

Establishing and Managing Processes Enabling Delivery and Returns of Investigational Medicinal Products (IMPs) to Patient's Homes

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This article overviews the regulatory environment and the potential supply strategies for shipping clinical supplies Direct to Patient (DTP) homes.

The clinical trial environment is expanding. Many sources have documented that in order to meet regulatory demand more studies are 'going global' and have an increasing number of countries included. Studies are increasing in duration and patients are participating in studies for longer. Additionally, the portfolio of products being investigated is changing with more emphasis on biological products.

However, data suggests that while the number of trials being conducted worldwide is increasing, the number of sites is remaining relatively constant.¹ Moreover, 83% of US sites only participate once in a clinical trial suggesting that there is increasing pressure for involvement for new studies on "good clinical sites."² Additionally, there is an increasing interest in undertaking "remote" or "e" clinical trials where most or part of the clinical protocol assessments are undertaken away from the clinical site.

Patients themselves are becoming more knowledgeable about medication they are taking, while at the same time they are looking for flexibility. A recent ISPE survey found that 78% of patients would find it helpful to have their clinical

trial medication delivered to their homes rather than having to visit an investigator site. Interestingly, this finding was much more prevalent among the younger demographic who may be more time poor.³

In some countries, patients may have to travel long distances to visit clinical sites and this can influence their willingness to comply with site visits and hence the clinical protocol. Product stability also may be a concern in these situations for temperature sensitive products, because unless suitable transportation containers are provided to the patient, there is the risk that the storage conditions for the product may be compromised on the return journey to the patient's home.

Evidence from contributors to this article suggests that many clinical sites are already shipping clinical trial medication direct to patients on an "ad hoc" basis. This is a concern/consideration for the sponsor who is ultimately accountable as processes must be appropriately documented. Implementation of controlled solutions is therefore preferable.

Benefits in employing a Direct to Patient (DTP) shipping solution may include those shown in Table A.

Beneficiary	Benefit
Patient	<ul style="list-style-type: none"> • Supports patients who have long/difficult travel to site • May eliminate need and burden of transporting large returns back to site • May prevent treatments/dosing being missed • Assists those with disabilities or other health issues that impacts their ability to travel • Supports patient lifestyle, e.g., work travel or holidays • Reduced travel costs
Site	<ul style="list-style-type: none"> • Simplified processes • Reduced storage burden • Possible to increase visit windows
Trial	<ul style="list-style-type: none"> • Increased patient retention • Improved patient compliance/ adherence • Manages the “last mile,” full end to end control of product/stability right to the end users • Optimized drug accountability and returns • Reduced waste

Table A. Direct to Patient (DTP) shipping solution benefits.

Definition

There are two possible supply strategies when considering shipping clinical trial supplies direct to patient’s residences.

- **Site to Patient:** in this scenario, supplies are still shipped via the investigative site, but then a specialist courier manages the ultimate distribution to the patient’s home.
- **Depot to Patient:** in this scenario, IMP is shipped directly to the patient homes from either the original packaging/distribution facility or regional/country depots.

Both of these strategies will be discussed in this article although it should be recognized that even if a site to patient shipment strategy is permitted by local country regulations,

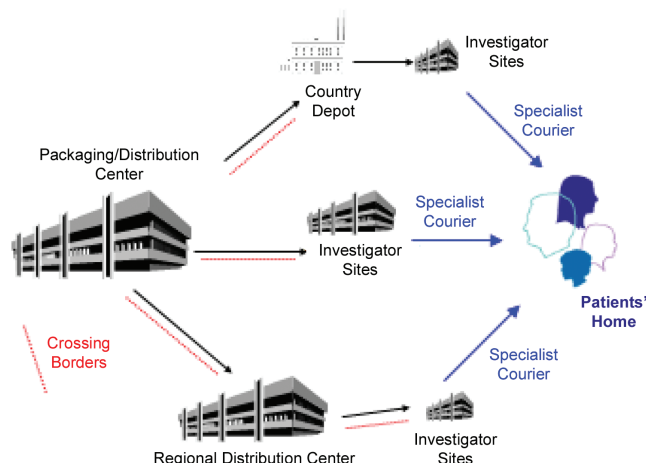


Figure 1. Distribution Network for DTP from site.

these same regulations may not permit direct depot to patient shipments.

