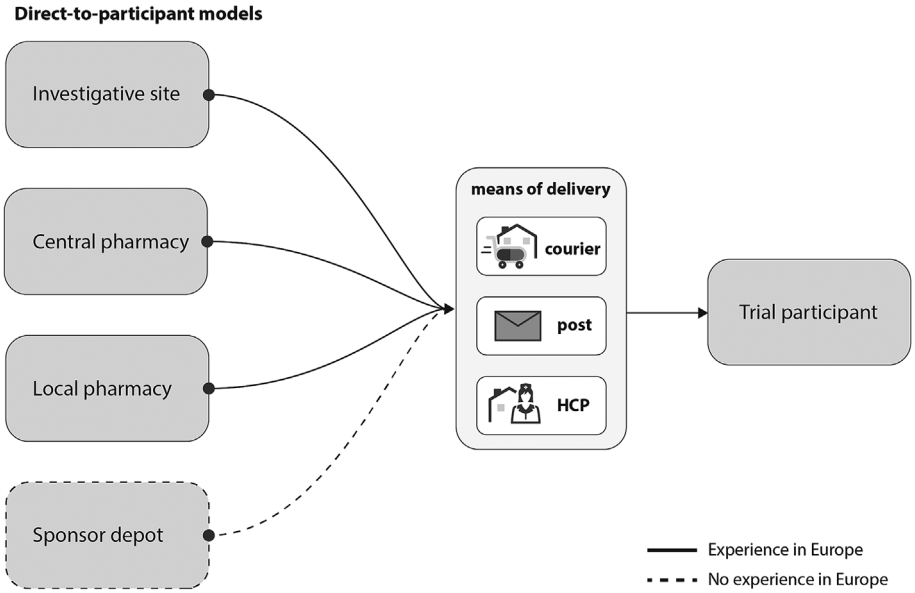

FIGURE 1 Direct-to-participant models and means of investigational medicinal product delivery based on the interviews.

TABLE 3 Definitions of the different models and the potential advantages and disadvantages.

Model	Definition[a]	(Potential) advantages and disadvantages	Example
Investigative site-to-participant	Model in which the IMP is shipped from the investigative site or site's pharmacy to the participant's home or other address.	• Few regulatory barriers • Increased burden for site staff	Box 1, Box 3
Central pharmacy/ pharmacy depot-to-participant	Model in which the IMP is shipped from a central (or remote) pharmacy depot with distribution facilities under the control of a pharmacist, and not the investigative site's pharmacy. In a multicenter clinical trial, one site's pharmacy could act as a central pharmacy, shipping the IMP to the trial participants. This can also include cross-border shipments.	• Reduced costs and IMP spillage • Enabling direct-to-participant delivery of IMP with stringent stability requirements • Increased distance between site study staff/ pharmacist and the participant • Not accepted by regulators in all EU countries	Box 2
Local pharmacy-to-participant	Model in which the IMP is picked up by the participant or legal authorized representative at, or shipped from, a local pharmacy. A local pharmacy is a community or hospital pharmacy that is not the investigative site's pharmacy.	• Enabling low-intervention trials with authorized IMP • Increased burden for local pharmacists (eg, training)	Box 2, Box 4
Sponsor-to-participant	Model in which the IMP is shipped from a private company sponsor depot, or a contracted manufacturing site, wholesaler depot or distributor location without the involvement of a pharmacist, to the participant.	• Respondents had no experience with this model in Europe	

Abbreviations: EU, European Union; IMP, investigative medicinal product.
[a]Based on interpretation of the respondents' comments.

Box 1 Investigative site-to-participant IMP supply involving home nurses

A courier-service representative supported phase 2 and 3 trials investigating monoclonal antibody infusions in oncology patients. The trials were conducted in several European and north American countries. IMP was shipped from the investigative sites to the patient via couriers, and patients were administered intravenous infusions at home by home nurses. For a patient residing near the site, the home nurse was given the possibility to collect the IMP before visiting the patient.

