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Research review paper

Decentralised manufacturing of cell and gene therapy products: Learning from other healthcare sectors

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ABSTRACT

Decentralised or 'redistributed' manufacturing represents an attractive choice for production of some cell and gene therapies (CGTs), in particular personalised therapies. Decentralised manufacturing splits production into various locations or regions and in doing so, imposes organisational changes on the structure of a company. This confers a significant advantage by democratising supply, creating jobs without geographical restriction to the central hub and allowing a more flexible response to external pressures and demands. This comes with challenges that need to be addressed including, a reduction in oversight, decision making and control by central management which can be critical in maintaining quality in healthcare product manufacturing. The unwitting adoption of poor business strategies at an early stage in development has the potential to undermine the market success of otherwise promising products. To maximise the probability of realising the benefits that decentralised manufacturing of CGTs has to offer, it is important to examine alternative operational paradigms to learn from their successes and to avoid their failures. Whilst no other situation is quite the same as CGTs, some illustrative examples of established manufacturing paradigms are described. Each of these shares a unique attribute with CGTs which aids understanding of how decentralised manufacturing might be implemented for CGTs in a similar manner. In this paper we present a collection of paradigms that can be drawn on in formulating a roadmap to success for decentralised production of CGTs.

1. Introduction

Despite the potential of cell and gene-based therapies (CGTs), the promise of such therapies has yet to come to fruition in the light of limited commercial and clinical success. With over 900 clinical trials globally for these advanced therapies (Hanna et al., 2016), the outlook for the CGT sector is improving. The majority of these trials are in early phases and led primarily by academic research groups, a trend broadly reflected worldwide (Bisson et al., 2015). Eight CGTs have received European Union Marketing Authorisation detailed in Table 1. Of these, Zalmoxis® and Holoclar® have only received conditional approval, and ChondroCelect®, Provenge® Glybera® and MACI®, have all subsequently lost marketing authorisation due mostly to business operating considerations (Hanna et al., 2016) (EMA, 2016). Despite this, there has been significant progress and globally, over 60 studies in phase III are poised at near-entry to the marketplace (Hanna et al., 2016).

While for some CGTs the MOA is related with a high degree of confidence to specific Critical Quality Attributes it remains the case that for others the link is based upon the experience in clinical studies and may need to be refined with further discoveries about the product performance post-launch. This is further compounded by the difficulty experienced by the industry in manufacturing cost-effective, well-defined CGT products with the required reproducibility in quality. Addressing these manufacturing challenges is not an issue that can easily be resolved in isolation. Both the ever-expanding scientific knowledge of the biological systems, the method of product distribution to the end consumer and follow-up patient care must be considered when developing a manufacturing strategy for CGT products. Decentralised manufacturing or redistributed manufacturing will be a production paradigm which will be considered for production of advanced healthcare therapies, in particular those with a high degree of personalisation. Fig. 1 provides an overview of how a centralised hub and spoke or a decentralised hub and node manufacturing solution for CGTs may operate in the European market.

Centralised manufacturing has been the dominant operational model for the creation of goods since the industrial revolution. Increasing centralisation of manufacturing capability has remained the dominant model for private enterprise because of its impact in terms of

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Table 1
CGTs receiving EMEA marketing authorisation.

Product	Mechanism of action	Status
Glybera®	A gene therapy product repairing faulty fat metabolism	Authorised
ChondroCelect®	An autologous cartilage cell therapy which expands patient biopsies	Withdrawn
Provenge®	Treatment for metastatic castration-resistant prostate cancer	Withdrawn
Holoclar®	Treatment for burn induced limbal stem cell deficiency	Conditional
MACI®	A cultured chondrocyte product for cartilage defects	Suspended
Imlygic®	A viral treatment for recurrent melanoma	Authorised
Strimvelis®	A gene therapy for a type of severe combined immunodeficiency	Authorised
Zalmoxis®	An adjunctive T-cell therapy for use with stem cell transplants	Conditional

economy of scale as first seen most clearly in the early 'Fordist' factories in the US and elsewhere. Consequently, decentralised manufacturing represents a radical departure for most existing healthcare supply systems. Small-scale manufacturing goes against most of the existing concepts developed over the last two hundred years and shares similarities with the dispersed piece-rate cottage industries of old, addressing local needs in a more agile manner based on local knowledge and creating jobs and income across a network of supply. Whilst some attributes of a mass-market product can be dictated by, and customised to, consumer requirements as in a 'post-Fordist' model, there remain fundamental specification features that define the product identity for the purposes of quality, safety and efficacy which must be retained. Compliance with these features must be enforced by rigorous standards and by suitable manufacturing controls. This makes an automated solution attractive if it permits some degree of personalisation whilst maintaining quality and ensuring traceability.

These defining attributes that a decentralised CGT manufacturing model must possess add significant complexities. Many of these challenges have featured in other healthcare sectors and the resulting paradigms can be used to propose solutions for the challenges that decentralisation of CGT manufacture will face.

2. Decentralised manufacturing - healthcare paradigms

Due to the unique characteristics that CGT manufacturing presents, there is no precedent framework on which to model this emerging healthcare production system. Nevertheless, there exist a number of healthcare research and treatment paradigms which provide frameworks with features suitable for such a system. As the CGT landscape evolves, these paradigms can provide insight into fundamental organisational structures within which it is possible to identify opportunities and to identify limits to decentralised manufacturing.

Useful paradigms include the manufacture of radioisotopes for nuclear medicine, personally-titrated anti-cancer agents, total parenteral nutrition (TPN) products and blood and platelet supplies. The essential, identifiable attributes of decentralised manufacturing are: responsiveness to evolving requirements, personalisation to patient requirements as well as aseptic manufacture, shipping and release. These paradigms are described here as they all, in their various ways, contain certain attributes that are similar to the unique set of challenges presented by the decentralised manufacture of CGTs. This manufacture could initially conceivably be within a clinical setting particularly if government money is supporting the endeavour, but equally the insights could inform a future commercial setting.

It is important to note that tissue transplants historically represent a field which has contributed enormously to the CGT field over the course of decades of success. Transplant medicine represents an important