Regulatory Overview

There are very few clear regulatory references to Direct to Patient (DTP) and thus it is always best to be transparent to authorities and ethics review boards regarding such procedures in a trial application. Clearly, there is no single strategy that can fit all situations; however, there may be inclusion/exclusion criteria. For example, in the case of “take home” drugs, this approach may be limited by the hazardousness of the product, e.g., it is not likely to be appropriate for controlled substances. To date, only a few companies have implemented this type of distribution strategy for some clinical protocols in a restricted number of countries.

An increasing number of countries are becoming more “open” to sponsors employing a DTP strategy and as it has been already stated, early dialogue with the regulatory authorities/Ministry of Health (MOH) is recommended. The acceptance of this approach varies depending on the protocol and planned supply chain and one country that initially may, based on missing or incomplete study information, decline this strategy, later may accept DTP when fully recognizing the patient benefits.

US Regulations

Investigator responsibilities are described in the US regulations, (for example, 21 CFR 312.60-312.69) where it is mentioned that the clinical investigator “is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator’s care.” This statement could allow the interpretation of providing the drug “directly” to the trial subjects. Contrary to this, 21 CFR 312.61 seems to challenge the possibility to “mail” the

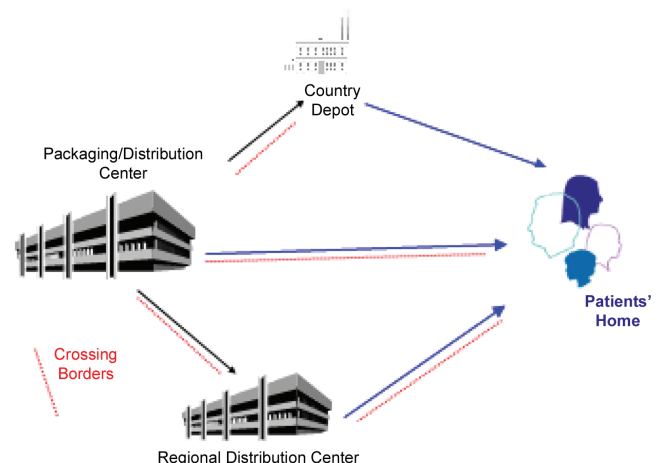


Figure 2. Distribution Network for DTP; not via clinical site.

clinical trial supplies to the patient, as it requires that “an investigator shall administer the drug only to subjects under the investigator’s personal supervision or under the supervision of a sub-investigator responsible to the investigator.”

The FDA is concerned that the investigator:

- May lose control on the product and its quality (e.g., controlled temperature storage)
- May supply the drug to a person not authorized to receive it
- May not keep appropriate documentation.

The FDA does permit that in rare circumstances (e.g., distance from site, difficulty to travel), the drug could be dispensed via a family physician or local pharmacy, but this must still occur under direction from the investigator.

In addition, it would be prudent also to consider any Health Insurance Portability and Accountability Act (HIPAA) implications as HIPAA does mandate procedures for protecting the privacy of individual’s health information and thus is applicable to patient/trial subjects.⁴

However, acceptance of DTP practices within the US is gaining more widespread acceptance. If the DTP process is described in the protocol in addition to the ethics committee submission/patient informed consent, as the approver of the clinical trial, FDA regulations should take precedence over any state regulations with respect to the approval of that clinical trial, as long as the investigator is still dispensing the IMP. However, it would be wise to consider any applicable individual US state laws that may need to be complied with, particularly in the case of any proposed strategy that did not involve the clinical site directly with dispensing IMP. For example, the sponsor would need to consider the laws in the state in which the dispensing facility is located, as well as the laws in the states into which the drugs are shipped.

