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Comparison between centralised and decentralised supply chain of autologous CAR-T therapies: a UK case study based on discrete event simulation

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Abstract

Decentralised (or distributed) manufacturing that takes place close to the point of care has been a manufacturing paradigm of heightened interest within the cell therapy domain due to the product being living cell material and the need for highly monitored and temperature-controlled supply chain, which has the potential to benefit from the close proximity between manufacturing and application.

To compare the operational feasibility and cost implications of manufacturing autologous CAR-T products between centralised and decentralised schemes, a discrete event simulation model was built using ExtendSIM 9 for simulating the patient-to-patient supply chain from the collection of patient cells to the final administration of the CAR-T therapy in hospitals. Simulations were carried out for hypothetical systems in the United Kingdom with three demand levels, low (100 patients per annum), anticipated (200 patients per annum) and high (500 patients per annum), in order to assess resource allocation, cost per treatment and system resilience to demand changes and to quantify the risks of mix-ups within the supply chain for the delivery of CAR-T treatments.

The simulation results show that, whilst centralised manufacturing offers better economies of scale, individual facilities in a decentralised system can spread facility costs across a greater number of treatments and better utilise resources at high demand levels (annual demand of 500 patients), allowing an overall more comparable cost per treatment. In general, raw material and consumable costs have shown to be one of the greatest cost drivers, of which genetic modification associated costs have shown to account for over one-third of the raw material and consumable costs.

Turnaround time per treatment for the decentralised scheme is shown to be consistently lower than its centralised counterpart, as there is no need for product freeze-thaw, packaging and transportation,

although time savings is shown to be insignificant in the UK case study due to its rather compact geographical setting with well-established transportation networks. In both schemes, sterility testing lies on the critical path for treatment delivery and is shown to be critical for treatment turnaround time reduction.

Considering both cost and treatment turnaround time, point-of-care manufacturing within the UK does not show great advantages over centralised manufacturing. However, further simulations using the model can be used to understand the feasibility of decentralised manufacturing in a larger geographical setting.

Keywords:

decentralisation, centralisation, supply chain, CAR-T, manufacturing, discrete event simulation

Introduction

With the expanding catalogue of cell and gene therapy products such as the first autologous chimeric antigen receptor T (CAR-T) cell therapy (Kymriah) in August 2017 [1] and Luxturna in November 2018 [2], the cell and gene therapy industry is moving from bench to bedside. In this transition, post-approval challenges such as reimbursement, delivery and supply chain issues have proven to be a difficult hurdle for autologous therapies and were cited as one of the reasons for Dendreon's commercial failure[3].

Traditionally, the biopharma industry has benefitted from the "Ford-ist" centralised manufacturing paradigm where the manufacturing is centralised, large-scale, highly efficient and standardised[4]. Through manufacture scale-up by moving from inefficient manual processes to automated large-scale bioreactors, manufacturers of biologics were able to bulk produce consistently complex biological products such as monoclonal antibodies and drive down the cost of goods, deliver effective treatments to patients [5], growing into an industry predicted to reach nearly $125 billion global annual sales in 2020[6,7]. This manufacturing and distribution model has been shown to offer benefits such as more efficient resource planning, easier monitoring and reducing cost per treatment through spreading regulatory, equipment and capital costs over a large volume of products[8]. The manufacturing of autologous cell products such as those for CAR-T therapy, however, does not benefit from the same extent of economies of scale. Firstly, due to the autologous personalised nature, manufacturing has to be scaled out and not scaled up, i.e. by using multiple sets of equipment running in parallel instead of using single larger equipment to deliver more products [9–11]. Secondly, autologous cell products are living cells that are very sensitive to environmental changes, have short shelf lives and are specific for patients. To enhance the flexibility of scheduling and manufacturing of these products, cryopreservation is usually performed[12] and hence the products must be delivered in a highly regulated, temperature-controlled and time-efficient manner[13]. Thirdly, variability in donor-specific raw material, manufacturing process, lot release testing and point-of-care handling and delivery techniques can all contribute to the product quality differences[14].

To tackle these challenges, the decentralised manufacturing model has been proposed as a potentially more attractive alternative to the centralised system [15,16]. Decentralised or distributed manufacturing refers to a manufacturing paradigm with which manufacturing is smaller scale and distributed into a

number of locations closer to end-users of the products[17]. This allows less transportation time and raw material/ product freeze-thaw cycles, hence reducing transportation-related costs and risks and preserving product quality. In other industries such as food[18,19] and energy production[20], decentralised manufacturing models have been evaluated with respect to economic costs, resource consumption and environmental impact [12], as well as supply chain reliability[20]. For the manufacturing of autologous cell therapies, Harrison et al. discussed the regulatory challenges and implications on the cost of goods [21,22]. Using the United Kingdom (UK) as an example, Harrison et al. conducted a high-level study on the hub-and-node model, where a 'hub' facility is responsible for support functions (administrative work, research and development, process development, etc.) and 'node' facilities are responsible for the manufacturing[21]. Their study looked into the cost disparity amongst different regions in the UK and compared different degrees of decentralisation of quality control (QC), with a hybrid QC model where part of the QC burden is centralised[21]. Referring to the European Union (EU) guidelines on Good Manufacturing Practices (GMP) of Advanced Therapy Medicinal Products (ATMP) issued in 2017, the "hub" site would need to hold the marketing authorisation and is responsible for the oversight of the "node" sites for batch certification, release and quality assurance audits. The Qualified Person (QP) can use data/information/batch record established in the "node" site to release the product, and all deviations and non-conformity in the process must be well-documented and reported back to the "hub" site[23].

While decentralised manufacturing has been studied for cell therapies, a comprehensive comparison with the centralised model with respect to not only costs but also other performance aspects is still lacking. For example, therapies such as CAR-T which are intended for patients in critical conditions, e.g. in late stages of cancer, the time for the overall needle-to-needle delivery (and the associated risks of manufacturing and logistic failure) is critical for the patient's wellbeing. This was demonstrated in the ZUMA-1 trial, where out of 111 patients, 8% did not make the wait for treatment due to reasons including adverse events (3.6%), death from disease progression (0.9%) and non-measurable disease before conditioning chemotherapy (1.8%)[24]. Therefore, evaluation of distributed manufacturing in aspects associated with time criticality is important [25].

This study aims to understand the operational performance of decentralised and centralised manufacturing with respect to the cost per treatment, resource utilisation, time required from collection to delivery, system performance under demand pressure and system resilience to risks such as mix-ups and equipment failure. In particular, the manufacturing of autologous CAR-T therapies in the UK is considered, with integrated and automated processing equipment, such as Miltenyi CliniMACS Prodigy (Miltenyi Biotec, Germany). Using closed and automated equipment reduces the hands-on time of highly skilled labour and manufacturing process variability[26]; the importance of using such equipment in decentralised manufacturing has previously been highlighted[27,28]. The quantitative assessment has been enabled by using a discrete-event simulation (DES) model built in this work.

