KNOWLEDGE SHARING SERIES

4G CLINICAL

Direct to Patient (DTP) Clinical Trials

Leveraging Modern Randomization and Trial Supply Management (RTSM) Systems to Overcome Supply

Bringing crucial medicines to those who need them, faster.

4GCLINICAL.COM

About 4G Clinical

4G Clinical is driven by a single purpose: bring crucial medicines to those who need them, faster. 4G Clinical believes that the way to accelerate clinical research is by disrupting the way trials are executed. That's why we have revolutionized RTSM (randomization and trial supply management) and supply forecasting capabilities and services from the ground up.

4G Clinical is committed to helping sponsors and CROs follow the science, wherever it may lead, as quickly and as safely as we can. While we will not discover the next novel compound in the lab, we are doing our part by leveraging our extensive experience and technological innovations to bring speed and agility to clinical trials.

"We reduce the time it takes to commercialize vital medications by delivering validated, easily extendable RTSM capabilities to Pharma and CROs faster than anyone in the world."

About 4G's RTSM

4G's RTSM platform, Prancer RTSM®, utilizes natural language processing alongside integrated clinical supplies forecasting and management functionality to slash development timelines, increase operational efficiencies and offer exceptional quality.

"Our 100% configurable and agile RTSM is built for the clinical trials of today and tomorrow."

Overview

With more and more studies focused on disperse patient populations, the industry has been exploring alternative trial designs to improve enrollment and ease the burden on patients to access trial sites. One of these alternative designs is Direct-to-Patient (DtP).

DtP trials are a win-win for patients and sponsors. Patients gets better service, travel less, get their treatment where they are and sponsors accelerate trial timelines and reduce cost. The challenge lies in designing it correctly so the integrity of the study remains intact - such as addressing significant impacts on the supply chain, including timing, shelf-life and temperature.

The purpose of this white paper is to provide in-depth information on the various DtP approaches while offering insight into best practices when incorporating DtP into the protocol. Additionally, resulting supply chain challenges are explored as well as how Randomization and Trial Supply Management (RTSM) systems can be leveraged to overcome those challenges.

What is DtP?

In traditional clinical trials, patients travel to and from an investigator site ("brick and mortar site") for all clinical trial tests and assessments that are generally performed by investigators and their delegated study personnel.

DtP, however, is considered a type of Decentralized Clinical Trial (DCT) because trials are conducted at locations outside of the investigator site (e.g., patient's home, work place, travel destination) and may be executed through the use of mobile/local healthcare providers, wearable/sensor devices, telemedicine, eConsent, etc. DCTs may involve any phase, but must have at least 1 investigator with a physical location. Some DCTs are completely remote, while others are hybrid (only a portion is conducted remotely).

It is important to clarify that DtP trials are not synonymous with virtual or site-less trials. Virtual trials have no investigator and no sites, and are primarily computer modelling studies.

Three Types of DtP Models

There are three main types of DtP Models: Depot-to-Patient, Site-to-Patient and Hybrid:

Depot-to-patient

The IMP is shipped directly from the main or sub depot (e.g., central pharmacy) to the patient home. Nurse services may be added.

Site-to-Patient

The IMP is shipped from the depot to the site, and from the site to the patient home.

Hybrid

A mix of DtP / traditional site visits. In other words, when patients have site visit(s) and also receive IMP at home (from depot or site) in other visits.

Site-to-Patient or Depot-to-Patient can be selected based on the country and local regulations or unique product considerations. Whether to ship to the patient home or ask the patient to come to the clinic may be a choice of the patient and/or investigator due to the protocol design and constraints.

The Hybrid model is the most utilized in the industry. However, it is also the most complex because it needs to support two processes in parallel. The first process is to ship from the site/ depot to the patient and provide remote support (calls/videos/tracking). The second process is managing inventory at the sites, treating patients at the clinic and maintaining a list of who is part of the DtP trial and who is not. Shipment costs rise exponentially (per patient per visit vs. per site). The courier is in direct contact with the patient. A pharmacist is required at the depot/central pharmacy and blinding at the depot level may be considered.