EU Regulations

In the European Community, the recently issued EU Clinical Trial Regulations 536/2014, (which repeal the current Clinical Trial Directive 2001/20/CE), there is no mention of a DTP option. It states that IMP shall be traceable.⁵ However, there are other laws and regulations throughout the EU that may prevent a manufacturer or wholesaler from distributing a medicinal product directly to a patient’s home (e.g., German Drug Law Arzneimittelgesetz (AMG)), so such laws would need to be considered.⁶

In the MHRA Good Clinical Practice

Guide,⁷ the chapter related to storage and distribution makes a clear reference to the possibility of “Supply of Investigational Medicinal Products by Post” either as a pre-planned activity or in special circumstances with the major objective of facilitating patient accessibility to drugs and treatment compliance. The guide suggests that if clinical trial supplies are to be shipped/posted to patients, strong attention needs to be paid to:

- Compliance to storage requirements
- Assurances of a documented chain of custody
- GCP compliant drug accountability procedures

These details and processes would be subject to audit if DTP was employed for a study as part of any MHRA GCP audit of the clinical site or sponsor. Critical consideration must be given to the prescription being compliant with applicable laws and regulations at the point of dispensing if DTP models that do not use an investigator site are used.

In accordance with the above guidance, several websites of medical schools, National Health Service (NHS) hospitals and institutions describe the DTP practice as a viable option, particularly for studies where the same institution is also the sponsor of the trial. In general terms, it is a common understanding that the act of drug “dispensation” is “usually” performed by a pharmacist (or otherwise qualified individual) unless a differing prior agreement is in place with the pharmacy.

In collecting benchmarking information from the ISPE IP COP global community, extremely variable results were obtained with different justification for use of DTP. Some examples include:

It is well recognized that the number of clinical studies is growing and sponsors are increasingly turning to innovative solutions to recruit and retain patients. Patients themselves are requesting options for study participation that fit their clinical trial involvement around their lifestyle.

Although shipment of clinical trial supplies direct to patient homes is a relatively new concept, it is an option that is likely to grow in use to support the increasingly challenging and changing environment of clinical supplies. Until recently, this technique has been employed on an “emergency” or ad-hoc basis often without documented procedures or sponsor control. In addition to the potential benefits to the patient, the study site and the overall trial of a direct to patient shipment strategy for clinical supplies, the growing shift toward “virtual” or home based trial participation including home administration of clinical supplies by study nurses, will also fuel the demand for this type of approach.

This article provides an overview of the regulatory environment and potential supply strategies and practicalities for shipping clinical supplies direct to patient homes.

- There are countries considering that the IMP can only be administered under physician's care so the "act" of giving the drug to the subject should be undertaken by the investigator.
- Some countries could allow the delivery from investigator sites to patient home only as a deviation to current legislation and so it should be described and approved in the protocol documentation.
- A country describes in their legislation that the IMPs "must" be received, from the sponsor, by the investigator or site pharmacist with the aim of prohibiting alternative supply chains

In all the cases referenced, DTP is applied to IMP shipments going from the investigator site to the subject, so the step of having the drug arriving at the clinical site is always fulfilled.

The alternate scenario of having the IMP shipped from the sponsor's depot directly to the subject home seems not to have been utilized to any extent as the task team found that a general requirement of the respective country's laws is the involvement of a "pharmacist." However, even considering to have (and document) a pharmacist performing the "order dispensation" of the IMP to the patient's residence from the depot, it is likely that a risk assessment and/or some form of formal agreement will need to be in place between the investigator sites and the depot's pharmacist, as each clinical site Principal Investigator (PI) has the overall responsibility for his/her patients.