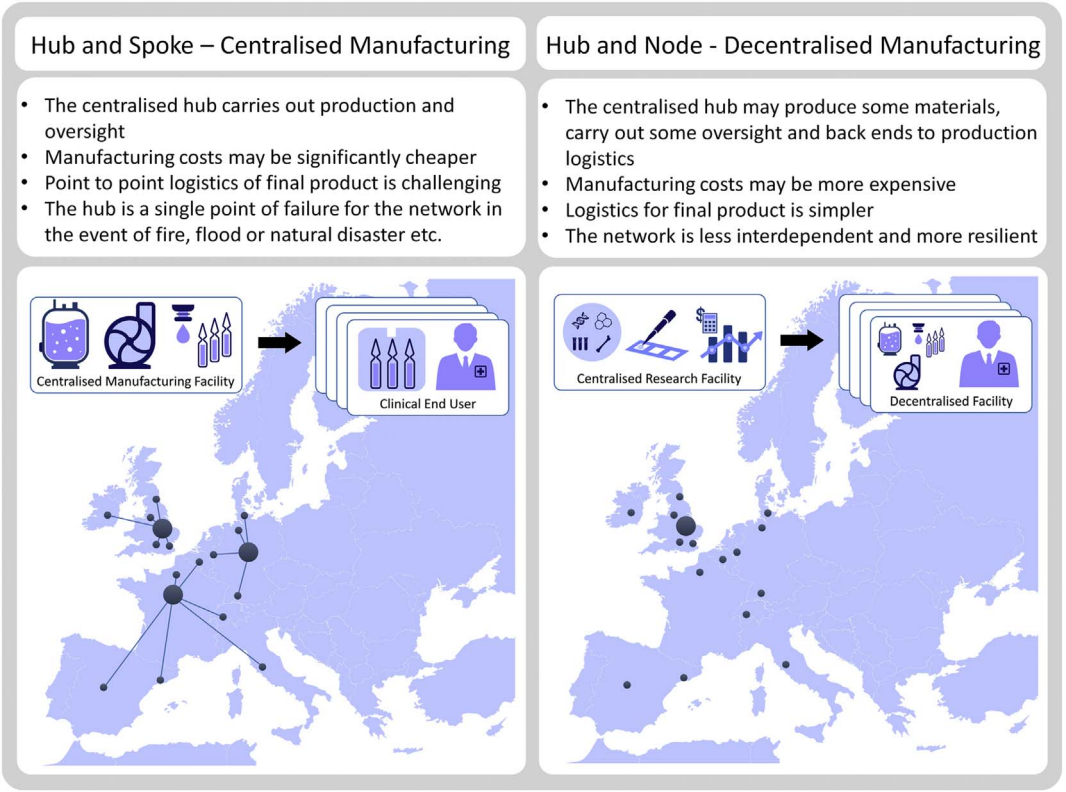


Fig. 1. Hub and spoke vs. hub and node for manufacturing and delivery of CGTs. The centralised model relies upon delivery of finished product to multiple users from one or more centralised hubs. This is closer to traditional methods of manufacturing and has drawbacks for CGTs. Decentralised manufacturing is more akin to a hub and node. In this scenario, the nodes deliver product to their immediate surrounding supported by the hub, but nodes are not fully dependent upon the hub.

source of knowledge for manufacturing and handling, but these products are in most cases conducted under tissue or transplant regulations which are unlikely to apply for manufactured CGTs. For this research we examined products where GMP applies which would be produced under similar licensure to CGTs.

For the purposes of these paradigm comparisons, the CGTs can be defined as some allogeneic, but mainly autologous products whose mode of action depends on living cells or genetic content that are more than minimally manipulated and that depend for their efficacy on administration at a systemic level or to a restricted compartment of the body or involve tailoring in a personalised, craft-based manner.

2.1. The Total parenteral nutrition paradigm

Total parenteral nutrition (TPN) is the name given to the feeding of a person intravenously. Despite the connotations of this term, this does not have to include the whole nutritional spectrum and some individuals may only need a few supplemented chemicals, minerals or vitamins. TPN is a highly customised formula which has to be prescribed for the individual patient requirement. In this regard, it is likely similar to many aspirational CGTs in that the end user receives a truly customised product for their needs and the product must be sterile or aseptic. Despite these similarities, the TPN market could be considered more mature, with a larger number of products in routine use rather than remaining aspirational goals.

Patients undergoing TPN require assessment by a trained dietitian and, depending on their needs, may receive a pre-prepared solution, a few simple constituents or a fully customised formula. This assessment and preparation is not trivial and the potential consequences of mismanagement can be severe and potentially life-threatening.

Unlike the majority of potential CGT products, the constituents of a TPN therapy are relatively stable components with long shelf lives. The TPN paradigm is similar to the potential decentralised model in a number of critical ways. The constituents are, unlike those involved in CGT manufacture, largely simple, well-defined and stable, but parallels exist in their susceptibility to contamination, both with trace elements (Pluhator-Murton et al., 1999) and, more seriously, infectious agents (Tresoldi et al., 2000). This vulnerability to contamination has presented seriously on two notable occasions in the UK. The 'Devonport incident' 40 years ago resulted in the deaths of 5 people due to a failure in endpoint sterilisation. This was not picked up through routine testing because samples were not taken from suitable representative locations of the batch (Meers et al., 1973). A similar incident occurred more recently with a bacterial contamination by Bacillus cereus in 2014 (Public Health England, 2014). Whilst the impact of the Devonport incident was evident the impact was minimised as it occurred on a relatively small scale. In addition, the Devonport incident led to the development of modern validation techniques aimed at proving that the manufacturing equipment is functioning as intended and that the personnel training is up to date and suitable. Sterility assurance in TPNs is based on the parametric release of autoclaved goods that have been made to a known ceiling for the allowable bioburden. While CGTs must be made aseptically it is nevertheless desirable, though not always the current practice, to make the goods to a control strategy in which the design space is defined in such a way that the process features that exert the most influence over product parameters are known to be controlled within ranges that will not result in a failed batch to a tolerable level of confidence. While the 6-log sterility assurance level of an autoclaved product is a very high level of assurance it is not unreasonable to expect that, with time and growing understanding of unit operations for CGTs, we will see six-sigma-level assurance of quality with respect to other CQAs.

This challenging manufacturing supply chain of TPN is remarkably similar to that posed by emerging CGTs which require a complex 'bill of materials' including chemicals and solutions, all drawn from certified sources. The number of potential constituents of a TPN therapy is large and their properties varied. Of particular concern, a large number of these constituents are listed as being in short supply which may have serious implications for patient health (Mirtallo et al., 2012). Part of this supply challenge is due to the 'just-in-time' inventory practice of many healthcare providers. This is further compounded by the fact relatively few manufacturers produce each specific constituent. If one supplier is removed either through failure to comply with cGMP manufacturing practices or voluntarily because the corporate strategy changes, the ramp-up times to change supplier can be long and may result in a short-term failure in supply. Some healthcare providers stockpile products which they consider to be at risk of being in short supply or may switch to another supply chain, neither of which is ideal (Mirtallo et al., 2012). Modern cost-saving measures are driving down inventory volumes in hospitals in favour of predictive ordering (Moore, 2016; Romero and Lefebvre, 2015). This commoditised supply chain enabled by tight procurement procedures combined with frequent finishing operations in clinic as part of supply represent the key areas this sector could contribute to efficient management of the emerging CGT sector.

2.2. The nuclear medicine paradigm

Nuclear medicine involves the use of radioactive materials primarily for diagnosis and imaging purposes. This paradigm is in many ways distant from CGTs but shares certain key attributes namely the relative instability of the product and the requirement for its specialised handling. In addition to this, it is a particularly relevant paradigm to decentralised manufacturing of CGTs as it has exceedingly high sunk costs for manufacturing and emerging manufacturing platforms are currently being evaluated which may move towards decentralisation.

The principal radioisotope used in medical imaging worldwide is technetium-99 m (^{99m}Tc). This makes up around 80–85% (30 million procedures) of all diagnostic activity using nuclear medicine globally. The isotope is derived almost exclusively from uranium-235 in a small number of research nuclear reactors. The shipped precursor of technetium-99 m is molybdenum which has a half-life of around 66 days, allowing worldwide shipping. However, for nuclear medicine purposes, the half-life is much shorter at around 6-h (Amin et al., 2014). For positron emission tomography (PET) imaging, the transport distances are much reduced as the isotope-labelled agent, ^{18}F–fluorodeoxyglucose (the principal radiopharmaceutical for PET imaging), has a half-life of only 110 min, which limits the effective transport distances to journeys of around 2 h as a maximum. The short efficacious durations for these isotopes limit the flexibility in pause steps following certain processes and fix the temporal relationship between product, practitioner and patient in a similar manner to CGTs.

These radioisotope examples represent the same dilemma facing the manufacturer of CGT products. Investment in the manufacturing platform is expensive not only in the form of infrastructure and equipment, but also in terms of amortising the costs of the strong and active research base that is required to push the manufacturing technology towards innovative platforms. Similarly, shipping and transport is complex due to the requirement for robust and secure containers. This necessitates online monitoring and tracking systems to ensure that the products comply with the release criteria once they reach their destination. Finally, once the radiopharmaceuticals reach the end user, they have to be reconstituted and/or prepared for use by technically-competent person/s. Current shortages in the supply of radioisotopes are partly due to a shortage of raw materials, but also to a highly complex supply chain in which each step is susceptible to influence by external stressors. This inherent fragility has led to global shortages in supply.