	Burden on Sites	Reduced Waste	Increased costs	Process Complexity
Site to Patient	↑	↓ ~~↑~~	↑	↓
Depot to Patient	↓	↓	↓	↑
Hybrid	↑	↑	↑	↑

Despite the above complexity, the benefits of DtP remain clear. The next steps you should take before starting or transitioning to a DtP trial is to understand if this is appropriate for your particular study, then carefully looking at the supply chain risks and building a solid process (aligned with key stakeholders) that is supported by a robust Randomization and Trial Supply Management (RTSM) system.

Key Considerations – Is DtP Right for Your Clinical Trial?

It is critical to determine if you are going to use a DtP approach prior to drafting the study protocol. There are too many complications, regulations and requirements to switch to that approach after the study is live. The question remains, when is a DtP approach the right decision for your study?

Here are some examples of studies that may be a fit for DtP:

- **Phase II/ III or post commercial** – Since there are less risks of adverse events (AE), it is safer to run he study and allow patient to be dispensed at home.
- **Study trial is > 2 years** – As study duration increases, so does the expected dropout rate and number of patient engagement challenges. DtP is a good fit for longer trials as they A) allow time for shipping processes to stabilize and B) show significant improvements in dropout over extended periods of time.
- **Robust stability profile of IMP** – During phase II/ III, the product is more stable and the shelf life is longer. This should alleviate some of the stability and logistical concerns of a DtP approach.

- **Patient visit window are > 3 months** – This is only a recommendation to make the process simple. As protocol deviation may be on risk, the dispensing is dependent on the shipments to the patient home. If the visit window is narrow, a delay in shipment or damaged kits arriving and such other cases may jeopardize and introduce new risks to the study.
- **No training required for dispensing the IMP (assembly / trainers / sophisticated devices)** – The "Keep it Simple" principle plays a role here. Adding more complexity may cause misuse of the product, as the patient is not present at the site and can't ask all the questions or receive additional training.
- **Patient population is remote from clinical sites** – This may emphasize a high motivation to choose DtP and allow patients to participate from far distance.

Supply Chain Risks with a DtP Trial

After you have determined DtP is right for your trial, there are key decisions that need to be made regarding the supply chain to ensure getting the drug to the patient at precisely the right time – whether it be at the site, the patient's home, the pharmacy, etc. The main areas to consider are: shipping coordination and logistics; full accountability/traceability of drug; and how technology (specifically the RTSM) will ultimately play an important role in study execution.

Shipping Coordination and Logistics

One of the main supply chain risks of a DtP trial is shipping coordination and logistics. In traditional trials, the courier could easily schedule delivery of the drug during the operating hours of the clinical site. With DtP, the courier is patient-facing which introduces challenges with delivery. The arrival window is only 2–3 hours vs. site opening hours. When nurse services are required it may be even more challenging to coordinate all to arrive on the same time. To complicate matters even more, patient privacy data concerns arise (e.g. the patient requests a shipment to be sent to an alternative address).

Another possible complexity arises when the pharmacist needs to be involved to prescribe medication being delivered from the depot direct to the patient.

Who is responsible to ensure that coordination between the courier and patient (and potentially the pharmacist, nurse services) is solidified and followed for each and every delivery of medication? What role does the sponsor play? The courier, depot and site? This is a very unique risk and this process needs to be determined and agreed upon ahead of study start so the patient receives their drug.

Full Accountability/Traceability of Drugs

Another supply chain risk of DtP trials is the ability to know exactly where the study drug throughout the study duration. If the process is tracked manually, sponsors are relying on the CMO for this information. CMOs typically rely on excel where the element of human error is introduced. Accurate traceability is critical in the case of managing temperature excursions, shipment cancellations and accountability/returns. If the process involves both the sponsor and CRO involvement (e.g. approving temperature excursions), this can be challenging to communicate and resolve quickly.