Discrete event simulation (DES) is a method of simulating the behaviour and performance of a real-life process, facility or system. Modelling systems as a series of events over a time period, DES can be used to quantify risk of disruption on the supply chain and hence test strategies that can mitigate these risks and identify strategies for making the system more efficient in resource-use or cost[29]. It has been applied for complex systems in diverse fields including healthcare[30–32], biofuels supply chain[33] and agriculture[34–36]. DES has also been used in biopharmaceutical companies such as Genentech for quantifying risks within their supply chain network and inform inventory decisions[29]. Autologous CAR-T manufacturing and delivery is a process of a defined structure, but with uncertainty in process parameters and variable risks, for which we show in this work that DES can offer a realistic tool for the analysis of various decision alternatives, particularly for the comparison between centralised and

decentralised paradigms. The learning from this work has the potential to inform the future decisions of relevant companies on the manufacturing paradigms for autologous cell therapies.

Methods

This section describes the process flow and performance indicators of a typical autologous CAR-T therapy from cell collection to final product delivery based on published literature. The data collection process, assumptions and parameters used for the UK case study and the method of cost calculations are also presented. The process flow and the associated parameters form the basis of a discrete event simulation model of the CAR-T therapy manufacturing and delivery, which has been used to support the evaluation of costs and other performance aspects of the centralised and decentralised systems.

Process description

A representative process flow of a CAR-T therapy delivery, as modelled in this work, is shown in **Error! Reference source not found.**[37,38]. A typical treatment process involves the patient first being treated at, or referred to, a designated approved treatment centre. Such centres have to be trained on processes for cell collection, cryopreservation, transport, chain of identity, safety management and logistics handling, and need to be FACT accredited[39]. If the CAR-T treatment is deemed suitable for the patient, the treatment centre will coordinate with a manufacturing centre to discuss whether there are available slots for processing. T cells will then be collected from the patient by leukapheresis at the treatment centre. These T cells will then be cryopreserved or frozen and packed for shipping via a qualified cold chain logistics provider which has to work closely with the treatment centre[40]. The shipping process for such temperature-sensitive patient live cells is monitored closely[41]. If at any point the process fails, on a case-by-case basis, the manufacturer decides whether to collect new samples from the patient or for the out-of-specification product to be administered through an expanded access protocol free of charge[42].

All starting materials, cells, consumables and reagents arriving at the manufacturing facility have to first be checked by the quality assurance team before entering the manufacturing process. Quality assurance (QA) plays an important role in autologous therapies to ensure all the processes conducted in parallel are produced in a consistent manner[25]. In the context of CAR-T manufacturing, it is to manage the batch record of each batch of product, visual inspection of materials and general production oversight. Quality Control (QC) tests to check for mycoplasma in the sample from donors are conducted upon receipt of sample. NAT-based mycoplasma testing is assumed to reduce the time required for testing[43].

The sample received is thawed and processed using an enclosed automated equipment where it is enriched and activated with CD3/CD28 conjugated beads before transduction with a lentiviral vector, which is then expanded, washed and formulated. The product is finally cryopreserved in vapor-phase liquid nitrogen for despatch. The expansion media used is prepared in an isolator in a Grade D environment or a biosafety cabinet in a Grade B cleanroom environment. Throughout the manufacturing process, in-process control tests to check for viability, cell count and phenotype of the cells are conducted. The formulated product is subjected to QC release tests (Table 1) before getting released by the Quality Personnel (QP) [15,37]. For the decentralised paradigm, the Qualified Person (QP) is shared across facilities in different geographical locations. In accordance with the Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products issued in 2017 by the commission of European Communities[23], the QP can rely on data and information supplied by decentralised sites for batch release.

Table 1 QC testing for a typical autologous CAR-T product [39]

Test	Purpose
Virology screening	Ensure starting material is disease free
Cell count and viability testing	In-process: to ensure cell expansion process is as intended Product release: to check if cell count and viability meet specification
Flow cytometry	Determination of cell composition, viability and phenotypes (transduction, differentiation, proliferation capacity, exhaustion) [44]
Enzyme-linked immunosorbent assay (ELISA)	Functional assay for gene expression levels
Mycoplasma testing (PCR)	Ensure raw material and product released are free of mycoplasma contamination
Sterility testing	Culture test to ensure product sterility
Endotoxin testing	Ensure product is free of endotoxins

Throughout the manufacturing process, the treatment centre has to be updated with the progress in order to schedule pre-conditioning chemotherapy over 4 days for the patient 2 to 14 days before the infusion. Once the treatment centre is ready, the cryopreserved product is packaged into a liquid nitrogen dewar for despatch and sent to the treatment centre via a qualified cold chain logistics provider. The shipment is then received by the hospital, verified and prepared. The thawing of the product should be coordinated with the transfusion. The patient receives acetaminophen and an antihistamine 30-60 minutes before the CAR-T cells get administered through standard IV infusion which lasts less than 30 minutes. This procedure can be either in-patient or out-patient, but due to the risk of adverse reactions, emergency equipment and intensive care units should be available at the treatment centre[41,45,46].

The key performance indicators (KPIs) considered and the rationale for their consideration are shown in Table 2. Through simulation studies on systems with different configurations, this work predicts these KPIs and identifies the process bottlenecks for further optimisation.

Table 2 Key performance indicators and rationale for choice of KPI

Key performance indicator	Rationale
System throughput	Maximise the total number of therapies delivered within the time horizon specified
Cost of each therapy delivered	Minimise the cost of each therapy
Turnover of each therapy	Minimise the time required for each therapy from needle-to-needle: including cell collection, manufacturing, quality control and packaging and treatment delivery time
Resource utilization:	
Personnel	The higher the utilisation, the less wastage in the system
Equipment	The higher the utilisation, the less wastage in the system