Current supply of radiopharmaceuticals has evolved from a large number of research reactors which initially produced ^{99m}Tc as a by-product. As its value increased, production was re-oriented to produce more ^{99m}Tc. The initial investment in labour, research and infrastructure for these research reactors was extremely high and one that

has not, for the most part, continued (NEA, 2010). This issue is exacerbated by the fact that ^{99m}Tc is not sold for a price which reflects the high sunk capital and research costs which went into the initial investment cycle.

More recently it has been recognised that full cost recovery (to cover wear and tear and re-investment of the money spent on production facilities) is needed to make the supply sustainable. This picture is almost a mirror of the tissue engineering, regenerative medicine and CGT marketplace which currently has few sustained marketplace successes and a handful of commercial failures. Notable success stories for patient outcomes tend to be small studies in which the high costs are borne by a research, clinical trial or medical infrastructure (Cuende et al., 2014; Hourd et al., 2014) rather than a typical re-imbursement model for an off-the-shelf product (Cohen et al., 2006). Whilst this arrangement allows exploratory research studies to progress, it remains a disincentive to investment in large-scale manufacture. One of the directions that the UK has decided to pursue for isotope generation is that of distributed manufacture using cyclotrons (a type of particle accelerator) on a smaller scale. This is already the case for PET tracers and technical barriers for producing ^{99m}Tc are being addressed in the medium term. This incremental approach to investment is well-suited to the current economic climate in which single, large-scale capital investments in novel plant are difficult to finance until market success has been demonstrated.

The complex financial arrangement of nuclear medicine as well as the recent interest in decentralised production make this paradigm an interesting proposition for comparison particularly around shared liabilities of financial responsibility. Additionally, the release at risk nature of radiopharma combined with the need for rapid QC provide additional similarities to be considered. Interestingly, there are regulatory disparities between regions for nuclear medicine which constrain manufacturing strategies between regions. This regulatory constraint is similar to the CGT landscape.

2.3. The personalised anti-cancer drug paradigm

'Personalised', 'patient-specific', 'targeted' and 'stratified' are a number of terms which collectively describe better matching of therapies to the patient needs. This approach describes care in which individual's unique characteristics and genetic profile guide the clinical decision-making process. The aim of this process is to increase the chance of successful treatment through matching the right patient with the right dose of the right product at the right time. This evidently shares a number of key similarities to the CGT approach where a highly personalised product is presented for each patient.

Personalised medicine has evolved rapidly in the last few years as we begin to gain a better understanding of the complex molecular and genetic factors which make us unique. These unique characteristics are not only part of our physical identity, but play a part in our health. As this understanding has advanced it has become more apparent that some patients are more easily treatable than others. In no field is this more apparent than the field of cancer medicine. The mechanisms in each case have become clearer more recently(Jackson and Chester, 2015).

The personalised anti-cancer medicine paradigm shares a number of similarities with the manner in which a CGT may be rolled out. Personalised medicine has to be based on a deep understanding of the patient's individual needs. In the medium- to long-term, individuals may undergo a health screening which includes this information as standard. Currently the most comprehensive screening is only undertaken by the wealthy, the curious or those who require it for a medical investigation following a diagnosis. However, there is significant progress towards both driving the costs of these tests down, as well as utilising them for a more complete understanding of patient and product (Harrison et al., 2017a). This initial screening imposes delays to treatment while samples are taken, sent for analysis, clinical decision making occurs and a customised therapeutic option is formulated.

One of the recent evolutions in cancer medicines is the use of 'dose banding'. This repackages therapies into different doses which are then distributed to specific patients. This has helped to reduce wastage of drugs and monoclonal antibodies by personalising the therapy and by dictating the degree of personalisation within the framework of the established banded dosimetry (Mayor, 2016). This approach of functionally-targeted personalisation is an excellent example of a patient-specific product which has similar degrees of personalisation, dictated by efficacy and cost, to the approach that decentralised manufacturing must undertake. This approach has the potential to progress further as the screening of patient genetic data becomes more routine. Patients can be stratified into populations specifically to aid in delivering the correct doses of drugs that have a narrow therapeutic range. In the case of autologous CGTs from a diseased patient population, it is important to note that there may be little room for flexibility in formulation and dosing. Rather the patient may need to be qualified for treatment by meeting a threshold decided by a prognostic text or assay prior to manufacturing.

Combination drug therapies are used to treat difficult cancer cases. As nano-medicines and theranostics advance further, the therapeutic options will allow decisions relating to formulation, the preferred mechanism of action and the preferred delivery route for each case (Hare et al., 2016). Already this has strong parallels with the situation for an autologous regenerative medicine product. In this scenario, patient material would be taken, processed or expanded and returned to the patient as a treatment.

Personalised nanomedicines for cancer are also very similar to CGTs in the way that they are targeted. Prognostics are needed in order to identify patients that are likely to respond positively in many circumstances (O'Brien et al., 2004; Park, 2013; Venditto and Szoka, 2013). More effective use for future CGTs will, like cancer nanomedicines, benefit from a move away from administration according to fixed formulations towards personalised posology based upon disease- or pathology-driven research. This will depend on a better understanding of the underlying mechanisms by which the therapeutic effect occurs and their relationship to the specific patient.

2.4. The blood supply chain paradigm

Patients around the world depend on a fresh supply of blood products each day. The entire blood-products supply chain relies on donors and efficient transport from multiple distributed facilities to sorting locations and finally back out to multiple end users. There are over a hundred different products which can be derived from blood, making it a complex supply chain proposition.

The most important products are red blood cells (63.4%), plasma (17.8%), platelets (13.6%) and cryoprecipitate (5%) (Whitaker and Hinkins, 2011). These products are able to be further processed into irradiated or washed forms or used as raw materials for the manufacture of recombinant products.

The decision to donate blood is dependent upon many factors such as convenience, accessibility, comfort and risk all of which must be managed in order to establish supply to meet demand. Often there are periods in which supply becomes more challenging and for this reason some stockpiling must occur. Supply of blood products also requires immunological-matching. This means that a range of products must be held to match the estimated demand. This is a similar situation to that facing haplobanks of cells which are partially patient-matched therapies cell therapies with an acceptable partial immunological match between donor and recepient. The overall goal of the blood supply chain is to ensure that demand is met whilst minimising wastage.

The blood supply chain can be understood in terms of collection, production, inventory and supply echelons. These are similar to those of a potentially centralised manufacturing process for CGTs (Fig. 2). Sourcing of blood and production of blood products is dictated more by

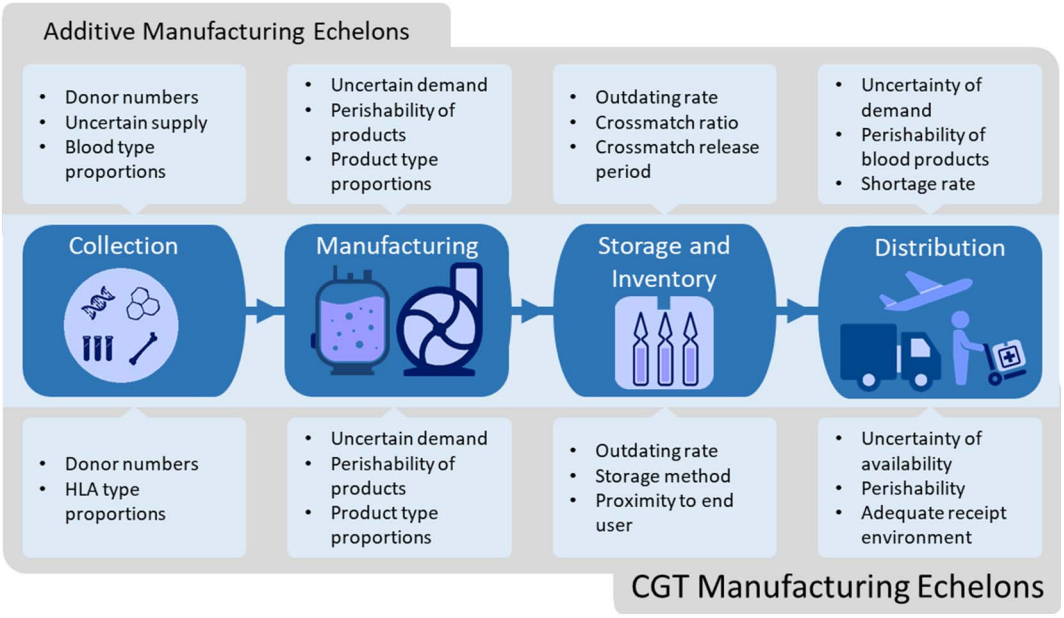


Fig. 2. The major echelons of the blood supply chain compared and contrasted with a case study with characteristics typical of a centralised model for manufacturing cell and gene therapy products.