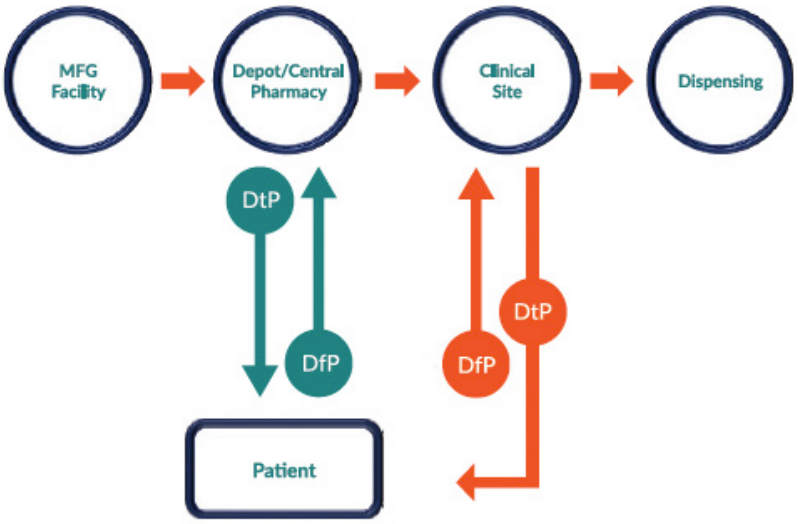
Additionally, contingency plans for emergencies in case of a recall are much more challenging when you don't have full visibility into the supply chain.

Role of Randomization and Trial Supply Management (RTSM) Technology in DtP Trials

RTSM (Randomization and Trial Supply Management) systems play a critical role in ensuring the right medication gets to the right patient at the right time. Leveraging an RTSM can enable DtP trials, effectively mitigating the supply chain risks mentioned above and ensure the integrity of a DtP trial.

The use of an RTSM dramatically reduces the risk of shipment coordination. Shipments can be generated automatically or manually and the forecasting algorithm can manage different methods of shipping. Inventory can be managed on all levels.

Process in RTSM:

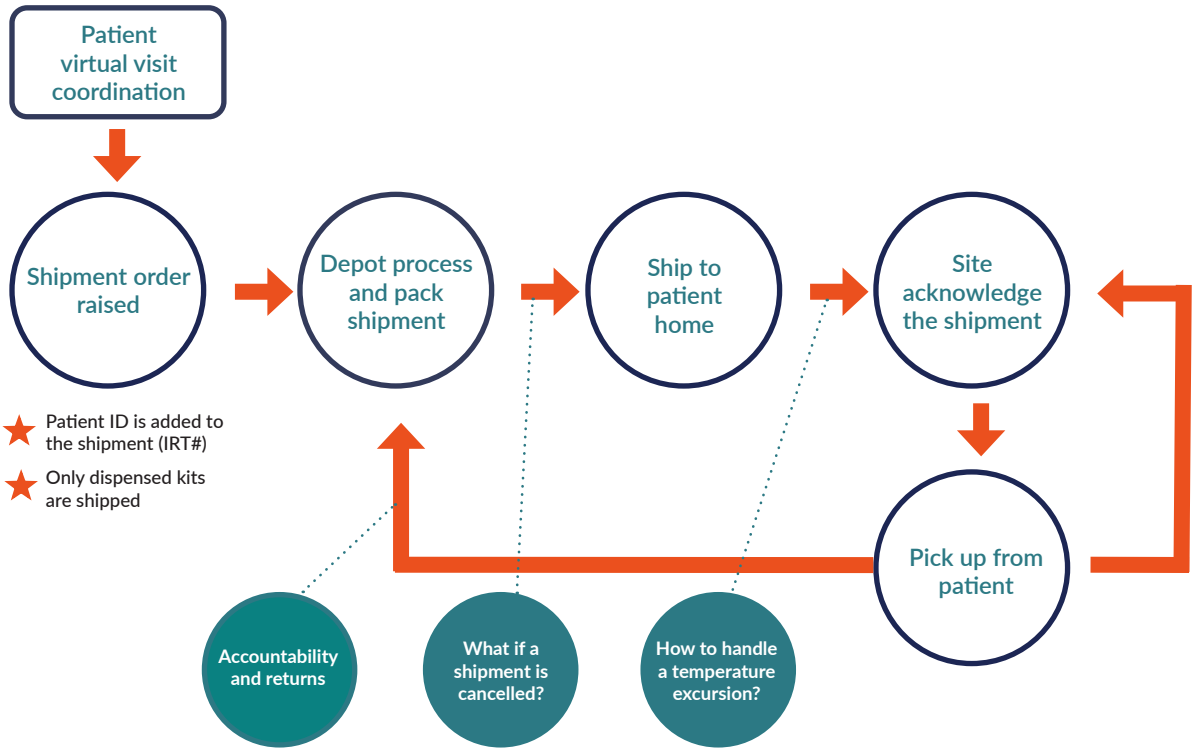


Example: When a shipment is raised, the depot, courier and site are notified. After delivery to the patient's home, the site receives a notification and in parallel the data logger was sent to the depot to upload it to the RTSM. After reviewing the data, the sites receive a notification the shipment was received at the patient home and can guide the patient of how to take the medication and next steps remotely.