Box 2 Central and local pharmacy-to-participant supply using postal mail

Respondents involved in a postauthorization safety trial discussed this trial of urate-lowering therapies in patients with gout, which was conducted in the UK, Denmark and Sweden. In this clinical trial, the IMP was authorized and supplied directly by post from the central pharmacy to participants in the UK and Denmark. In Sweden, participants were supplied with the IMP from the central pharmacy via local pharmacies. The relatively low costs of the DtP IMP model enabled this clinical trial.[15]

Not all models were considered suitable for all types of IMP, and the IMP characteristics, such as safety profile (and phase of development), stability, need for complex preparations and route of administration, should all be taken into account when considering DtP IMP supply solutions. Drugs with a marketing authorization are particularly suitable, as indicated by one respondent:

> With the upcoming legislation, the ECTR [regulation EU 536/2014], if a medicine is investigated conform to the SmPc [summary of product characteristics], then it does not have to be labelled as an investigational product. Thus, a participant could pick up this medicinal product with a prescription at a local pharmacy.
>
> (Hospital pharmacist)

Advantages and disadvantages of the different delivery methods

Although shipment via postal mail was considered financially attractive, this method does not allow for ascertaining the identity of the recipient, which may be a problem for certain IMPs (eg, strong painkillers). Another concern with postal mail involves

Box 3 Investigative site-to-participant model using a courier service

A representative from a large pharmaceutical company discussed a phase 2 clinical trial designed to investigate temperature-controlled tablets for psoriasis and which used a site-to-participant model. This trial was conducted in France, Germany, Poland, Spain and the UK. Each country had an investigative site from which couriers collected the drug for delivery to the participants' homes. However, the relatively large IMP packaging and the need for temperature control (ie, the IMP had to be stored in a refrigerator) impeded at-home storage and required multiple IMP shipments.

Box 4 Local pharmacy-to-participant model

A hospital trial pharmacist discussed an investigator-initiated clinical trial in which a "local model" was employed. In this study, a registered injectable antibiotic was investigated for an indication other than the authorized indication. Local healthcare professionals were involved in the clinical trial and trained in GCP. General practitioners were involved in the recruitment of study participants and community pharmacists were responsible for dispensing the IMP. According to the respondent, the use of an authorized IMP enabled the use of this DtP IMP supply model.

the lack of control over the IMP shipment, which may result in participants having to report nonreceipt of the IMP. Courier-service representatives indicated that they allow for flexible IMP deliveries (eg, to workplaces), which may support participants to continue their daily lives. However, the use of courier services may be more expensive and organizationally complex, as mentioned by several respondents.

Direct from participants

Unused products and biological samples can be shipped back direct from participants for reconciliation purposes and analysis. The respondents indicated that unused and empty IMP packages are typically returned to site pharmacies for reconciliation and destruction purposes. Processes similar to DtP can be implemented, such as postal mail or courier collection, although a pharmacist involved in postal mail deliveries indicated that participants may be less diligent regarding the return of unused IMPs through postal mail, which may influence adherence monitoring.

3.2.2 | Drivers of direct-to-participant supply implementation

Covid-19

Some respondents indicated that they had no experience with DtP IMP supply before the Covid-19 pandemic. The interviewees explained that the pandemic was an important motivation to explore DtP approaches, as it could ensure clinical trial continuation. Moreover, courier-service and industry representatives suggested that the Covid-19 pandemic could provide an opportunity to change future clinical trial conduct. However, one hospital pharmacist reported that, after the initial Covid-19 outbreaks, IMP was no longer shipped directly to participants but once again had to be collected at the investigative site.

Patient-centricity and engagement

Most respondents indicated that the implementation of DtP IMP supply, alongside other decentralized trial activities such as remote data collection, contributes to making clinical trials more patient-centric by reducing the need for on-site visits. Additionally, travel expenses are reduced and the participation of those who live further from investigative sites, have mobility challenges or experience distress during visits is facilitated. Furthermore, respondents from all categories of interviewees said that recruitment and retention of participants could improve because interest to participate (eg, from participants living in more remote areas) may increase when the need for on-site visits is reduced through, amongst others, the implementation of DtP IMP supply. This was considered to be of particular importance for clinical trials with long follow-up and limited on-site procedures. It was suggested that, although they may be more challenging to organize, trials could employ an opt-in/opt-out approach in which participants can choose between DtP IMP shipment or collection of the IMP at the investigative site. Industry representatives, based on their interactions with participants, mentioned that participants generally react positively to the implementation of DtP approaches, although personal and cultural differences exist. The interviewees explained that it is important to incorporate the patient voice when designing a trial:

> Does it fit the patient's needs? Things cannot just be like, Okay, let us just simply move this over to the home. Other things are going to have to be looked at, so we are looking at the patient's perspective and the hurdles they might see: do they like it, do they not like it? [...] We are trying to learn from them as well. What challenges do they see and where do roadblocks come up?
>
> (Pharmaceutical company representative)