supply for blood than by selling price as reimbursement for the core products is relatively plentiful in health services. Conversely CGT sourcing and production is likely to be driven by commercial opportunity for specific at-risk or high-value patient groups. The shelf life of blood products ranges from 5 days (platelets) to 42 days (red blood cells) whilst plasma and cryoprecipitate may be stored at low temperature for up to 1 year. This makes storage, inventory management and distribution different for each constituent and necessitates rigorous track, trace and oversight procedures. Just as for CGTs the efficacy of blood transfusions can decrease with shelf life. Shelf life, scheduling and the preservation of efficacy is one of the biggest challenge for effective inventory management for CGTs. Demand-led distribution is easier for blood products because they are lower value and easier to store. Maintaining local inventory is more cost effective. For CGTs, the products are highly specialised, difficult and costly to store and transport and require a specialist environment for receipt of goods. This in turn increases the risk of logistical breakdowns. The financial implications of wasted blood products are costly at around £120 per unit of blood to over £1000 for some products (NHSBT, 2016). This cost is a fraction of that from even one missed treatment of a CGT due to the much higher costs involved.

Breaking the blood supply chain down into discrete echelons allows examination of complex interactions. These include managing the risk of substitution (or mismatching) of products, refining inventory levels, applying scheduling models, location-based decision making or transhipping. Supply and demand affect decision making in all echelons. Modelling the process as a whole better represents the relationship between supply and demand and how they are linked to all the intermediate steps. Without this whole system perspective, it is challenging to enact effective policies. Integrated models for the blood supply chain have been around for over 30 years (Page, 1980) and can be used to evaluate strategic proposals to the overall distribution strategy.

The blood supply chain in its current form has evolved over the years, driven by a requirement to cut costs, to maintain patient safety and to correct some notable failures. The most well-known failures are the historic tragedies with infectious pathogens the first of which manifested in the form of hepatitis B in the blood-transfused survivors of World War Two. It took decades to positively identify a screening solution through a chance finding by a geneticist in 1963 (Alter and Klein, 2008). This tragic spread of infection through the live-saving blood transfusion service was again repeated in 1981 as strange symptoms began to be reported in isolated patient groups. This was of course later identified as the human immunodeficiency virus (HIV) (Centres for Disease Control and Prevention (CDC, 2006). These cases of infection are strong reminders that rigorous screening processes must be in place to identify and to prevent contamination of patient material. This is particularly pertinent as endpoint pathogen reduction techniques available to the blood supply services, such as UV exposure or chemical cleansing (Alter and Klein, 2008), are not as yet suitable for CGTs. Treatment of the blood supply chain more as a manufacturing process and integration of operational management practices have been instrumental in identifying and reducing failures (Blake, 2009) due to less obvious causes. These include practices such as reducing wastage by extending shelf lives of platelets and reducing shelf lives of erythrocytes as they may lose efficacy (Williamson and Devine, 2013) over time.

The current blood supply chain model could be used as a blueprint for centralised manufacturing of CGTs. The high-speed, high volume management of procurement and administration with full track and trace, segregation of lots and accompanying QC which has evolved to manage the blood supply chain could provide valuable insights to future CGT supply chains. The collection of autologous material, processing/expansion and subsequent supply closely mirrors the blood service system. Similarly, expansion and supply of multiple haplobanked donor materials which are then used to treat large portions of the patients with a matching profile, are similar in many respects to the current supply of typed blood products. Indeed, as a relatively mature industry, the blood supply chain can utilise fixed and variable, mobile locations for acquisition and processing of blood products. As the CGT field similarly matures, mobile manufacturing centres may become a possibility. These interesting parallels allow for exciting postulations on the operation of future CGT businesses based on the operational experiences developed with blood products yet they operate under very different regulatory frameworks and this limits the direct translation pf practices.

The centralised model has limitations. For blood supply a level of wastage is accepted in order to meet an unknown and variable demand. For CGTs this aspect can only be exacerbated by the shorter shelf life of many CGTs. The current reality is that blood products are derived from multiple donations by a small percentage of the population. This is

similar to some features of a centralised model and of a decentralised model. Two key features of the blood supply paradigm are relevant to CGT. Firstly, the entire process from source to supply should be considered and, secondly, the semi-personalised nature of blood products must be matched to patient requirements.

2.5. The additive manufacturing paradigm

Additive manufacturing (AM) is the process of generating a three-dimensional construct from a set of design specifications via the layer-by-layer deposition of starting material. Advances in this field have had a profound impact on the manufacturing industry, enabling the decentralised production of small lot sizes of complex components, and moving make-to-stock products to a make-to-order business model with the accompanying inventory reduction and without the need for highly specialised manufacturing equipment and skilled operators (Weller et al., 2015).

Current applications for AM are widespread, with such technology being adopted in the aerospace, automotive and biomedical industries among others. Energy and emissions-saving potential of AM has also been highlighted (Huang et al., 2016). In the biomedical industry, AM is now a focus of many medical research projects as a potential method for the fabrication of three-dimensional products and devices, allowing custom-made patient-specific constructs to be produced at point of care. These constructs range from relatively simple prosthetics or implants to highly complex combination products containing cellular and scaffold components. This is now commonly known as biofabrication (Pavlovich et al., 2016).

The revolutionary potential of such technology is highlighted by the recent successful facial reconstructive surgery of a patient involved in a severe road traffic accident. Computer-aided design and AM were applied to every stage of the process, from planning to surgery. Computed tomography scan data was used to generate a symmetrical three-dimensional model of the patient's skull, which enabled the design of ISO 13485-(Quality management systems for medical devices) accredited surgical tools. Traditionally such tools and devices would be crudely measured for production in the operating theatre with the risk of error and sub-optimal surgery results, requiring further corrective operations (Peel et al., 2016). Furthermore, 3D–printers have also become available to the mass consumer market. The lower prices appeal to designers and offer a reliable way to replace spare parts for appliances. ‘Black–box’ technologies such as 3D printers shift the development requirements of the product manufacturer away from process design and towards product design (Baumers et al., 2016; Huang et al., 2015).

Whilst there is great potential within the AM sector to revolutionise the supply of customised goods, there remain barriers to its adoption. These constraints stem both from the relative immaturity of the technology as well as the path towards successful commercialisation and regulation of an additively manufactured healthcare product. The RiHN feasibility study conducted examining this issue highlighted the technology immaturity as well as regulatory uncertainty (Hourd et al., 2015) as key limiting factors for the commercial success of AM (Kapletia, 2015).

For the decentralised manufacturing of the more complex scaffold-based CGT products AM, when coupled with appropriate cell expansion technologies, can be a key enabler if the regulatory challenges regarding customised combination products can be overcome. This technology holds the potential to manufacture low-volume products reproducibly at numerous sites. Time from manufacturing to theatre is likely to be critical for this class of product. Thus, release of these products should rely on a fast and preferably non-invasive testing methodology for produced products (Hourd et al., 2015). Additionally, the relationship between customer and manufacturer should as a minimum be governed by an enhanced quality agreement and future clinical manufacturing models may be able to operate as a joint venture.