RTSM Enables Full Traceability of Medication – Even at Patient's Home

Allowing most of the transactions to be in an RTSM system helps to manage kit status, control the supply and maintain the study. The RTSM can track data for temperature excursions, shipments received, etc. Sponsors will have full accountability of how much was dispensed, how much was taken, etc.

Virtual Dispensing:



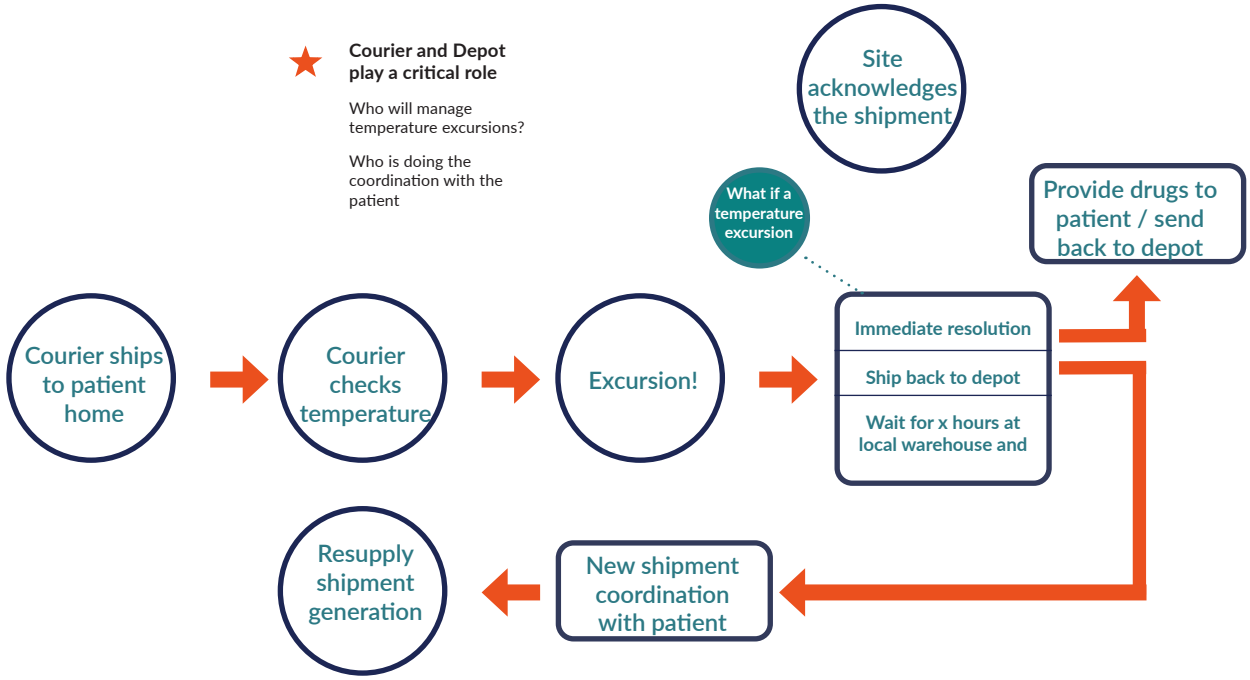
The RTSM Mitigates Supply Challenges including:

- Temperature excursions
- Shipment cancellations
- Accountability, returns & destruction

Temperature Excursions

Temperature excursions can be tracked and managed leveraging the RTSM. The first step is determining the process to handle temperature excursions for the study. For example, the RTSM can help facilitate an immediate decision such as if a shipment is quarantined. Would a replacement need to be shipped right away (automatic resupply) or wait for a decision? Urgent shipments can be raised in the RTSM to make sure we are still on time for the visit window. Below is a suggested workflow, with considerations for temperature excursions.

