“The Last 100m”: Managing the Logistics of Advanced Therapies in an Acute NHS Hospital Setting

This document was produced by Simon Ellison, Simon died in the Spring of 2020 after a short illness. He is much missed within the Northern Alliance. He played a transformational role in adapting and enhancing supply chains for cell and gene therapies, part of his commitment to rapid and effective delivery of these advanced therapies to patients over a number of years. We remember Simon with admiration. In recognition of his contribution we note it here.

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"The Last 100m": Managing the Logistics of Advanced Therapies in an Acute NHS Hospital Setting

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Background

Advanced Therapies are making rapid progress towards becoming widely commissioned as therapeutic options outside the research setting - and the first few products have already crossed this hurdle. The numbers of Advanced Therapies in clinical trials are increasing significantly (Cell and Gene Therapy Catapult Clinical Trial Database) and there are a significant number more in the preclinical pipeline (Cell and gene Therapy Catapult preclinical database). The numbers of patients receiving Advanced Therapies is forecast to reach 50,000 per annum in the US by 2030 with 30-60 products reaching market (Quinn et al 2019 - Estimating the Clinical Pipeline of Cell and Gene Therapies and Their Potential Economic Impact on the US Healthcare System; VALUE HEALTH. 2019; 22(6):621–626). If the UK is treating just 10% of this volume of patients then that would represent a significant number of therapies (and their starting materials) being shipped around the UK each week - and a potential challenge for healthcare providers for managing these at scale.

Advanced therapies bring with them specific challenges, particularly in their logistics and tracking. Many have time-dependencies between acquisition of starting materials and start of manufacture or completion of manufacture and administration to a patient. It is therefore critical for the whole end-to-end process to be transparent and integrated. Whilst much work has gone into being able to ship patient-specific samples around the world, how therapies get from the point at which a courier drops them off at a hospital or intermediary (e.g. blood service) and their chain of custody to a patient has not yet been defined (i.e. the "last 100m"). Whilst this is manageable for the currently small numbers of therapies that are used in commissioned therapies (1 or 2 per month at each site), or for highly regulated research projects, the challenge of how this would be managed at scale needs to be addressed so that the logistics pathway doesn't become a blocker to adoption. To explore some of the challenges, a workshop was held at Leeds Teaching Hospitals on 11th October 2019 as part of the Northern Alliance Advanced Therapies Treatment Centre (NA-ATTC) programme.

The workshop content and structure was created collaboratively by representatives from World Courier and Leeds Teaching Hospitals NHS Trust, in response to the needs of industrial partners and the hospital itself. World Courier were keen to learn more about how the interface with drivers could be improved and how the delivery process could be optimised / standardised at sites. Leeds Teaching Hospitals NHS Trust (LTHT) has significant experience of handling viral vectors in clinical care (both for research purposes and as part of commissioned services), but wanted to look at how it could optimise the management at scale of both "fresh" and "frozen" cellular therapies within the organisation. Attendees included clinical staff, hospital managers, pharmacy staff and nurses from within LTHT, along with representation from other NHS sites, NHSBT, the Welsh Blood Service and industry partners - both therapy providers and companies involved in logistics management

(Autolus, Trakcel, World Courier). The make-up of the attendees reflected the close collaborative working relationship between NHS partners and industry within the UK's ATTC programme.

The workshop addressed the following issues:

- Product arrival at site
- Internal moving and handling of Advanced Therapies within a hospital
- Local storage requirements - both at site or at an intermediary site
- Training needs
- Enabling infrastructure and processes that might already be available

Product Arrival

Leeds Teaching Hospitals NHS Trust is made up of 7 different hospitals (Leeds General Infirmary, St. James's University Hospital, Chapel Allerton Hospital, Seacroft Hospital, Wharfedale Hospital, Leeds Children's Hospital and Leeds Dental Hospital), the majority of which are complex sites with multiple buildings, specialties and wards, making it potentially difficult for delivery drivers to identify exactly where Advanced Therapies should be delivered to. Adding to the challenges in the next 5 years will be the construction of 2 new hospital buildings on the Leeds General Infirmary site and the move of clinical services into those buildings. The hospitals are served by a Pharmacy services on each site and specialist Asceptics facilities at the St. James's University Hospital site in which viral vectors are routinely processed for clinical trials.