3. Technical and social barriers to the advancement of redistributed manufacturing

CGTs have potential to produce huge benefits for societal health. Even with the correct choice of manufacturing and distribution models, challenges remain when navigating the difficult technical and social decisions which affect translation.

3.1. Technical barriers

There are various technical barriers that must be overcome such as poor understanding of the underlying biology and mechanism of action as well as gaps in process monitoring, cell expansion and cell processing technologies.

CGTs rely upon a wide range of mechanistic approaches involving stem cells, immune cells, gene therapy, multi-cellular constructs and bio-engineered scaffolds. Emerging cell therapies, and some on the market, show a lot of therapeutic promise, yet is no single universal functional or potency assay that can be relied upon adequately to measure all the CQAs and to predict clinical efficacy. Whilst potency remains challenging to measure for certain cell types, progress is being made particularly in the chimeric antigen receptor T-cells (CAR-T) field (Quintarelli et al., 2016). Despite these advancements, the recent deaths during the clinical trial of Juno's CAR-T therapy highlight the challenges in simplifying function to a limited assay panel (DeFrancesco, 2017). The promising results in the CAR-T field demonstrate simplification of functionality to a handful of in vitro measurements is ambitious but possible, and vital for realising hypothesis-driven mechanism of action assays suitable for use across a decentralised manufacturing network (Galipeau et al., 2016) (Bravery et al., 2013).

Effective collection and management of in-process data is key to the success of decentralised manufacturing of CGT products. Through effective Manufacturing Execution System (MES) the pre-process, in-process and release data can be leveraged to both apply controls to the manufacturing process, but also examine the trends emerging from such data and to tighten, when appropriate, controls across the other sites and not just the one where the observations arise. Petabytes of data may be collected and the management, archiving and re-interrogation of such data must feature in the operational management plan with transmission integrity validated for the distributed network.

With CGTs, there is the need to release product batches as close to real time as possible due to inherent product instability. As CGTs are live products, cannot be terminally sterilised and should thus be treated as aseptic goods. Thus there will need to be a high level of confidence in the ability of the process to prevent entry of microorganisms and minimise deviations from parameters. This may rely on development of validated and automated procedures to demonstrate the level of control. For asepsis this could include media fill studies as in protein manufacture or a process step to measure the bioburden of the goods. In cases where end-point characterisation cannot be eliminated completely, batch hold times could potentially be reduced and/or products released ‘at risk’ pending further results by showing alignment with past in-process data. For sterility data, referring back to the demonstrable bioburden earlier in the process is simpler, for product characteristics, this is more challenging, although emerging label free monitoring methods based off physical characteristics may pave the way for more informed release criteria (Vaillier et al., 2016).

Controlling variation across multiple sites is pivotal when designing any CGT manufacturing process. Sources of variation arise in both autologous and allogeneic based processes. The source of this variation will primarily be derived from patient starting material for the former, whilst the process itself is likely to be of primary concern for allogeneic products with a constant starting material. For decentralised manufacturing process considerations become even more important as significant process variation between manufacturing sites cannot be

tolerated.

It is currently challenging to reduce user-related variability during upstream cell-expansion and downstream processing. This inherent reliance on manual operations and their concomitant variability is one of the greatest technical barriers to decentralised manufacturing. By mapping the degree of variation that can be accommodated through process manipulations within certain boundaries (e.g. expansion duration, content of cytokines), in-process control feedback loops can be established to predicted scenarios. These changes can then be applied until the desired outcome is achieved in a responsive manner. Whilst desirable, this scenario potentially relies upon removing operator interventions and replacing them with automated processes. This 'adaptive automation' remains largely aspirational currently with only simple introduction or transference of materials possible with existing production platforms.

Maintaining security of both the manufacturing process and the supply chain feeding into it are essential for ensuring quality. Supply chain management, from inputs to outputs, becomes increasingly challenging when cooperation between partners is poor. A key value proposition for an effective re-distributed service of manufacture will be the timely supply of goods and services without the customer having to worry about it, yet it is particularly susceptible to fragmentation of the chain of custody and good communication and alliance management must be applied to avoid this. Checks must be in place to mitigate deviation from the manufacturing specification and subsequently to avoid product variation from site to site. Examples of systems which facilitate the integrity of this supply chain already exist both in the consumer space with the range of smart appliances, and in the commercial life-sciences and healthcare sector with OptiMed-ID and ThermoFisher Smart Monitoring systems some of the leading examples. These smart systems are driven by the increasing ubiquity of smart computer-like devices and a network of these devices are likely the solution for maintaining integrity of the decentralised network.

3.2. Social barriers

Perhaps more challenging than the technical requirements are the radical changes needed for wider societal acceptance of decentralisation of manufacturing. These include not only a substantial change in the organisation of labour and roles for human operators, but also a shift of the burden of responsibility as operators are removed from the process and replaced with automated solutions.

Realisation of the potential of decentralised manufacture will require automated solutions to many of the process steps, but will not remove the necessity for a highly-motivated and skilled workforce. Similarly, it has been highlighted that there is an apparent skills gap in the sector (Medicine Manufacturers Industry Partnership, 2016) and as the field progresses, there may be the necessity to have a new specialist training regimen to supply the growing demand for skilled labour. Traditional centralised manufacturing concentrates labour and, in turn, creates a pool of collective expertise. The success of decentralised manufacturing relies upon portioning out the workforce into tranches of skilled operators. One of the key weaknesses of decentralised manufacturing is the threat of a poor skills pool and ageing workforce in a localised economy (Shucksmith and Brown, 2016) and this must be taken into account. Successful relocation of labour could involve 'technology transfer champions' from the current rising researcher base who are young, mobile and keen to make a difference at the interface between manufacturing and practice of translational medicine. Additionally, due to the dispersed operational nature of the workforce effective personnel management utilising licensed remote site operations, mandatory re-training and centrally managed control standards blinded to the remote facilities to check performance.

It is traditional to regard many aspects of manufacturing and quality control as proprietary knowledge. While interoperability of manufacturing equipment has been successful for some consumer product manufacturing it is still lacking in many sectors where the goods are specialised. Achieving technology platforms for manufacturing CGTs involving equipment from multiple manufacturers will require not only technical expertise but a willingness to share pre-competitive information.

The roles and responsibilities of the agents in a decentralised manufacturing network require careful definition. CGT product development is largely pursued by academia, hospitals and small to medium sized enterprises (SMEs) which typically do not have the resources available to big pharmaceutical companies (Celis and Salmikangas, 2011). Recently, there have been a number of high profile cases of funding, mergers and acquisitions in the sector (American Association for Cancer Research, 2017) which highlight the value present in the industry (Caplan et al., 2017).

it is highly likely that decentralised manufacturing processes will involve multiple stakeholders in terms of the equipment and expertise that is needed. In decentralised manufacturing, some of these stakeholders might also share commercial rights to the process, technology or product. Due to the high set-up costs of any infrastructure, it is preferable that any manufacturing platform should be used to create multiple product types for multiple stakeholders in order to spread the fixed costs of operation. In doing so, the stakeholders might share the responsibility for reliable manufacturing and enjoy a portion of the associated revenue while spreading the capital investment by 'sweating the assets'. Achieving this shared decentralised facility model is challenging, particularly with the diverse range of CGT products available. However, by creating a typology of manufactured CGTs which groups products by common unit operations, standardised production lines may be able to be established. As the field matures, new production lines may be established which cater for particularly lucrative products within emerging typologies.

To understand the extent of the socio-economic benefits that decentralised manufacturing could yield, it is important to understand where real value can be created. In this case, value can be described as the stored investment in terms of the proportion of selling price build up in the work in progress plus inventory at any one time. Locating most of the production and servicing activity close to the end user has the highest potential to capture value (Moreno and Charnley, 2016). This could be through a multitude of avenues of which reduction in loss of manufactured batches has proven to be significant in the case of MySkin (Hernon et al., 2006), Advanced Tissue Sciences and for pharmaceutical clients of eXmoor Pharma (Personal Communication, Nicholas Medcalf). This is a radical model and, as such, re-imbursement will present challenges because of the dispersed ownership of the chain of custody.