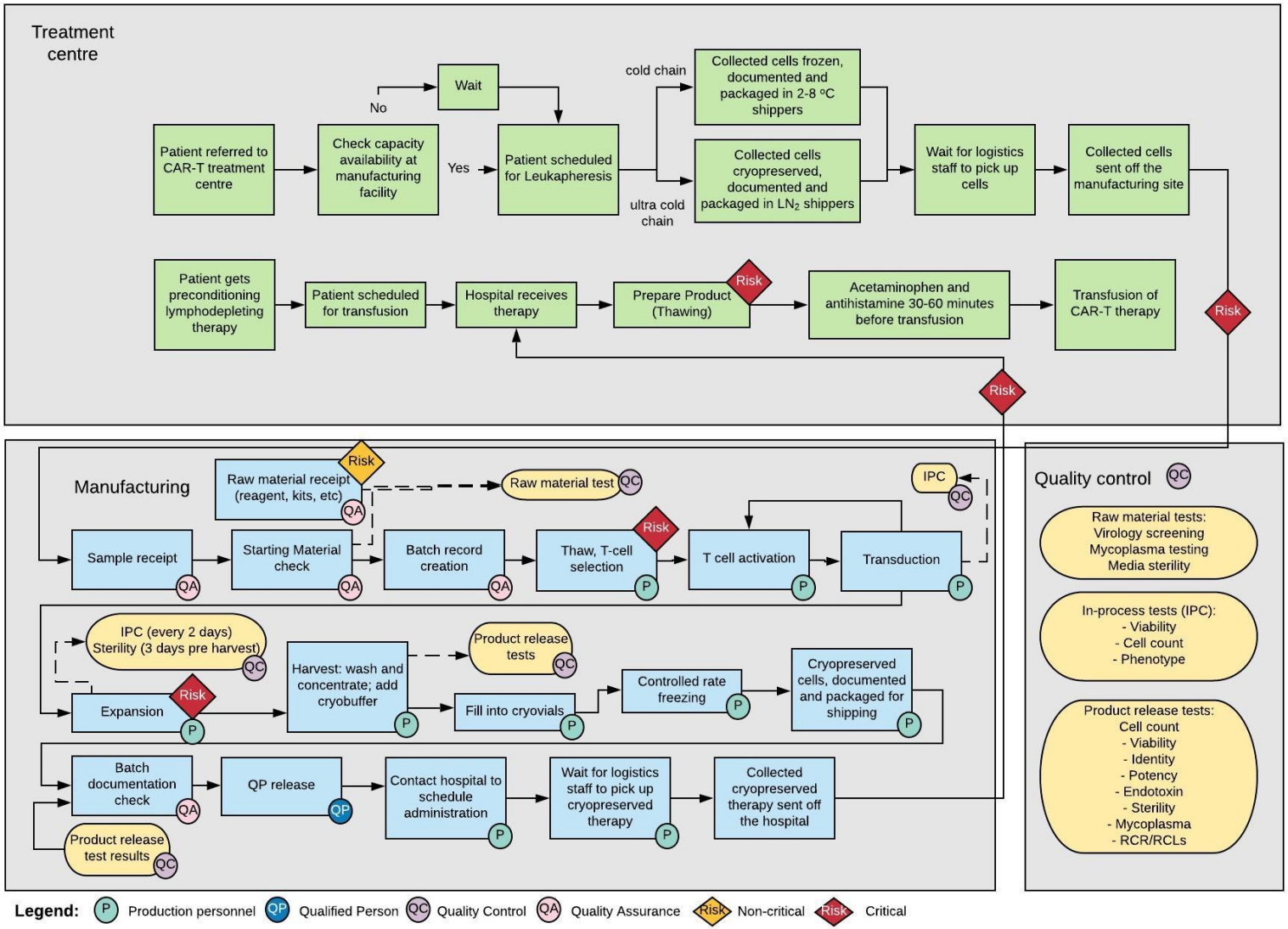


Figure 1 Typical process flow of a CAR-T therapy delivery (Green: events in hospital/treatment centre; blue: production activities; yellow: QC activities

Data collection process

The process flow, duration and material requirements were collected through review of literature (as cited in the process description section).

One-on-one interview sessions were carried out with experts from four companies to supplement process data collected from literature. Process requirements and cost data for the manufacturing process and quality control panels were kindly provided by Miltenyi Biotec (Cologne, Germany). Logistics and supply chain related data were collected through discussion with a blockchain-based supply chain platform (Farmatrust, United Kingdom). Equipment cost data was provided by China Regenerative Medicine International (Hong Kong), a contract manufacturing facility based in Hong Kong. Environmental monitoring system design and cost assumptions were based on discussions with Pharmagraph (Wokingham, United Kingdom).

Cost calculation

Costs per treatment are calculated through the addition of all fixed and variable costs over a year divided by the total number of treatments delivered in the year. Cost assumptions are available in Appendix 2.

Annual facility costs (F)

The facility costs for hospitals (F_{H}) are calculated by multiplying the number of hours required for usage of an operating theatre (H_{OT}) by cost per hour (h_{OT}) (Eq 1). It is assumed that the preconditioning lymphodepleting therapy and the final transplant will be conducted in an operating theatre.

Facility capital costs are proportional to the anticipated demand and manufacturing capacity. Facility costs for manufacturing (F_{M}) and QC facilities (F_{QC}) are calculated by summation of capital costs and operating costs (Eq 2a-2c). Capital costs are based on floor space required by equipment multiplied by the number of each equipment (n) depreciation factor (d). One meter is allowed around width (W) and depth (D) of each equipment for exhaust. Extra working space for operation and cleaning and a GMP working space multiplier (g) is applied to account for indirect working space such as gowning activities (Eq 2a).

Operational costs for manufacturing facilities are calculated based on the cleanroom classification and area (f) multiplied by the number of air changes required per hour for the cleanroom class, A_{D} for Grade D and A_{CNC} for CNC areas respectively, and the HVAC utility cost per square meter per hour (c_{HVAC}). The Lang factor (Lf), a cost factor used for capital cost estimation, is applied to account for the installation and supporting costs of the equipment. (Eq 2d-e)

The summation of all facility costs incurred in the hospital, manufacturing and QC gives the total facility cost (Eq 2f).

$$F_{H} = H_{OT} * h_{OT} \qquad \textit{Eq 1}$$

$$f_{m,D} = \left(W_{m,D} + 1\right) * \left(D_{m,D} + 1\right) * n_{m.D} * g \qquad \textit{Eq 2a}$$

$$f_{m,CNC} = \left(W_{m,CNC} + 1\right) * \left(D_{m,CNC} + 1\right) * n_{m,CNC} \qquad \textit{Eq 2b}$$

$$f_{qc,CNC} = \left(W_{qc,CNC} + 1\right) * \left(D_{qc,CNC} + 1\right) * n_{qc,CNC} \qquad \textit{Eq 2c}$$

$$F\square M\square = f\square m, D\square * Lf * C\square D\square * d + f\square m, CNC\square * Lf * C\square CNC\square * d + v * 365 + f\square m, D\square * h\square m\square * A\square D\square * c\square HVAC\square * 24 * 365 + f\square m, CNC\square * h\square m\square * A\square CNC\square * c\square HVAC\square * 24 * 365 \quad \textit{Eq 2d}$$

$$F\square QC\square = f\square qc, CNC\square * Lf * C\square CNC\square * d + f\square qc, CNC\square * h\square m\square * A\square CN\square C\square\square * c\square HVAC\square * 24 * 365 \quad \textit{Eq 2e}$$

$$F = F\square H\square + F\square M\square + F\square QC\square \quad \textit{Eq 2f}$$

Annualised capital/equipment costs (E)

All equipment is assumed to be depreciated over ten years, i.e. depreciation factor (d) assumed to be 0.1. The total annualised equipment cost (E) is the summation of equipment used in the hospital ($E\square h\square$), manufacturing equipment in Grade D cleanrooms ($E\square m, D\square$), manufacturing equipment in CNC cleanrooms ($E\square m, CNC\square$), QC equipment in CNC cleanrooms ($E\square qc, CNC\square$) and equipment for transportation ($E\square t\square$) multiplied by the depreciation factor (d) (Eq 3). The list of equipment and their costs can be found in Appendix 2a. The number of integrated automated platforms (Prodigy, Miltenyi Biotec) available is pre-specified based on the anticipated demand level (Table 4).