The concept of a courier delivering manufactured therapies to the central store10s was explored, with the workshop attendees spending time in a delivery bay on the St. James's University Hospital site to observe activities and explore the suitability of such an environment for where couriers should deliver Advanced Therapies. A number of significant concerns were raised by the workshop attendees:

1. The delivery bay was noisy making hearing anything said very difficult, thereby creating a communication barrier
2. Multiple deliveries were happening simultaneously with lorries continually coming and going.
3. Deliveries were many and varied - with medical and non-medical supplies arriving at the same time and being treated in the same way.
4. A member of the clinical team may not be available to receive the AT directly from the driver - or the named person might not be available due to pressing clinical duties - or if a delivery has been significantly delayed (e.g. by bad traffic or a delayed flight) then their shift may have ended.
5. Delivery bay staff may not be fully aware of what they're actually signing for or how to check it when it arrives

6. Advanced Therapies could be left unattended in a corner or even lost if moved or taken to the wrong location. Delays in transfer to the right clinical area could be particularly damaging for "fresh" products with a limited shelf-life.

Options for how product arrival could be improved were assessed. Delivering therapies directly to a clinical area was discussed, but the complexity of individual hospital sites (not just in Leeds) was felt to be a barrier to this, even though some therapy manufacturers are requesting that their therapies are delivered straight to the ward area. Multiple delivery drivers would deliver to the same hospital and it could take significant time for a driver to actually find the right clinical area - let alone parking near it or taking the right lifts up to different floors - or transporting products through unsuitable areas. There would also be the question of whether the receiving person on the ward had been trained in receiving product and what would happen if they were off sick or otherwise engaged elsewhere. This model also posed concerns for the pharmacy team as they would have a lack of oversight of what had been delivered to where in the organisation (particularly when working at scale), and whether the right checks had been done on the product before final use.

Newer cryoshippers are starting to incorporate GPS trackers so that manufacturers can track where they are. However many companies are not yet using such shippers and there is a risk that GPS signals would be inhibited in remote/shielded hospital locations. It may also be difficult for clinical staff to actually still locate the shippers, even with GPS information.

The management of radiopharmaceuticals was felt to be a good exemplar for how sites could manage the receipt of Advanced Therapies better - these are currently delivered to a designated point in pharmacy and handled according to defined SOP's. It was therefore proposed that Advanced Therapies follow this model with delivery to a pharmacy department where trained individuals would be able to receive product, check the product and all the associated documentation and document the handover and transfer of custody of the therapy to that organisation. Delays in arrival would be countered for by ensuring that a trained member of staff was always on duty and GPS information from cryoshippers would be useful to alert staff to imminent arrival of a product (or to hold-ups in the delivery). Having a single designated drop-off point at a hospital site would also make life easier for delivery drivers and create efficiencies in the delivery process. Enhancing the communication between delivery drivers and receiving staff was also felt to be beneficial - with delivery drivers also being fully cognoscente of the products that they are delivering.

Recommendations

1. Products should be delivered to pharmacy - not a generic delivery bay or directly to the ward area.
2. Staff trained in how to handle and manage Advanced Therapies should receive the product
3. Defined and auditable handover processes should be developed where 3 “keys” are needed to authenticate the handover. Handover to the healthcare provider should be visible to the manufacturer of the therapy.
4. Paperwork has to be checkable by Pharmacy prior to the product getting to the patient bedside
5. Improved communication between the courier and receiving healthcare provider is essential

Internal Storage, Moving and Handling

Consideration was given to how both fresh and frozen products should be stored, handled and transported through an organisation once delivered to a central delivery point. Having resilience in systems was a key point for both fresh and frozen products in case of events such as power outages, internet failure, systems failure or major trauma incidents requiring diversion of beds to cope with casualties. The ability to manage at scale was considered a major challenge, with an organisation needing oversight of product management and use.