3.3. Perspectives

Over the last 20 years, the CGT industry has been rapidly advancing and real patient benefits from these approaches are being witnessed. Whilst significant progress has already been made, the relative infancy of this field still demonstrates a potential for major growth (Mason et al., 2013). This is made evident not only by the large number of clinical trials and by the over 800 companies focussed on CGTs (Alliance for Regenerative Medicine, 2017). This is reinforced by the forecast of the UK government who expect a number of CGTs to be available within five years (Science and Technology Committee, 2013).

3.4. Decentralised manufacturing progress: A case study of the UK

The UK is a key exemplar for the progress of CGT manufacturing. The high level of the skills base and strong support by central government make it an attractive place for innovation. The recent vote for the UK to leave the European Union, whilst disruptive to normal operating practices, has precipitated a flurry of dialogue about how the UK can benefit from new technologies, making it an interesting case in point for

feasibility-testing decentralised manufacturing.

A number of the themes presented in this article align strongly with recent recommendations from the UK Medicine Manufacturing Industry Partnership report: 'Advanced Therapies Manufacturing Action Plan' (MMIP, 2016). This plan advocates a strategy to capture investment, secure manufacturing capability and talented labour in the UK and embrace novel social and regulatory mechanisms to grow the CGT business community in the UK. Many of these action points focus on capturing and concentrating funding, technology, assets and people. We would argue that concentrating these into small decentralised facilities operating to a common quality management system (QMS), has the potential to add greater value to the UK as a whole than a centralised model. Additionally, this model will, by design, add resiliency to the network of provision of healthcare products as manufacturing platforms can accommodate for capacity shortfalls in the event of increased demand or in the event one facility is offline due to disaster.

The report identifies a talent management plan but places no emphasis on geographical demands for labour, which we believe is of critical importance for regional investment strategy. The topic of standards and regulation was recognised as a key stumbling block and the authors recommended early engagement with the regulator. We fully agree with this view and would argue that emphasis should also be placed on establishing guidelines for responsibility and liability between stakeholders involved in the product chain of custody. A large proportion of this would be covered in supply agreements between organisations, however a breakdown in the chain of custody can occur because of poor practice right up to the point of application and there needs to be an incentive to cooperate in maintaining asepsis at least.

Our view that automation of processes is critical to achieve process comparability while lowering the cost of goods is supported by the findings of the report. We have argued that the additional benefits afforded by automating processes allows for a decentralised model with manufacturing situated closer to patients and this is supported by the report. We have argued that manufacturing of some CGTs such as CAR-T cell therapies is best served by a decentralised manufacturing model (Yin, 2017). One of the most relevant proposals in the report is the establishment of CGT treatment centres. The aim of these would be to support the provision of CGTs by providing the infrastructure required to deliver advanced therapies.

The report recognises the powerful addition of the large scale manufacturing centre for the Cell & Gene Therapy Catapult that comes on stream in 2018. Decentralisation will remain a very attractive option for manufacture and delivery of CGT products in situations that demand a high degree of personalisation, where fresh delivery is desirable and where there is high value release from a low volume of products. Such an arrangement could be provided by an extension of the model described by Porter and Teisberg (Porter and Teisberg, 2006), in which specialised administration of CGT products is accompanied by specialist manufacturing in a clinical production unit.

3.5. Summary findings and vision

As the CGT field develops, it becomes evident that the strength of many products comes from personalisation for specific uses. This personalised approach offers enormous possibilities for patients but necessitates alternative manufacturing models.

A centralised model for CGT manufacturing is much closer in design to existing manufacturing infrastructures where economies of scale could be realised. A theoretical flow diagram for a centralised manufacturing model is presented in Fig. 3. In a centralised model, a large number of products are delivered to a central location where they are completed and a finished product is supplied to the end user. This manufacturing model, whilst familiar, is likely to incur disadvantages from its distance from the user, geographically and in terms of responsiveness to end-user requirements. Logistical management may result in product wastage as the longer the supply chain, the more opportunity for error and mis-timing of delivery.

By situating manufacturing closer to the end consumers, it is hoped these shortcomings can be overcome and additional benefits can be gained in the formation of enduring, effective alliance management. A theoretical framework which draws on the paradigms described in this paper is presented in Fig. 4. This assumes that research and development will be carried out off-site to generate standards and to ensure comparability across sites. The manufacturing process for the 'Drug Product' itself is assumed to be located adjacent to the clinical facility and that appropriate transit trials would be conducted for the transit points described in the figure (Harrison et al., 2017b).

In these process diagrams, three key areas (Fig. 5) are identified as pivot points which support decentralisation of the manufacturing process. The first and most obvious consideration is the starting material. Banked materials located in a central facility are much easier to incorporate into a centralised manufacturing process. If materials are to be collected fresh from a patient, situating a manufacturing centre close to the collection point significantly simplifies collection logistics. The second consideration is transport which can have a significant impact on the underlying biology of CGTs and thus shipping and stability must be suitably qualified. In addition to this, fresh transport can be very costly as it requires active management of the product which is effectively still in culture. Packaging containers and chemically based environmental management products such as the Sanplatec Culture Pal® have been developed to aid in fresh shipping but if time is a critical factor in product shelf-life then costs can quickly mount up for dedicated transport over anything other than short distances. In cryopreserved products the maximum transit duration increases which allows pooling of deliveries and thus freight costs drop (Personal Communication, Steve Langron, Lime Associates). Consequently a number of companies are developing cryogenic distribution strategies including ThermoFisher, Trust Express, CryoSend Mitsui Soko Holdings, Cryoport and Medipal Holdings (Sampson, 2017). Currently this does limit the number of clinics able to receive a cryopreserved product due to the rarity of low temperature goods inwards facilities and suitable thawing areas.

Another barrier for large scale manufacture of CGTs is the high cost of wet consumables such as culture medium. Manufacturing to order as closely as possible is essential to minimise wastage. Location decisions for blood centres, for example have to be strategic and decision-making models for calculating supply and demand taking into account proximity and perishability already exist. These principles could be utilised for CGT products to determine serviceable locations for differing product categories from each manufacturing facility.

Of the exemplars chosen, blood and blood products such as bone marrow transplants, represents in our view the best basis for decision making about processes. This is due not only to the similarities of the product type, but also the similarities of the whole process. The blood supply chain can be examined as a whole unit, from sourcing to end user, making it distinct from other industries which are rather a subset of a larger manufacturing ecosystem (Pierskalla, 2005). The blood manufacturing supply chain in its current form is a relatively mature area. However, it has not overcome the natural variation in supply and demand and is constantly optimising in response to supply challenges. The maturity of the field and the paramount requirement for reducing both cost and wastage has yielded a number of detailed models which have increased in complexity over the last thirty years (Beliën and Forcé, 2012). These models capture best practices that result from experience and provide the groundwork for developing similar models to guide a CGT manufacturing supply chain and avoid product wastage due to oversupply, errors or failed delivery (Hernon et al., 2006).