$$E = (E\square h\square + E\square m, D\square + E\square m, CNC\square + E\square qc, CNC\square + E\square t\square) * d \quad \textit{Eq 3}$$

Annual maintenance and service contract costs (M)

Maintenance and service contract costs per year (M) are assumed to be 20% (ms) on the depreciated capital cost for both manufacturing equipment ($M\square m\square$) (Eq 4a) and QC equipment ($M\square qc\square$) (Eq 4c**Error! Reference source not found.**). The annual maintenance and service contract costs are given by the summation of both (Eq 4c)

$$M\square m\square = E\square m, D\square + E\square m, CNC\square\square * ms \quad \textit{Eq 4a}$$

$$M\square qc\square = E\square qc, CNC\square * ms \quad \textit{Eq 4b}$$

$$M = M\square m\square + M\square qc\square \quad \textit{Eq 4c}$$

Annual raw material/consumable costs (R)

Raw material and consumables used throughout the supply chain including the hospital ($R\square h\square$), manufacturing ($R\square m, D\square$, $R\square m, CNC\square$), QC ($R\square qc, CNC\square$), transportation ($R\square t\square$) and personnel gowning ($R\square gown\square$), are summed. The personnel gowning costs are given by the cost of each aseptic gown ($c\square gown\square$) multiplied by the shifts of production staff ($s\square p\square$) per day and the number of days in a year. The costs are accumulated within the discrete event simulation over the course of a year, and is computed using Eq 5b. The list of raw materials and associated costs is provided in Appendix 2a.

$$R\square gown\square = c\square gown\square * s\square p\square * 365 \quad \textit{Eq 5a}$$

$$R = R\square h\square + R\square m, D\square + R\square m, CNC\square + R\square qc, CNC\square + R\square t\square + R\square gown\square \quad \textit{Eq 5b}$$

To account for bulk material and equipment discounts, discounts are applied based on annual demand (Table 3).

Annual demand	Discount applied

100	0%
200	10%
500	20%

Table 3 Bulk discounts on raw material and equipment

Annual labour costs

Hospital based staff costs ($L\square h\square$) are calculated by the work hours ($h\square nurse\square$, $h\square pharmacists\square$, $h\square doctor\square$, $h\square support\square$) and the hourly costs of hospital staff including nurses ($L\square h, nurse\square$), pharmacists ($L\square h, pharmacist\square$), doctors ($L\square h, doctor\square$) and support staff ($L\square h, support\square$) (Eq 6). Transportation-related labour costs ($L\square t\square$) are calculated by logistics staff hourly rate ($L\square lt\square$) multiplied by product transportation hours ($h\square t\square$) as shown in Eq 7.

Manufacturing staff costs ($L\square M\square$) is given by the summation of the annual salaries of staff (production personnel ($L\square P\square$), quality control personnel ($L\square QC\square$), quality assurance personnel ($L\square QA\square$) and qualified person ($L\square QP\square$)) multiplied by the number of shifts of the personnel per day (number of shifts of QC personnel per day ($s\square P\square$), number of shifts of QC personnel per day ($s\square QC\square$), number of shifts of QA personnel per day ($s\square QA\square$), number of shifts of QP per day ($s\square QP\square$)) as specified in Table 4. (Eq 8)

$$L\square h\square = L\square h, nurse\square * h\square nurse\square + L\square h, pharmacist\square * h\square pharmacist\square + L\square h, do \quad Eq\ 6$$

$$L\square t\square = L\square lt\square * h\square t\square \quad Eq\ 7$$

$$L\square m\square = L\square P\square * s\square P\square + L\square QC\square * s\square QC\square + L\square QP\square * s\square QP\square + L\square QA\square * s\square QA\square \quad Eq\ 8$$

Annual transportation costs

Transportation costs (TR) are accounted for by the number of hours required ($h\square t\square$) and the cost per hour ($TR\square t\square$) as the amount of fuel, cold chain maintenance is time dependent (Eq 9). While LN_2 shipping dewars are limited, limitations of lorry capacity are not considered.

$$TR = TR\square t\square * h\square t\square \quad Eq\ 9$$

Total annual cost

The total cost (TC) is the summation of all aforementioned annual costs (Eq 10). The cost per treatment is the total cost per year divided by the total number of treatments delivered in the year ($T\square treatment\square$) (Eq 11).

$$TC = F\square H\square + F\square M\square + F\square QC\square + E + M + R + L\square h\square + L\square m\square + TR \quad Eq\ 10$$

$$C\square treatment\square = TC\square\ T\square treatment\square\square \quad Eq\ 11$$

Model implementation

The discrete event simulation model was built with ExtendSim 9 (ImagineThat! Inc, San Jose, USA), which is a software platform purposefully built to model continuous, discrete event, discrete rate and agent-based systems[47]. The simulation was set up to run for 50 repeats. To look into a short-term operational decision, the time horizon of one year was selected for each of the studied scenarios. The adoption of the same random input variables between the centralised and decentralised schemes, for

fair comparison, was ensured by using the same random seeds for a pair of demand scenarios. A first-in-first-out approach is adopted for queues. On top of this, triangular distributions were applied on the patient interarrival times, unit operation process duration and risk of mix-ups to understand the risk and process robustness of these decision alternatives using Monte Carlo simulations. The assumptions and cost data used in this study can be found in Appendix 2.
Results from the simulations were exported to Microsoft Excel 2016 (Microsoft Corporation, WA) for computing the cost of goods per treatment, treatment turnaround time and resource utilisation.

Hypothetical case study

The aim of the simulation case study is to develop a discrete event simulation to examine the needle-to-needle process of autologous CAR-T. A hypothetical case study with the United Kingdom as an exemplar is used and the results are compared with other published cost models.

Case study set-up

Figure 2 Distribution of advanced treatment centres in the UK

The UK has been chosen as a case study to demonstrate the application of the simulation model at several annual demand scenarios. In the UK, there are currently 10 advanced treatment centres. Figure 2 shows the distribution of these centres around the UK and the coordinates of these locations can be found in Appendix 1. The distance between the facility and treatment centre locations impacts

the transportation time and hence related costs. For the centralised scheme, it is assumed that one facility will satisfy the demand from all the 10 advanced treatment centres while for the decentralised scheme, each treatment centre is assumed to have its own small-scale facility to meet its local demand (10 manufacturing facilities in total across the country) with a centralised QP for product release.