There are some other aspects that should be considered in the overall objective of fulfilling general regulation requirements where they apply:

- Ensure appropriate description of the DTP distribution strategy in the protocol and obtain upfront approval from competent authorities to guarantee it won't be interpreted as Good Clinical Practice (GCP) non-compliance/protocol deviation
- Ensure correct information to the subjects and acceptance about the planned distribution approach (Ethics Committee approval and subject informed consent)
- Ensure appropriate control and GCP compliance for confidential information, like patient home address and contact details
- Ensure compliance with any applicable local laws and regulations

Practicalities of Direct to Patient (DTP) IMP Management

As described above, there are two main supply chain paths for delivery. First is to provide a route from a clinical site to the patient location, the second is to provide a route from a distribution depot to the patient location. In either case, the sponsor supply chain must be designed to provide clear

chain of custody from an order by the site investigator to the delivery to the patient. The distribution route should resource personnel trained in GMP and GCP procedures and chain of custody documentation. For depot to patient, this is especially important.

Typically, the patient will visit the investigative site for the initial dispensation of study supplies and thus it is usual for only re-supplies to be provided direct to the patient's residence. As mentioned previously, depot to patient delivery is less common as local pharmacy laws and regulations or Ethics Committee interpretations of GCP may prohibit such a delivery option. In practice, the site investigator must place an order for the supplies to be sent to the patient. This order then is received at the distribution depot and documented to be from the investigator. For site to patient delivery, the site performs a dispensing visit as per normal practice, but the distribution vendor or specialist courier is contacted to pick up the materials and deliver to the patient. In either case, the distribution network must make arrangements directly with the patient for the delivery of the materials and establish a chain of custody with documentation and signed acknowledgement of receipt of the materials by the patient.

Additionally, it will be necessary to undertake a risk assessment of the distribution network to identify required procedures including those that may be necessary, dependent on the mode of delivery, to prevent un-blinding, document product stability as well as verifying that the materials have arrived in good condition prior to release of the materials to the patient. Finally, documentation for the investigator and sponsor must be provided. In the case of documentation to the sponsor, all patient identity information must be removed to be in compliance with data protection regulations.

Reverse engineering of the supply chain for used or expired patient materials also should be considered. In these cases, the same chain of custody requirements are applied from the pick-up of the materials from the patient to the site of destruction either at a depot or at the site. If destruction occurs at a depot, the site should be provided with all accountability documentation.

Appendix 1 provides some outline guidance on the types of study criteria that may benefit from a DTP strategy.

Some frequently asked questions around the management and practicalities for employing a DTP strategy include:

Overall, how is the supply chain organized to keep control?

The supply chain needs to be clearly laid out and documented before submission to the regulatory bodies as this will be one of their main areas of focus during their review. It is particularly important to show how any recall procedures would operate, how the patient is able to be supplied the materials in a timely manner, and how patient compliance

can be assured. Sponsor, depot and sites will need to be very clear on their documentation control as they will be open to inspection from the local regulators, this can cross all variants of GxP.

Who can ship? What type of courier?

A key part of the DTP distribution network/supply chain may need to be delegated to a courier; this is an important aspect to the success and compliance of the trial. It also may be possible to co-operate/coordinate with a home nursing/care network. A clear contract and Quality Agreement should be in place with the courier, or the Clinical Research Organization (CRO) that is managing them on your behalf. Specific training also will be required for the courier involved. If a courier is involved, they should not enter the patient's residence or initiate any dialogue around the study or signs and symptoms, but depending on the requirements of the protocol, this training could involve waiting for the named patient to be present to receive the supplies and/or taking the data logger and excess packaging back to the depot. There is also the potential for additional interaction requirements within the Interactive Response Technology (IRT) system in use for the protocol.

It is critical that the courier company involved operates to GxP standards and has a level of compliance that at the very minimum will meet Good Distribution Practice (GDP) requirements for all aspects of the shipment. This includes assurance that all related documentation is provided to the appropriate Trial Master File. The courier company needs to have a well-designed and clear set of SOPs in place, which also describe contingency plans, e.g., what happens when they cannot deliver to a patient if there is a temperature ex-

cursion in transit to the patient and whether it is acceptable to deliver to anyone but the patient. The courier company also would need to ensure compliance with local laws and regulations (e.g., obtaining and maintaining the appropriate permits and licenses if required) to provide such a service.