4. Concluding remarks

Centralised manufacturing is highly suited for products where the product life-cycle and shelf life are long, where the unit operations are

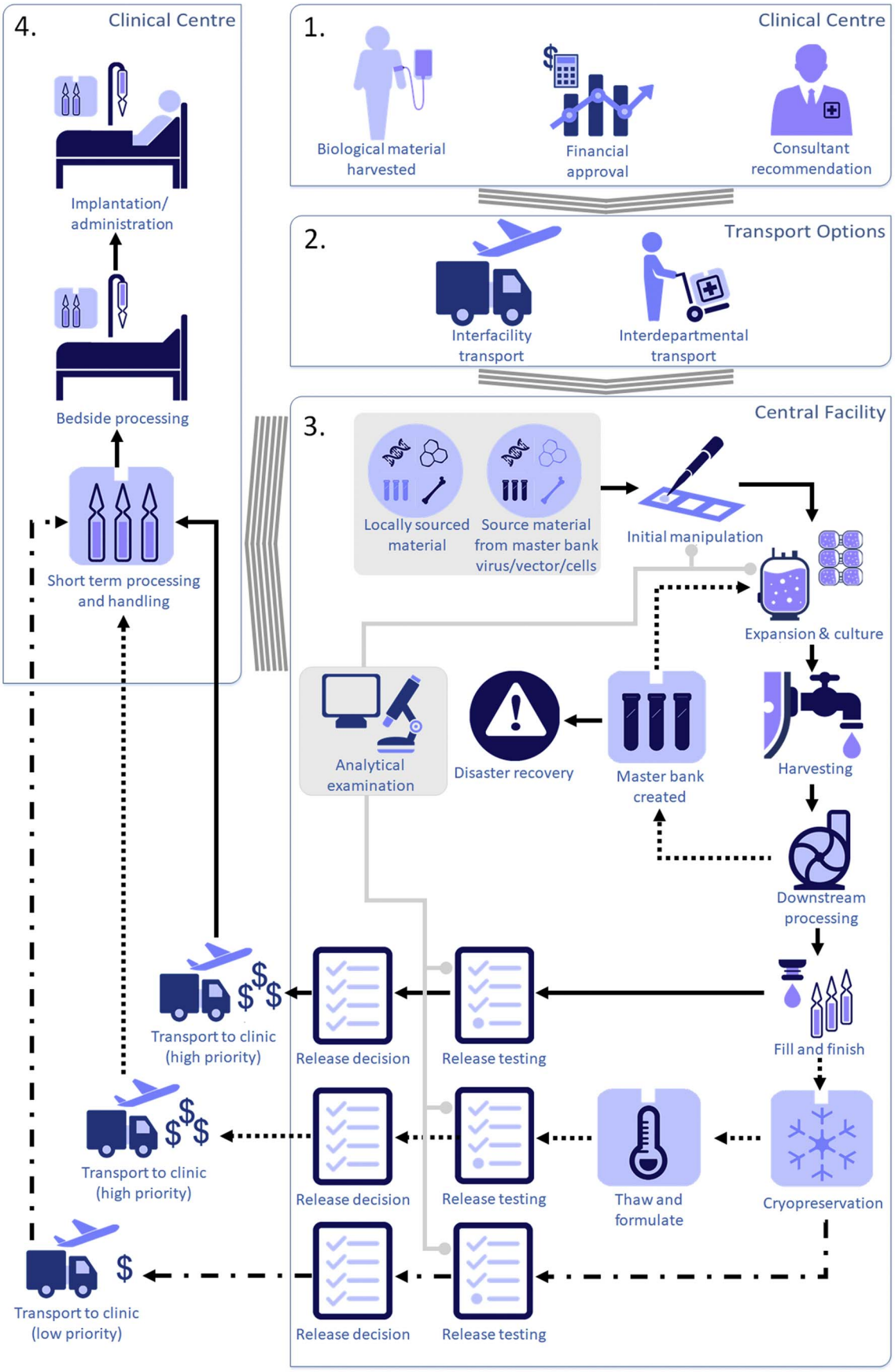


Fig. 3. Model process diagram for centralised manufacturing of cell and gene therapy products. Starting materials can originate at a clinical facility for an autologous product (1) or from the master cell bank for an allogeneic product (3). Product manufacturing steps which are likely to contain a significant analytical monitoring component are linked with the grey process lines. Alternative process steps are signified by dotted and dashed lines. The thaw and formulate step alternative is an example of a process where the Drug Substance is managed as a hold step before formulation to give the Drug Product.

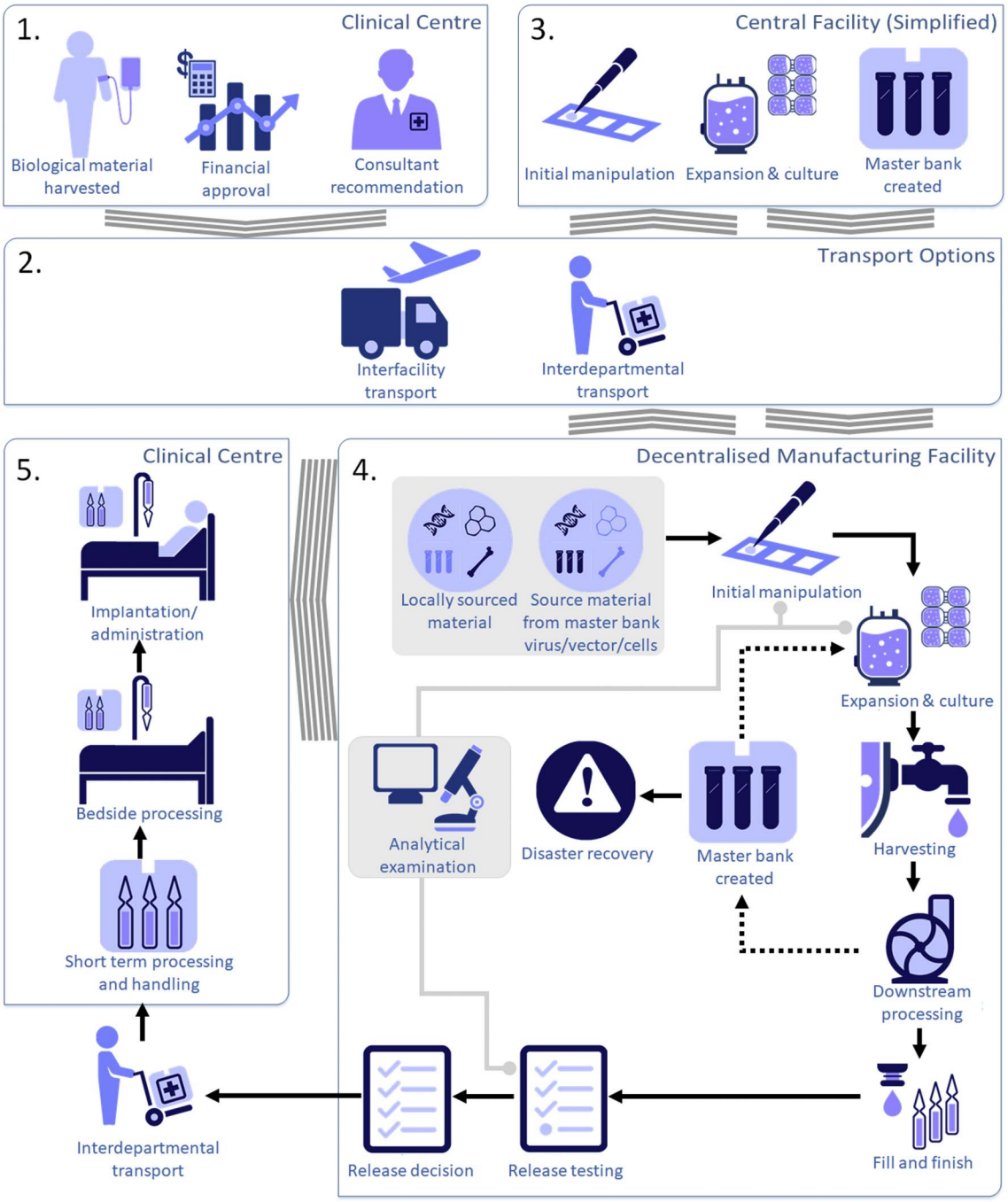


Fig. 4. Model process diagram for decentralised (redistributed) manufacturing of cell and gene therapy products. Starting materials can originate at a clinical facility for an autologous product (1), which may be transferred to the central facility (3) as part of the manufacturing process. Alternatively, a master bank containing an allogeneic product may be shipped out to decentralised manufacturing facilities from a central facility. This movement of material to and from the central facility may involve the creation of a mater bank or it may be created at the decentralised facility (4). Product manufacturing steps which are likely to contain a significant analytical monitoring component are linked with the grey process lines. Alternative process steps are signified by dotted and dashed lines.

well-established and where the degree of personalisation is low. The increasing need for personalisation of CGT products is best addressed by low-volume, multiple manufacturing lines at least for the finishing unit operations. Such a system is difficult to implement in a centralised operation while maintaining capacity. This makes the entire process a trade-off between degrees of personalisation and throughput. Examples of these personalised products might include engineered tissues other than hyaline cartilage and epidermis as well as bio-printed constructs.