3.2.3 | Impact of regulations

Unharmonized regulations

A lack of specific or harmonized regulations was reported to be a barrier to the implementation of DtP IMP supply. Regulations concerning

the DtP IMP supply models, home health visits, and the import and dispensing licences were reported to differ within Europe and globally. Although not experienced as a barrier in the EU/EEA, cross-border shipping was considered by several respondents to be an important barrier to DtP shipments more generally, as it typically requires a lot of time. Due to an absence of regulation, the implementation of DtP IMP supply must be assessed on a case-by-case basis:

> Based on our experience, we can provide information to clients, but that does not necessarily mean […] that they will allow the same for your study, because they might think that for this specific project there is an additional risk, meaning that they will not allow it. We have no general answer about whether something is allowed or not, because there might be differences across the [clinical trial] protocols and depending on the product.
>
> (Courier-service representative)

Others explained, however, that a lack of regulation, or a lack of clarity in existing regulation, could be regarded as a facilitator, as this allows for the integration of DtP solutions on a case-by-case basis. To allow for country-specific adjustments, one sponsor representative suggested the use of "flexible protocols" regarding IMP provision (ie, not detailing the specifics per country). However, others emphasized that specificity in the protocol or dispensing plan is needed to obtain regulatory and ethics approval.

Additionally, the requirements for DtP supply models were not considered consistent with conventional dispensing practices. For example, one respondent indicated that IMP storage requirements are not considered when participants collect their IMP on-site, whereas additional requirements, such as temperature monitoring, are imposed when courier services are used.

Privacy

Compliance with data privacy regulations was discussed frequently in the interviews. It was indicated that the data privacy considerations of the investigative site-to-participant model are not fundamentally different from those of the conventional clinical trial conduct. Privacy considerations, which are particularly evident for the sponsor- and central pharmacy-to-participant models, are principally related to shielding personal data from trial sponsors and contract manufacturing/research organizations. The respondents indicated that no personal data should be accessible to the trial sponsor per the ICH E6 guideline and that personal data should be solely used for the delivery of the IMP. To that end, couriers should have the minimal data needed to deliver the IMP parcel and confirm the authorized recipient's identity. For example, the respondents indicated that the protocol numbers and the participants' full names and dates of birth should be left off the parcel label. In addition, informed consent forms should contain sufficient information regarding the DtP IMP supply processes. Therefore, the success of the DtP model is dependent on the set-up and design of appropriate privacy controls to ensure access to data is granted per the needs of the trial. Courier-service representatives indicated that it is appropriate to hand the IMP only to the participant or authorized representative, reach out to the participants prior to the delivery to agree on a specific delivery time window and to return the IMP shipment to the sending party when the participant is not there to receive the delivery.

Investigator oversight

It was reiterated by most respondents that, per ICH E6, the overall responsibility for the IMP-dispensing process, IMP return, IMP-adherence monitoring and participant safety rest with the investigator, who may delegate tasks to third parties (eg, courier services, central or local pharmacies). Although the respondents indicated that investigators are generally willing to participate in DtP solutions, several respondents had experienced investigators who were hesitant about delegating, or unwilling to delegate, tasks to third parties. This hesitation may occur because the investigator is ultimately responsible and may not be confident with the offered DtP solution or vendor, or may want to use their own infrastructure. Engaging site staff in the set-up and execution of the DtP processes and the provision of an opt-in/opt-out possibility for the site may enable DtP IMP supply by fostering investigator confidence in their oversight.

4 | DISCUSSION

This study explored the experiences with DtP processes in the context of a clinical trial in Europe. Investigative site-to-participant, local and central pharmacy-to-participant supply models are employed across Europe. The respondents suggested that the most important drivers of the implementation of DtP IMP supply solutions were the Covid-19 pandemic and the need to centre clinical trials around participants. A lack of harmonized regulatory perspectives was experienced as a barrier to implementation, but may allow for DtP approaches on a case-by-case basis.

4.1 | Experience with the direct-to-participant investigational medicinal product supply models

DtP supply has been used previously in a diverse set of clinical trials,[15–23] including trials to evaluate drugs for Alzheimer's disease[16] and antithrombotic therapies in patients with Covid-19[17] and to investigate drug adherence.[18] In line with the results of the current study, DtP IMP solutions are reported to be advantageous in clinical trials because of a "geographically dispersed rare population", as well as being more convenient for participants' daily lives,[16] enabling more pragmatic[19,20] and decentralized[21] trial approaches, limiting in-person interactions and thus allowing participants to quarantine during the Covid-19 pandemic,[17] facilitating the inclusion of a large number of physicians and patients,[22] decreasing the workload of the site study staff and minimizing potential interruptions in the

treatment course.[23] Although DtP IMP supply has been reported throughout different phases of clinical development,[24] not all types of IMP may be suitable for DtP shipment, such as products with an unknown safety profile, complex route of administration or strict cold chain requirement. As an example, a systematic review investigating decentralized methods in clinical trials found that DtP shipment was mostly employed for authorized oral IMPs.[25] Furthermore, the infrastructure, such as courier services and central pharmacies, that is available in the specific country of interest should allow for DtP IMP supply.