The annual demand and the number of treatment centres are based on the draft interim specification for the delivery of CAR-T therapy for treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, published by the NHS in 2017[48]. The annual demand has been estimated to be around 200 cases per year. For this study, we have looked into three demand levels in terms of the number of patients per year: low demand (100), anticipated demand (200) and high demand (500).
The assumed numbers of equipment and personnel shifts per day (8 hours per shift) for a total of 6 scenarios are summarised in Table 4, defined by combining the centralised ("C") and the decentralised "D" schemes with the three demand levels (100, 200, 500). To avoid mix-ups and potential of cross contamination, it is assumed that each production personnel can handle a maximum of two sets of integrated processing equipment at the same time during the core working hours from 08:00 to 24:00 (personal communication, Miltenyi Biotec). A production personnel is tasked with handling emergency and alerts outside core working hours. To account for training hours, vacation and sick days, the maximum utilisation of personnel is set to be 80%. These values correspond to the minimal amount of resources needed to allow no system bottleneck and a reasonable level of equipment utilisation rates (80±2%) at the designated demand.

Table 4 Resource input for centralised vs decentralised scenarios for different demand levels

	C100	D100	C200	D200	C500	D500
Production personnel (shifts per day)	5	30	5	50	21	50
QC personnel (shifts per day)	5	30	5	30	5	30
QA personnel (shifts per day)	1	10	1	10	1	10
Qualified Person (QP)	1	1	1	1	1	1
Integrated Processing equipment (#)	4	10	8	10	19	20

Demand stress
To investigate the impact of demand stress in case of poor estimation of demand at planning stage, we simulated each scenario at its designated demand level, referred to as the base case (100, 200, or 500 patients per year), and also at patient demand increased in 5%, 10%, 15%, 20%, 30% and 50%. As trained labour and equipment take time to become operationally ready, the availability of resources in each scenario is assumed unchanged with unexpected demand increase.

Risk assumptions
Quality risk points discussed by Trainor et al [25] are considered and risk probabilities are benchmarked and assigned based on published data. In this study, we simulated the risk of patient material mix up at two potential occurrences, hospital to facility and facility to hospital. The lower bound (0.02%) and higher bound (0.08%) of the risks were benchmarked against blood bag mix-ups documented by Bolton-Maggs et al[49]. Where mix-ups or failures occur, the batch will be reneged and discarded, as out-of-specification drugs cannot be sold[42].

Results

This section will discuss the results of simulation and the observed trends in cost and resource utilisation, timeliness of delivery and response of the centralised and decentralised schemes under demand stress.

Base case (under nominal demand levels): Cost and resource utilisation

The costs per treatment for three demand levels, accounting for both hospital, manufacturing and transportation costs, are shown in Table 5. The per treatment costs range from around $70,336 in the high demand centralised manufacturing scenario to $166,750.3 in the low demand decentralised manufacturing scenario. The results are reasonably comparable with the previously estimated cost of around $95,780 per dose for autologous CAR-T [52], and are significantly higher than the costs estimated previously for allogeneic CAR-T cell therapy, e.g. around $7,000 to 8,000 ([51], not including hospital or transportation costs) and $4,460 [52] per dose. Exact comparison of results from different studies can be difficult given their difference in the inclusion of various cost items. However, in general it is expected that autologous CAR-T is costlier than its allogeneic counterpart, as the latter allows better scale-up and production of off-the-shelf products. In both centralised and decentralised schemes, the per treatment cost is reduced as demand increases (Table 5**Error! Reference source not found.**). The required resources assumed for the decentralised scheme are greater than that for the centralised scheme to achieve the same production level (Table 4), hence the resource utilisation rates are lower except for production personnel at the high demand scenario (Figure 3A).

As the demand increases, resources such as labour, equipment and facility can be better utilised and shared amongst more treatments (Figure 3A). This is particularly apparent for the decentralised cases, where smaller local facilities in hospitals can benefit from better utilisation of all resources, especially with the use of integrated process equipment (Prodigy).

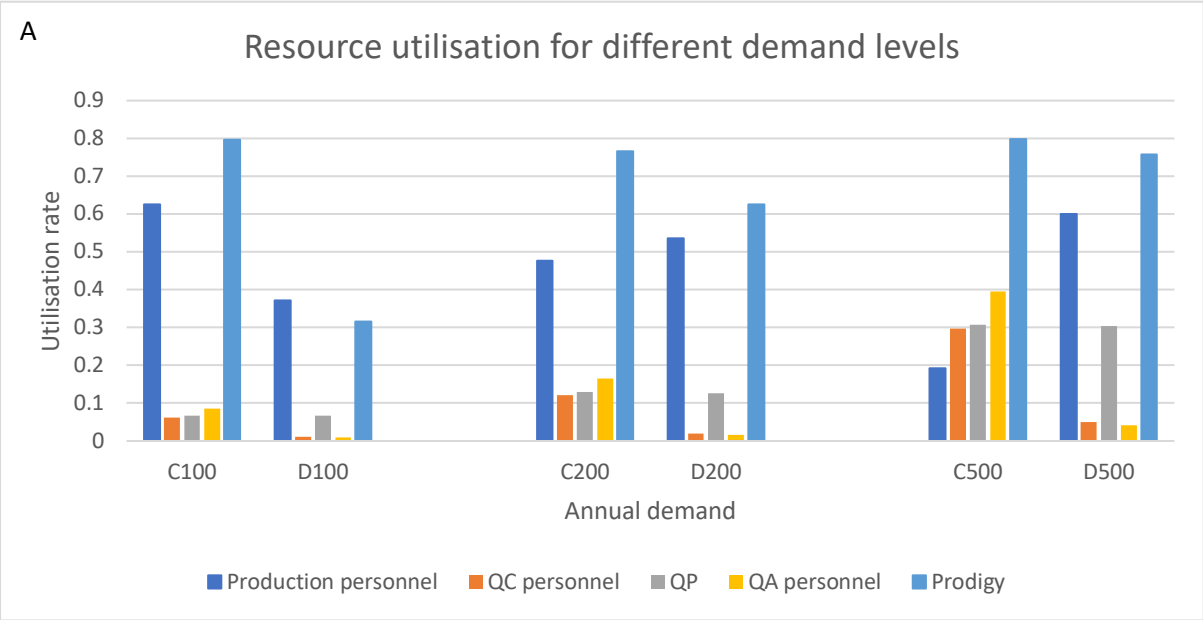
For decentralised manufacturing, there is a minimal number of equipment and personnel required at each facility and hence the utilisation rates of resources are low for demand levels of 100 and 200 patients per year. The difference in utilisation rate of production personnel and equipment between decentralised and centralised schemes reduces as annual demand reduces, while the utilisation rate of QC and QA personnel for centralised manufacturing increases at a much faster rate than in the decentralised scheme (Figure 3B). It is noted at high demand level, production personnel and equipment are better utilised in the decentralised scheme. This is due to the constraint of maximum of 2 equipment handled per personnel to prevent cross-contamination and mix-ups. If the constraint is relaxed, it would be easier to utilise resources to a better extent.

As the qualified person (QP) can sign off batches based on data sent from decentralised facilities, the utilisation rate of QP is based on the number of treatments delivered, hence there is no change in the utilisation rate of QP between centralised and decentralised facilities (Figure 3B).