Considerations for Temperature Excursions:



Shipment Cancellations

In addition to temperature excursions, there may be other reasons for a shipment to fail – shipment cancellations. The patient may forget and not be at home, there may be an error with address or the courier arrives too late in the day or too early.

Can a new shipment be generated and arrive on time without protocol violation due to the visit window? How should this be flagged and processed not to be missed? What other creative solution can be found? Those decisions can be managed in the RTSM as simple configurations.

Accountability, Returns & Destruction

Drug accountability can also be managed in the RTSM as it tracks kit status throughout the study and ensures a single source for performing reconciliation at the end of the study. With DtP trials, unused kits must be returned from the patient. The patient could return unused medication back to the site during a visit or the courier could collect the unused medication at the following DtP visit.

If it's a Site-to-Patient method, the courier is picking it up from the patient the same way and instead of shipping to the depot – ship to the site back which may introduce inefficiencies. So, for Site-to-Patient, the accountability process at site may remain almost the same. But for Depot-to-Patient, who is doing the accountability? Some unused kits, expired kits are at the site inventory. However, most of the dispensed kits are returned from patients home. Should they be returned to the depot? To the site? Who is accountable now?

Since this process is more complex than traditional studies, sponsors must clearly define the accountability process and leverage the RTSM to track the flow of drug. Performing accountability outside of the RTSM can be risky due to its complexity.

Beyond supply chain risks, the RTSM can help mitigate other risks from DtP trials including managing patient privacy data and adapting to new regulations as they become available.

Patient Privacy

Managing patient privacy data through the whole supply chain without compromising the patient personal data is a risk of DtP trials. Since medication is shipped direct to a patient's home, there must be records of patient names and shipping addresses. A question remains, should the RTSM house patient names and addresses or should this data remain with the CMO/courier to coordinate the process?

Lack of Regulations

Another risk that must be considered is there are no set regulations to guide DtP/Decentralised trials. Sponsors must follow best practices as they exist today, and the process will be approved through the protocol submission and follow with approval per country. In the event that regulations do arise, there may be country-specific refusals to deliver drug. A robust, modern RTSM can configure country/region-specific rules as required to adapt to any emerging regulatory requirements.

Conclusion

DtP trials are beneficial in attracting patients to join clinical trials, aid in retention and shorten enrollment. Patients are very involved and advocate for their own care, including easing the burden of getting to trial sites. However, these studies do not come without risk. It is important to understand how to design and execute these studies to protect patient privacy and supply chain integrity. To help mitigate these risks, sponsors should consider leveraging randomisation and trial supply management (RTSM) systems as they provide a consistent, reliable and transparent method to manage the unique requirements of the DtP supply chain. As the industry has only begun to embrace these studies, the flexibility of modern RTSMs are needed to adapt to this new and evolving trial design.

About the author

Neta Bendelac, 4G Clinical Senior Director of Strategy, has over 10 years of experience in Clinical Supply Chain Management. She headed the Clinical Supply Chain department at Teva Pharmaceuticals, where she established new and innovative approaches to managing IMPs in clinical trials, designing them with a highly acclaimed and unique patient perspective. Prior to Teva, Neta worked as an international Supply Chain consultant, providing simulations and optimization tools to clients worldwide.

Neta holds a BS in Industrial Engineering and a Master of Business Administration (MBA) from Tel Aviv University, Israel. Neta is always focused on execution, finding joy in creative solutions to help patients around the world.

Download our White Paper:
Disrupting Study Start-Up

Still have questions?
Contact us today to start a conversation.

US (Corporate Headquarters)
4G Clinical
370 Washington Street
Wellesley, MA 02481, USA
+1 (781) 694-1400
sales@4gclinical.com

Europe
4G Clinical
Herengracht 124-128, 1015 BT
Amsterdam, The Netherlands
sales@4gclinical.com

Japan
4G Clinical
Room 705 Forecast –
Shinjuku Avenue
2-5-12 Shinjuku, Shinjuku-ku
Tokyo, 160-0022, Japan
+81-12-054-2455
sales@4gclinical.com