We found that the investigative site-to-participant model is currently the most frequently employed model in Europe because there are few regulatory barriers to its implementation. It is also seen to be the closest model to the traditional pathway in a non-DCT setting, which may also support investigator willingness and uptake. Furthermore, the investigator should remain responsible for IMP dispensing and administration per ICH E6, although they may delegate these tasks to contracted external services per the EMA GCP inspector working group questions and answers (Q10 and Q11).[4] This can, however, cause additional barriers as the investigator would be expected to oversee trial-related activities delegated to individuals who are outside of the jurisdiction of the site, which may lead to unwillingness to delegate tasks associated with IMP shipment.

The respondents indicated to have no experience with the sponsor-to-participant model in the EU, owing to privacy issues (ie, shielding personally identifiable data from commercial trial sponsors) and the need for pharmacy controls required in the dispensing of the IMPs. While sponsor depots could involve pharmacists dispensing the drugs, this model was not explicitly mentioned by the respondents, and privacy and investigator oversight concerns may remain with such a model. However, a set-up comparable to source data verification, during which a monitor has access to personally identifiable information,[7] could be envisioned for IMP-dispensing by sponsor pharmacists. Additionally, models could be employed in which participants visit the investigative site for the initial dispensation, with resupplies then provided by a DtP IMP supply model. Other options may also include the addition of a home health nurse to the DtP service who is the responsible healthcare professional and may receive the IMP, and administer and observe the patient as needed per the requirements of the clinical trial protocol. Although such an approach would cost more and may not be as efficient as planned, it allows for generating more experience by trial sponsors and investigators.

4.2 | Toward more explicit definitions of the models

Based on the findings of the study, we conclude that the various DtP IMP supply models are currently not well-defined. Furthermore, it is not clearly defined which tasks may be delegated by the investigator while maintaining oversight per ICH E6 requirements in the various DtP models. The main changes in responsibilities when implementing DtP models may include (i) the sponsor selecting the pharmacy and process for distribution instead of the investigator using the site's pharmacy, (ii) the courier obtaining a more patient facing role and (iii) the patient obtaining a more substantial role in IMP accountability. Thus, we advocate the use of more explicit definitions in guidance documents and case study reports to share best practices, while acknowledging a panoply of variants and combinations of models and means of delivery. We distinguish four models of DtP IMP supply: (i) investigative site-to-participant, (ii) central pharmacy-to-participant, (iii) local pharmacy-to-participant and (iv) sponsor-to-participant. Our results show that essential elements of the description of an IMP supply model include the location from which the IMP is shipped and whether or not a pharmacist is involved in dispensing the IMP, the method of shipment and data privacy implications (ie, who has access to the personally identifiable data). When implementing DtP IMP supply solutions, at least these elements should be described in protocols or IMP-dispensing plans for regulatory and ethics review.

4.3 | Regulations and direct-to-participant investigational medicinal product supply

In Europe, different dispensing models may be implemented dependent on the risk profile and stability of the IMP, provided it is in accordance with national legislation,[26] which is known to be lacking or unharmonized.[5,6] In turn, lacking or unclear legislation may lead to careful selection of countries by the sponsor to ensure trial timelines are not unnecessarily delayed by rejection of the DCT element. Nonetheless, the impact of the Covid-19 pandemic on clinical trial conduct has been a driver of DtP IMP supply approaches and influenced the regulatory perspectives of DCT elements.[10,27] The guidance provided and experience gained during the pandemic can now become a starting point for the development of durable guidance regarding DtP IMP supply. Nonetheless, a hospital pharmacist mentioned a return to on-site dispensing post-Covid-19, which may reflect a perceived limited benefit or need for DtP shipment, particularly for trials that were initially set-up without DtP IMP supply and only moved to this model out of necessity during the Covid-19 pandemic. Recently, a European recommendation paper and national guidance documents on the implementation of decentralized elements, including DtP IMP supply, have been published (Supporting Information, Data S1).[28–31] Common themes in these guidelines include the responsibility of the investigator to dispense the IMP, the provision of sufficient information (including privacy implications) to participants and the suitability of IMPs, including the safety profile of the IMP and organizational aspects (eg, temperature control, accountability processes, compliance with GxP). Additionally, the European recommendation paper contains an annex with national requirements regarding DtP IMP delivery to trial participants.[31] According to this national overview, most EU countries allow for IMP delivery from the investigative site or pharmacy associated with the investigative site. Several EU countries further allow for IMP delivery from any delegated pharmacy or

dispensing by a local pharmacy, and only a few countries allow for delivery directly from the manufacturer or sponsor or are currently developing their respective regulatory framework. The recommendation paper does, however, not extensively discuss the conditions under which different means of delivery (eg, through postal mail or courier service) could be considered. Regulatory considerations on this aspect could be included in future recommendations.