Table 5 Cost breakdown per treatment for all scenarios

Scenario		**Centralised**			**Decentralised**	
Annual demand	100	200	500	100	200	500
Raw material/Consumables	**63,070.4**	**56,792.5**	**50,520.1**	**63,814.3**	**57,280.6**	**50,674.8**
Hospital	6,905.7	6,200.5	5,512.1	6,810.1	6,170.8	5,492.8
Transportation	-	-	-	-	-	-
Manufacturing	55,788.3	50,252.0	44,705.5	56,628.8	50,770.8	44,880.4
QC	376.4	340.0	302.5	375.5	339.0	301.6
Labour	**6,024.6**	**3,807.8**	**3,486.0**	**26,818.6**	**16,138.8**	**7,918.1**

Hospital	960.6	956.2	956.3	986.4	987.3	988.6
Transportation	288.9	30.4	331.0	-	-	-
Manufacturing	1,797.1	1,291.9	1,576.6	10,720.8	7,365.3	3,754.4
QC	2,978.0	1,529.2	622.1	15,111.3	7,786.2	3,175.1
Capital/equipment cost	**3,456.4**	**1,977.1**	**1,092.4**	**14,296.3**	**6,629.6**	**2,746.4**
Hospital	1,222.0	564.8	204.2	1,024.1	474.9	172.1
Transportation	205.4	94.9	34.3	-	-	-
Manufacturing	1,457.1	1,053.1	758.3	7,585.7	3,517.7	1,618.4
QC	571.9	264.3	95.6	5,686.5	2,637.0	955.9
Facility costs	**39,691.9**	**29,962.1**	**15,036.4**	**59,166.7**	**36,164.9**	**22,686.6**
Hospital	11,715.2	11,715.2	11,715.2	11,715.2	11,715.2	11,715.2
Transportation	-	-	-	-	-	-
Manufacturing	26,654.1	17,567.7	3,044.9	46,252.3	23,831.8	10,719.4
QC	1,322.6	679.1	276.3	1,199.2	617.9	252.0
Transportation costs	**30.3**	**64.1**	**30.5**	**-**	**-**	**-**
Hospital	-	-	-	-	-	-
Transportation	30.3	64.1	30.5	-	-	-
Manufacturing	-	-	-	-	-	-
QC	-	-	-	-	-	-
Others (Service and maintenance costs)	**405.8**	**263.5**	**170.8**	**2,654.4**	**1,230.9**	**514.8**
Hospital	-	-	-	-	-	-
Transportation	-	-	-	-	-	-
Manufacturing	291.4	210.6	151.7	1,517.1	703.5	323.7
QC	114.4	52.9	19.1	1,137.3	527.4	191.2
Total per treatment cost	**112,679.5**	**92,867.0**	**70,336.2**	**166,750.3**	**117,444.9**	**84,540.8**



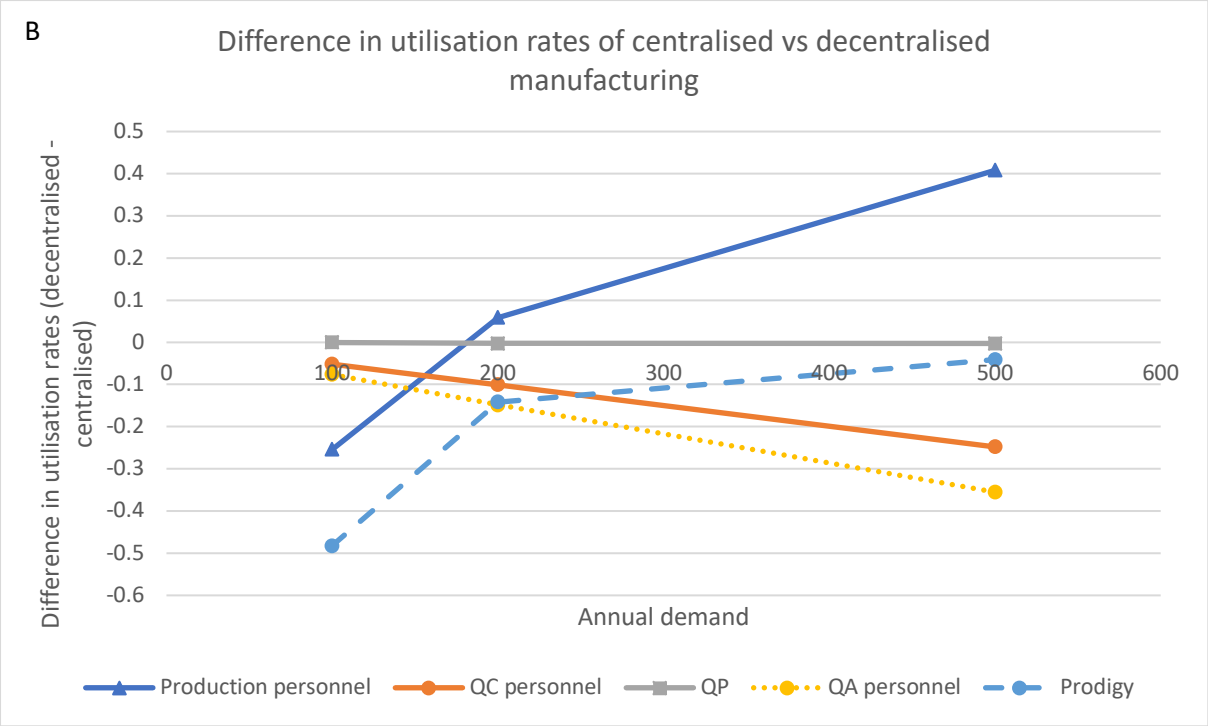


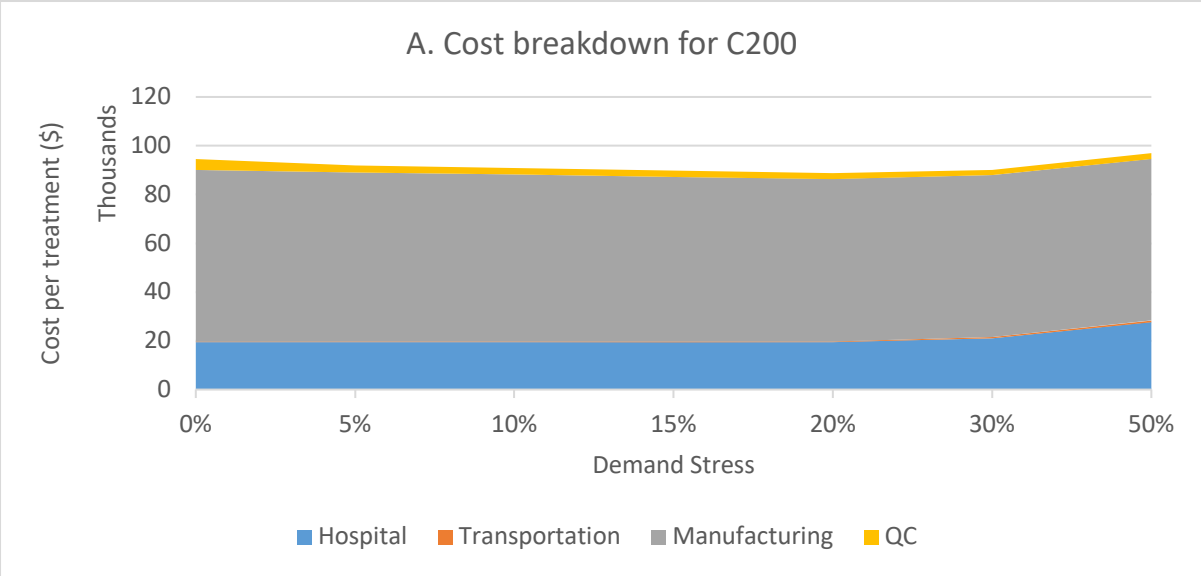
Figure 3 Resource utilisation in centralised and decentralised schemes. A: Resource utilisation comparison at 3 demand levels; B: Difference in utilisation rates between centralised and decentralised manufacturing for labour and manufacturing equipment.