Moving and handling of relatively bulky shippers through an organisation was discussed and concerns were raised about infection control implications of taking shippers into clinical areas, particularly those with seriously unwell patients in, as well as the challenges in transporting bulky shippers around a hospital. Having pharmacy unpack and check products prior to transferring them into a clean, smaller device for transport within the hospital further supported the recommendation made in section 1 for delivery to a central pharmacy point and the onward management from there. There would also be implications for the hospital and patients if there were a “spill” of a GMO in a highly public area (e.g. entrance lobby). The concept of members of the public being physical barriers should be explored when thinking about the internal logistics for an Advanced Therapy within a healthcare provider so as to avoid highly public areas and keep to staff-only or quieter routes. Whilst these may be longer and less-obvious, there would potentially be other benefits to this. This led to discussions on the need for SOP’s and an audit trail in place to govern the moving and handling of Advanced Therapies - particularly knowing where an individual therapy is at any one time within a healthcare provider and which patient it is intended for (which may not simply be achievable with GPS trackers). Clear lines of communication were also required with clinical teams with significant advance planning and notification of when a therapy could be moved from a designated “arrival and holding point” to the ward for administration. Roles such as “Advanced Therapies Co-ordinators” may be something that providers of therapies need to consider to manage products at scale and provide central co-ordination with clinical teams.

For frozen products, the need to store cryoshippers locally for short periods of time (up to 9 days) were identified. A degree of local storage is essential for if patients deteriorate and are no longer able to receive their therapy when it was originally scheduled. However this is difficult for providers and many rely in intermediaries such as NHSBT for local storage. The concept of having "rechargeable" shippers which could be topped up with liquid nitrogen beyond the 9 day period if required was discussed - whilst this is not currently possible, having SOP's and systems for transfer of product from one shipper to another (as World Courier have) would potentially be beneficial where products are being stored locally and continuity in chain of identify is required. Providers should have access to such short-term storage facilities. Having "mini shippers" for transporting the frozen product from pharmacy to the ward where a product would then be thawed prior to administration to the patient (ideally next to the patient in a highly controlled manner specific for that product) was also discussed - but again these would need to be clearly integrated into the logistics workflow with continuous chain of identity for the therapy. Systems, processes and equipment to minimise the risk of any uncontrolled thaw are essential.

It was felt that whilst frozen products were likely to be simpler and more standard to manage and move around an organisation because of more standardised approaches to arrival and a degree of flexibility in the timelines of getting a product to a patient. "Fresh" products were likely to be more challenging because of the narrow window in which they could be administered to a patient and the diversity of "boxes" in which they might arrive. Strong systems and processes should be in place for the management of these - but to minimise complexity for healthcare organisations, core SOP's for moving and handling of Advanced Therapies should be the same, regardless of the therapy.

A common topic raised was that of healthcare providers requiring systems for knowing exactly where an Advanced Therapy was in an organisation following arrival (having a £250,000 product go missing is not a liability that an NHS Finance Director wants on his hands) and being able to do that in a simple way at scale. Whilst GPS trackers are good for knowing where globally a product is, they are unable to distinguish between adjacent wards or corridors. Being able to track where a product is / has been would also create an audit trail for moving and handling SOP's to ensure only designated routes through an organisation have been followed, avoiding public areas. Other programmes of work in the NHS have focused on being able to trace medical device products (Scan4Safety). This programme has every location in a hospital barcoded with a unique GS-1 compliant barcode and all medical devices supplied also have unique GS-1 compliant barcodes. In this way, any medical device in the organisation can be found, its use recorded (and linked to a patient) and if the manufacturer needs to recall products due to a safety issue, all products linked to that recall can be removed from stock within an hour. Such a system could be used for the internal management of Advanced Therapies- including for documenting arrival of an Advanced Therapy and handover by a courier (and therefore digitally linking the chain of custody). It may also be possible for organisations to assign a barcode at acquisition of starting material (for an autologous product) and therefore have a single barcode follow a product around the world from patient to patient, creating a seemless digitally-linked supply chain.

Recommendations

1. The complexity of managing Advanced Therapies within a healthcare provider needs to be minimised to allow management to be done at scale with appropriate local oversight.
2. Manufacturers cannot expect healthcare providers to have a different management process (or system) in place for each ATMP - this will cause complexity and inefficiency.
3. Healthcare organisations need to be clearly and transparently part of the logistics chain of custody with internal logistics processes and mechanisms for tracking locations of therapies clearly set out.
4. Internal logistics pathways should avoid highly public areas
5. Organisations need to have a responsible person for ATMP management (based in Pharmacy) who can co-ordinate all processes and link with clinical teams
6. Internal systems needs resilience to cope with unforeseen major events