Under the Clinical Trials Regulation (EU 536/2014), low-intervention clinical trials which investigate authorized IMPs following the terms of the marketing authorization are subject to less stringent rules regarding the labelling and traceability of the IMP,[3] potentially facilitating the local pharmacy-to-participant model. Nevertheless, the interviewees in this study cited the training of local pharmacists in GCP as a challenge for the local pharmacy-to-participant model. The Salford Lung Studies, which involved 130 community pharmacies and over 2500 pharmacy staff being trained to dispense the study drug, have shown that the training of local pharmacists is feasible.[32] The challenges encountered included the involvement of locums and independent pharmacies, turnover in pharmacy staff and additional standard operating procedures.[32] Furthermore, the need for additional GCP training of local pharmacists in the context of a clinical trial investigating drugs with a marketing authorization is disputable, as pharmacist training may suffice and be compliant with ICH E6, which states that, "each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)".[7]

4.4 | Strengths, limitations and suggestions for future research

In this article, we explored case study examples of DtP IMP supply in the context of clinical trials conducted in Europe. We were able to interview a diverse set of respondents, including hospital pharmacists and representatives of courier services and pharmaceutical companies with experience in Europe and globally, thereby ensuring the applicability of the results. Nonetheless, the number of site study staff respondents, including investigators, was limited, which may have led to a skewed representation of their views. This research has shown that it is feasible to employ DtP IMP supply models in Europe, and the findings of this study could be used when discussing these supply models with regulatory bodies and ethics committees. The models and associated definitions described here could furthermore be used to identify best practices regarding DtP IMP supply.

This exploratory research primarily focused on the operational feasibility and acceptability of different DtP IMP supply approaches, whereas other perspectives should also be taken into account when considering the implementation of such activities in clinical trials. For example, the participant and ethical perspectives regarding the intrusiveness of DtP IMP supply are essential and may differ across patient populations and cultures. This study was further limited by the lack of information in some of the case study examples, which was potentially engendered by participants' hesitancy about sharing detailed information, therefore case studies should be shared and described in both scientific publications and grey literature to show the circumstances under which DtP IMP supply is feasible and acceptable. Furthermore, more empirical evidence is needed to support the use of the different models. For example, studies could investigate the impact of DtP IMP supply on IMP adherence and accountability. Additionally, further studies should focus on patient and investigator acceptability of these approaches.

5 | CONCLUSION

In Europe, investigative site-to-participant IMP supply can be implemented, provided the IMP characteristics including the safety profile allow for it, as there are few regulatory barriers to its use. However, this model could engender an increased burden for site study staff. Regulatory aspects that may influence the local and central pharmacy-to-participant models include a lack of harmonized regulations and acceptability, and the responsibility of investigators to oversee IMP handling and accountability, which may influence their willingness to delegate IMP-related tasks. The local pharmacy-to-participant model was considered most suitable for investigating IMPs with marketing authorizations, and this should be explored for low-intervention clinical trials under the EU Clinical Trials Regulation.

AUTHOR CONTRIBUTIONS

Amos J. de Jong: Conceptualization; methodology; formal analysis; investigation; writing. **Yared Santa-Ana-Tellez**: Conceptualization; methodology; formal analysis; writing; supervision. **Mira G. P. Zuidgeest**: Conceptualization; methodology; writing; supervision.**Renske J. Grupstra**: Conceptualization; methodology; formal analysis; investigation. **Fatemeh Jami**: Writing. **Anthonius de Boer**: Conceptualization; methodology; supervision. **Helga Gardarsdottir**: Conceptualization; methodology; writing; supervision.

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CONFLICT OF INTEREST STATEMENT

F.J. is employed by and holds stocks in AstraZeneca. No competing interests were disclosed for this work by the other authors.

DATA AVAILABILITY STATEMENT

Interview transcript data was used in this study. Participants did not consent to make the transcripts publicly available. Supporting quotes are available in the results section of this paper. Excerpts from anonymized transcripts can be made available upon request. Please contact the corresponding author for more information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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