Is it ever appropriate to post clinical supplies to patients?

In the UK, Royal Pharmaceutical Society of Great Britain (RPSGB) has provided guidance on when delivery and posting of medicines to patients is appropriate.⁸ Risk assessment by the clinical site is required and many hospital pharmacies may derive mitigation strategies which review packaging requirements, safe use of the medicine by the patient in addition to supporting the use of mail services that have acknowledgment of receipt as well as processes that ensure appropriate return of undelivered packages. Typically, these mailing mechanisms would be utilized only in the case of highly stable non-controlled (non-scheduled) or non-hazardous IMPs.

Shipment Request Process

The shipment request regardless of distribution route in many cases will be generated by the IRT system, and thus dispensing is generated by a "visit" recorded by the Principal Investigator (PI) and subsequent information being uploaded into the IRT system. Any level of manual oversight is dependent on the sponsor company, protocol design and system requirements. The important elements that must be captured is PI assessment of the patient and their assignment of the IMP to the patient, assurance that the IMP has been stored appropriately and has valid 'use by date/expiry date' and that in general, IMP is not dispatched unless all specifications of the protocol have been met.

What requirements are there at the patient end?

Training of the patient in these protocols also has an important significance. They need to know what to expect when the courier meets them, including formal identification, etc. In addition, the patient needs to know what they should do with the package and what they have to provide back to the courier. They need to be taught how to physically receive the supplies and in some cases depending on the set-up, they may be required to report information to the PI either through an IRT system or other mechanism. Given the burden of compliance on the patient, the trial design that accommodates DTP might be limited.

Returns and Reconciliation Process

As indicated earlier, ideally the supply chain should be reverse engineered to enable the returns to be collected by, where used, the courier company in the same way that the

Typical Criteria that support the benefits of a DTP Strategy

Study Trial duration is over 2 years
Robust stability profile of IMP
Distribution Chain is located in each country of operation
Distribution Chain is trainable on GMP/GCP
Patient visit windows are > 3 months
Trial employs dispensing only visits (no medical check)
Trials employs home administration by study nurse
Patient to site ratio is less than 3:1
Patient population is remote from clinical sites
Patient transport of IMP is burdensome (e.g. large amounts, temperature sensitive)
Ethics Committees/local regulations are open to direct to patient

Appendix 1.

deliveries are made (pre-calling and other arrangements). Once this has been done, the returns should be taken to a central location and there the reconciliation can be undertaken to the appropriate standard deemed by the protocol. The central location could be a CRO/CMO, courier company depot, the main investigating site or the sponsors own facility, but this should be a clear part of the supply chain design prior to the study start.

Implications for the Clinical Site

It must be very clear to the clinical site involved what their role in DTP is and what the expectations are for them in the management of the IMP. As this is not a normal process, they will need to have appropriate training and it is good practice to provide a clear diagram/process flow to show what they are expected to do and how this works with the patients and supply chain activities as well as timings and responsibilities.

Management of Interactions with IRT Systems

The IRT system, if well designed for the protocol, could be helpful in enabling a real-time picture of the status and location of the supplies. However, a poorly designed set-up could adversely affect the logistics of the protocol. It is necessary to define how reordering limits should be set-up in the system, who is going to acknowledge receipt of the materials at the patients home address, as well as more fundamental questions including should central facilities be shown in order to manage the levels of inventory.

Conclusion and Summary

There is a growing need from sponsors and clinical sites as well as a desire from the patient population for clinical supplies to be shipped direct to patient homes. The regulatory environment is changing, but as yet for many countries, this is “uncharted territory” although the rules of GCP for the most part prevail.

Options and frameworks do exist to support this strategy; risk assessment and early dialogue with the regulatory authorities/MOH being the key to success. This article presents and outlines our understanding of this capability at the current time; however, with increasing end user demand and industry experience, an updated and more detailed overview may be provided in the years to come.

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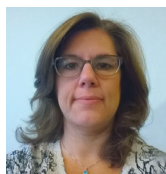
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