System performance under demand stress

As introduced earlier, demand stress is defined as unanticipated increase in demand which exceeds the planned capacity. This section considers the change in cost and resource utilisation as demand stress increases.

Cost per treatment

The cost per treatment decreases initially as the system handles more treatments and hence the overall cost can be shared amongst more treatments (Figure 4



). As demand stress becomes greater, at 50% demand stress, in the centralised scheme, the per treatment cost increased by 1.8%, 2.6% and 11.5% for low, mid and high demand levels respectively; whereas for the decentralised scheme, the per treatment cost decreased for low and mid demand levels by 11.6% and 8.3% and increased for high demand levels by 5.3%.

It is shown that when subject to greater demand stress, the difference in the per-treatment cost for decentralised and centralised systems is reduced. This is due to the insufficient manufacturing capacity causing wait queues and resource occupation at the hospitals (Figure 5). The turning point corresponds with the resource utilisation and throughput to be discussed in the following section.

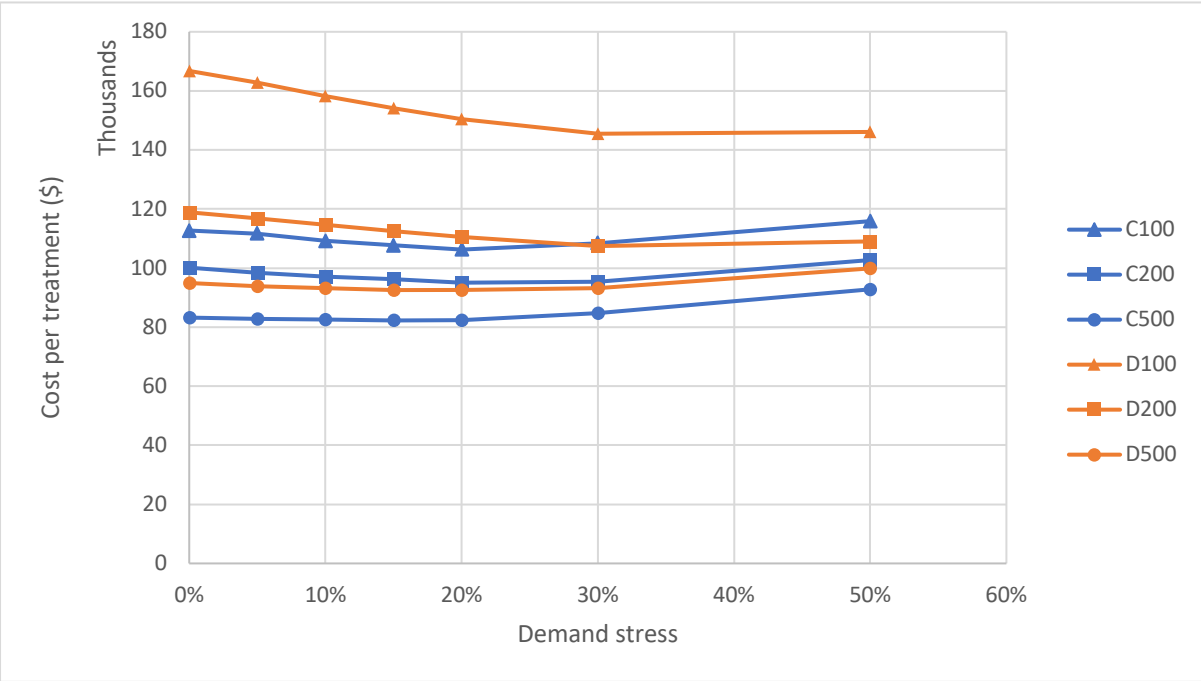
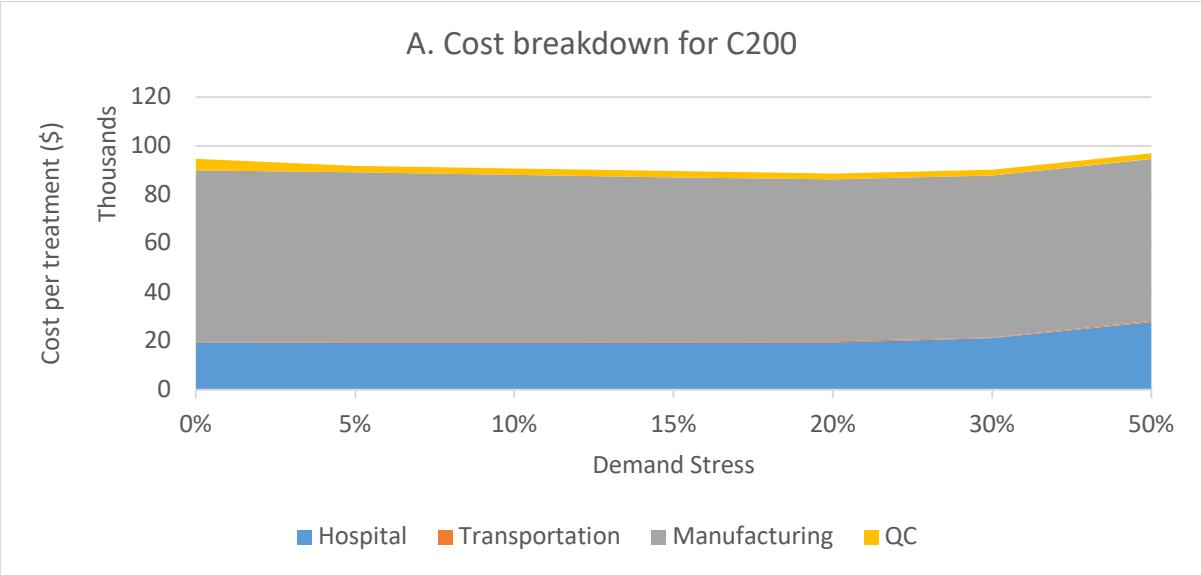


Figure 4 Cost per treatment as demand stress increases for centralised (blue) and decentralised (orange) manufacturing. Triangle, square and circle markers correspond to annual demand of 100, 200 and 500 treatments, respectively.