Training

High quality training of all staff involved in the management, transport and administration of Advanced Therapies is vital, and no member of hospital staff should handle an Advanced Therapy who hasn't been through an accredited training course. Such training needs to be documented as part of their training record with regular refresher courses provided in a similar way to other mandatory training programmes within the NHS. There may be specific requirements with individual therapies (e.g. thawing) and so these need to be clearly understood and delivered to specific groups. However, as much of the training as possible needs to be "generic" to cover multiple products and avoid complexity for providers handling multiple different products. Where bespoke training is required for individual therapies, these need to be delivered to key staff groups and backed up with online materials and videos which are easily accessible (perhaps linked to a product via its barcode). The need for online resources is particularly true for therapies which may be given less routinely - i.e. only a handful of times per year by an individual healthcare provider.

However, the training needs need to be understood and therefore a gap analysis is required of where training deficiencies are and what training is required by individual groups. The ability to do this relies on individual healthcare providers having systems and processes for managing Advanced Therapies with key groups of staff defined. A common language, common to both those working in therapy developers, logistics providers and healthcare providers needs to be developed so that there aren't barriers to communication through unfamiliar or different terms being used to mean the same thing. We would therefore strongly advocate industry professionals and healthcare staff being trained together so that a common language is adopted and all parties can understand the pressures.

Recommendations

1. Industry professionals involved in logistics should be trained alongside staff working in the NHS so that a common language is used.
2. A gap analysis of training across staff groups involved in internal moving and handling of Advanced Therapies is required to define where the training needs are and what is common
3. Training needs to be accredited with staff carrying out regular refresher courses
4. Much of the training needs to be general and not bespoke to individual products - however some steps will need bespoke training (e.g. thawing for individual products).

Conclusions

The management of Advanced Therapies at scale within a healthcare provider is potentially highly complex - and making the management of logistics at site too complex will become a barrier to the adoption of these products. Therefore, ensuring that complexity is minimised should be a goal that therapy developers, logistics providers and healthcare organisations need be working on together. Initiatives such as the Advanced Therapy Treatment Centres should be supporting further developments required in this area.

The overall recommendations from the workshop were that manufactured therapies should be delivered to a designated drop-off point within a pharmacy department, to designated members of the pharmacy team who have been trained how to receive and check advanced therapy products. Notification of the arrival time should be communicated ahead from the courier (in real time if possible) so that those receiving a therapy know when it's arriving and internal liaison with care teams in the organisation can occur, particularly for fresh products. Courier drivers should also be aware of their responsibilities and the nature of the product that they are handling and have clarity on where to deliver a therapy and who the person it is they are handing it over to. Handovers, the chain of custody and the pathway taken through the organisation (avoiding public areas) should be documented digitally. For autologous products, tracking should start at product acquisition and follow all the way back to the individual patient. Integration of systems should be backed up with integration of training - with logistics teams from therapy providers trained alongside NHS staff.

Therapy developers need to work in partnership with individual healthcare providers to ensure that high quality local processes are in place followed for the delivery and internal logistics associated with Advanced Therapies. "Dry runs" for individual therapies have proven to be very valuable for healthcare providers and logistics providers to ensure pathways work for specific therapies. There is a risk that each therapy manufacturer will require different things of healthcare providers; this is neither practical nor efficient for a healthcare provider and will become a barrier to providing these products. The industry is young enough to work with healthcare providers to solve these challenges - and accept that there may be slight differences in processes at different hospitals once a product has gone through the front door due to the different sizes and scales of individual organisations.

This should not be of concern to industry partners, but a series of standards should be in place against which the internal management of Advanced Therapies by healthcare providers are measured to provide assurance. A consistent "handover" point also needs to be defined at which a therapy becomes the custody of the healthcare provider - and this needs to be consistent across all therapies. This minimisation of complexity includes the use of IT systems within organisations for tracking and management. Whilst individual therapy developers may use different systems, these need to be interoperable with a system that hospitals can use for their needs - using multiple IT systems will cause particular complexity and challenges for healthcare providers.

Co-ordination and communication along the logistics pathway is key. The logistics pathway should start and finish with an individual patient and the handovers and chain of custody along that pathway should be seamless. Staff receiving therapies should receive ample notification from couriers of the estimated time of arrival, particularly if a therapy has been delayed in transit - and then there needs to be seamless communication within a provider to healthcare delivery teams, particularly for fresh products with a short shelf life.