Decentralised manufacture is similar to the cottage industries of old located close to end users and responsive to their needs. In order for decentralised manufacturing of complex healthcare products to succeed, it must address the key weakness that distance always presents, namely product consistency, not just from the process, but also from unanticipated risk factors such as accidents, human error, transport delays and failures and natural disasters. The industry cannot permit significant local variation in quality. Each site must demonstrate its ability to deliver an equivalent product regardless of location or operators. This is best assured by judicious use of automated systems. By removing human operators from key stages this problem should be ameliorated, presenting a responsive process without the drawbacks of variability. Managing this inherently complex network of manufacturing hubs requires integrated management systems. Automated

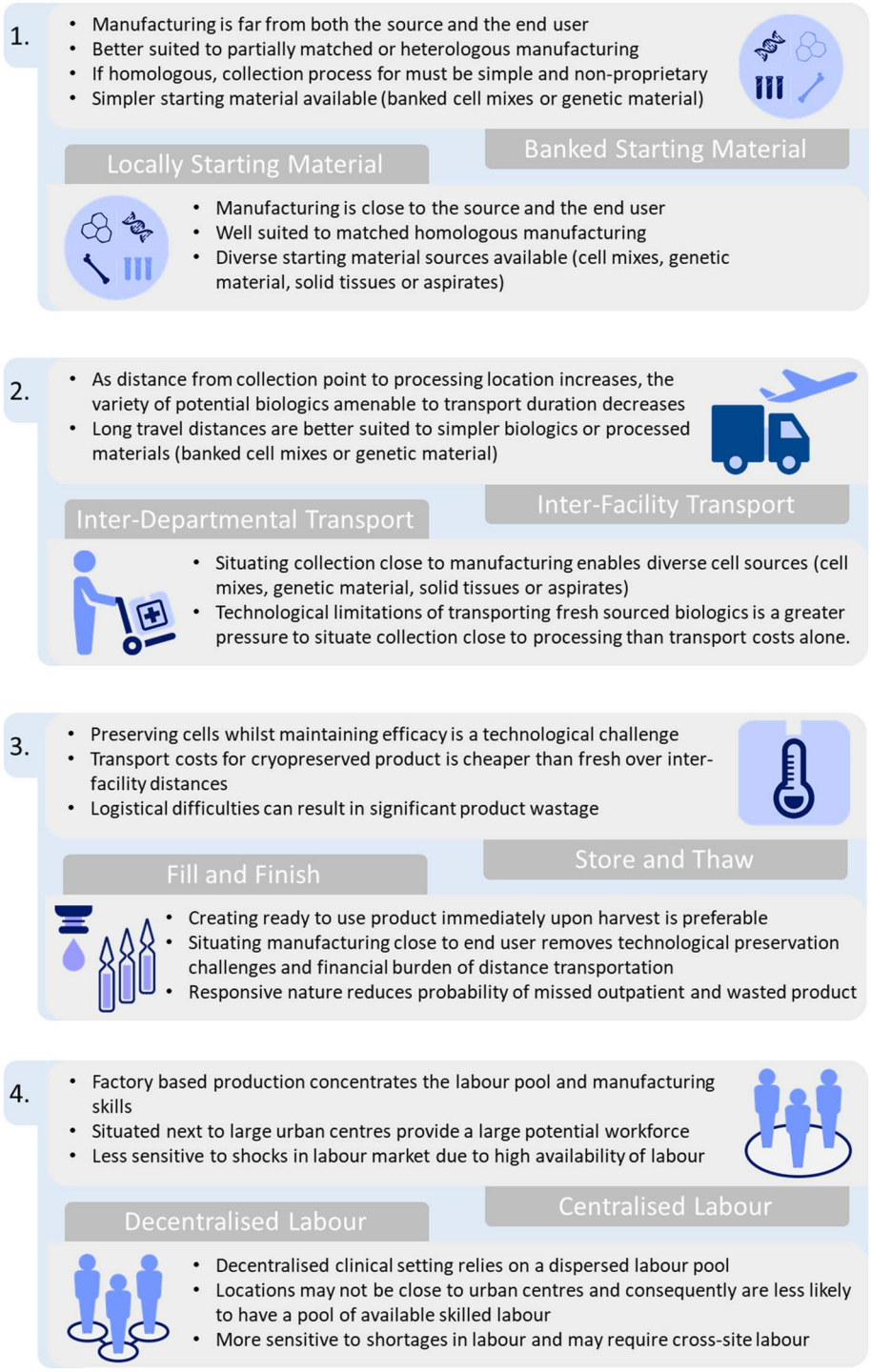


Fig. 5. Key decisions which influence the decision to decentralise manufacturing. Ease of sourcing of starting materials can be influenced by both on-site expertise and local collection capacity (1). Distance from the manufacturing centre to the patient or clinic can dictate what transport options are available for specific CGT product classes at a given operational size (2). Differing CGT product classes may have challenging logistical requirements (3). Centralised and decentralised facilities have differing labour requirements with the latter risking production if the skilled labour pool is weak. Managing talent across national boundaries may be challenging to administer (4).

systems promise to deliver both integrated management and compliance but significant challenges remain over implementation and regulatory acceptance.

In addition to the significant challenges associated with capacity and consistency, questions remain over effective reimbursement of these expensive products. The lessons from Sovaldi are clear, alternative reimbursement strategies are key to commercial success. In the paradigms presented here, high point-of-sale costs for radioisotopes may justify the high sunk costs of acquiring the manufacturing unit. This same strategy could be implemented for decentralised manufacture of CGTs.

Decentralisation of manufacture of CGT products is an attractive proposition for high-value, low volume goods that require personalisation. Suitable automation platforms need not reduce the need for human operators but they may change their role, creating a new layer of semi-skilled operators through the externalisation of some of the know-how to the machines themselves. The interdependence of such centres in a 'hub-and-node' network has the potential to make manufacturing resilient and largely immune to disasters and to demand fluctuations. A network of customer clinics, such as exists in the UK in the form of the National Health Service (NHS), offers the opportunity to create boilerplate training and quality management systems and framework agreements to facilitate roll-out and relationship management, between the manufacturer and the NHS. The social experiment of the

roll-out, the re-examination of reimbursement arrangements and the technical challenge of comparability in manufacture can be seen as the price that needs to be paid for an agile, environmentally friendly, responsive way of delivering advanced treatments. Indeed, the humanising influence of networks of such enterprise and their interdependence can be seen as an example of Schumacher's famous principle that “small is beautiful”.

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The opinion reflected in this report is the opinion of the authors and their interpretation and aggregation of the opinion of the individual thought leaders as members of a selected expert reference panel. It does not represent the views of their employers or any organisations they may represent.

Author contributions

Richard Harrison and Nicholas Medcalf were responsible for conception and design of the work. Drafting of the article was by Richard Harrison with contributions from Steven Ruck, Qasim Rafiq and Nicholas Medcalf. Diagrams and visual material was created by Richard Harrison with contributions by Nicholas Medcalf. Critical revision of the article was carried out by Qasim Rafiq and Nicholas Medcalf. Final approval was given by consent of Richard Harrison, Steven Ruck, Qasim Rafiq and Nicholas Medcalf.

Disclosure of interests

The authors have no commercial, proprietary, or financial interest in the products or companies described in this article.

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