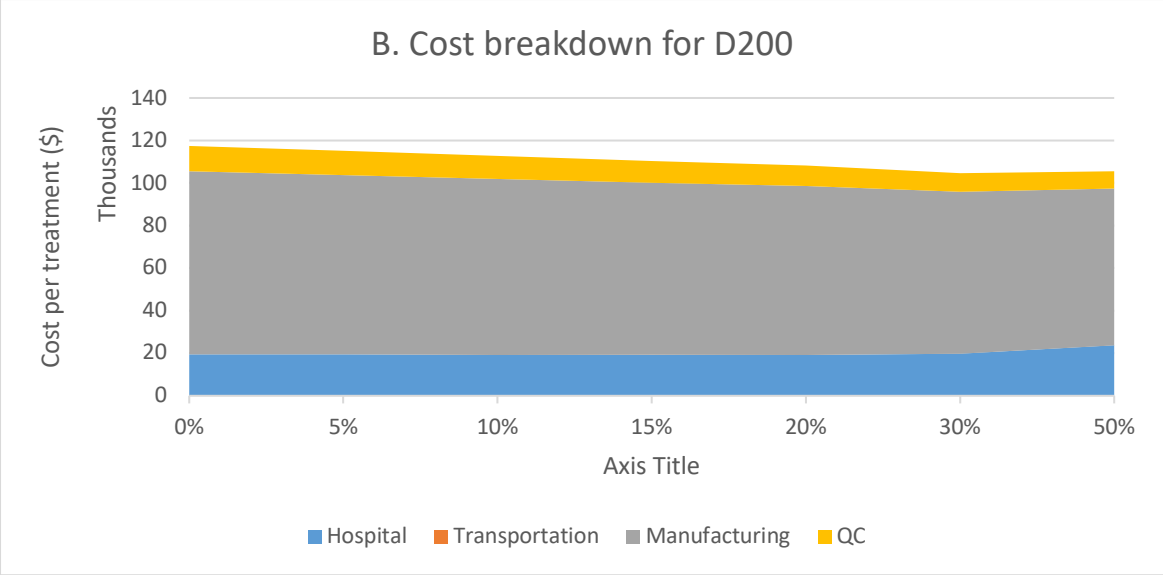


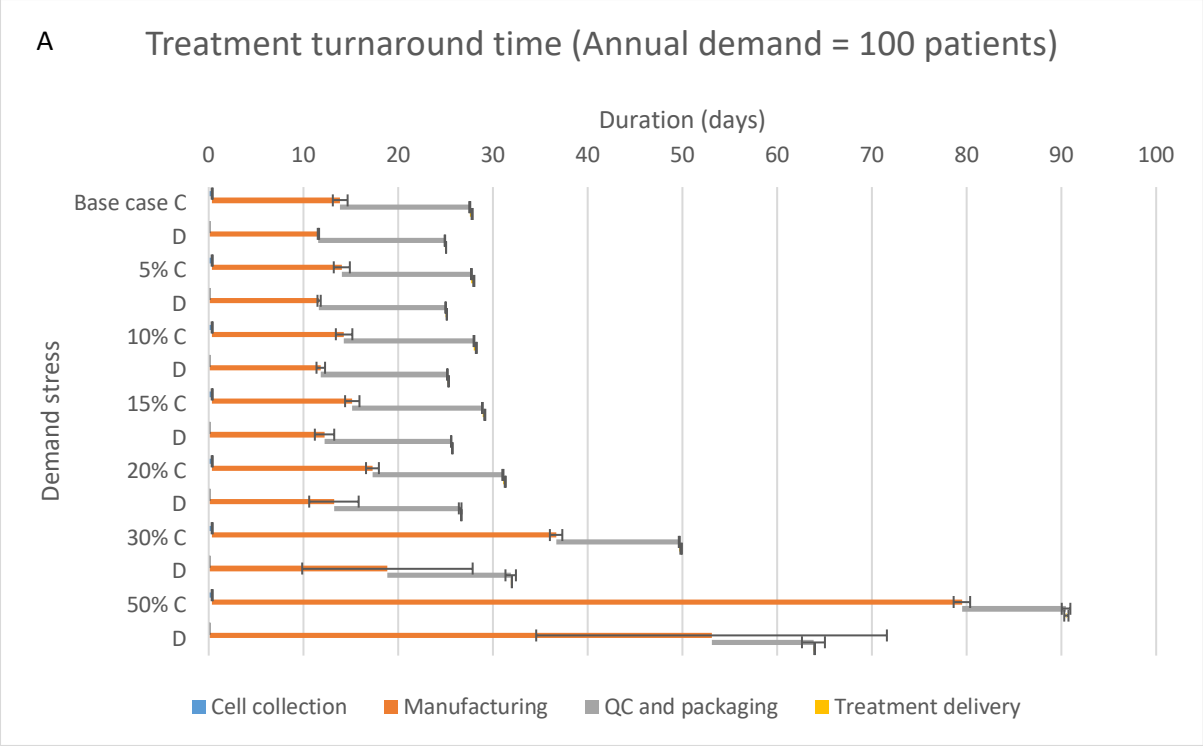
Figure 5 Cost breakdown for annual demand 200 patients per year. (A) Centralised; (B) Decentralised

Turnaround time per treatment

With the proximity of patients and manufacturing facility, the need for cryopreservation and cold chain transportation in the decentralised setting can be reduced subject to risk assessment and quick detection strategies to assure sterility and hence the overall duration for decentralised manufacturing is generally shorter than that for centralised manufacturing (Figure 6). The duration of around 24-30 days for the entire process from raw material collection to final delivery is consistent with the average time for Gilead's Yescarta (26-29 days)[50].

At high demand stress, whilst the hospitals take a similar amount of time to process each patient, the manufacturing facility is unable to cope with the incoming material, which is predicted in the simulation to cause long queues and long waiting times. In reality, hospitals need to liaise with manufacturing facilities to ensure capacity before the cell collection process to ensure that the cells maintain good viability and the patients receive treatments in a timely manner. This also highlights the importance of patient scheduling. Cryopreservation of patient cells is done to allow more flexibility in the collection and delivery scheduling as implemented in this model.

It is also noted, that the decentralised scheme has greater standard deviation values for the manufacturing turnaround time as demand stress increases (Figure 6). This is due to the assumption of different hospitals having different numbers of patients coming at various inter-arrival times. With greater demand fluctuations, the manufacturing equipment constraint can cause fluctuations of supply at individual facilities.


A
Treatment turnaround time (Annual demand = 100 patients)
Duration (days)
0
10
20
30
40
50
60
70
80
90
100
Demand stress
Base case C
D
5% C
D
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50% C
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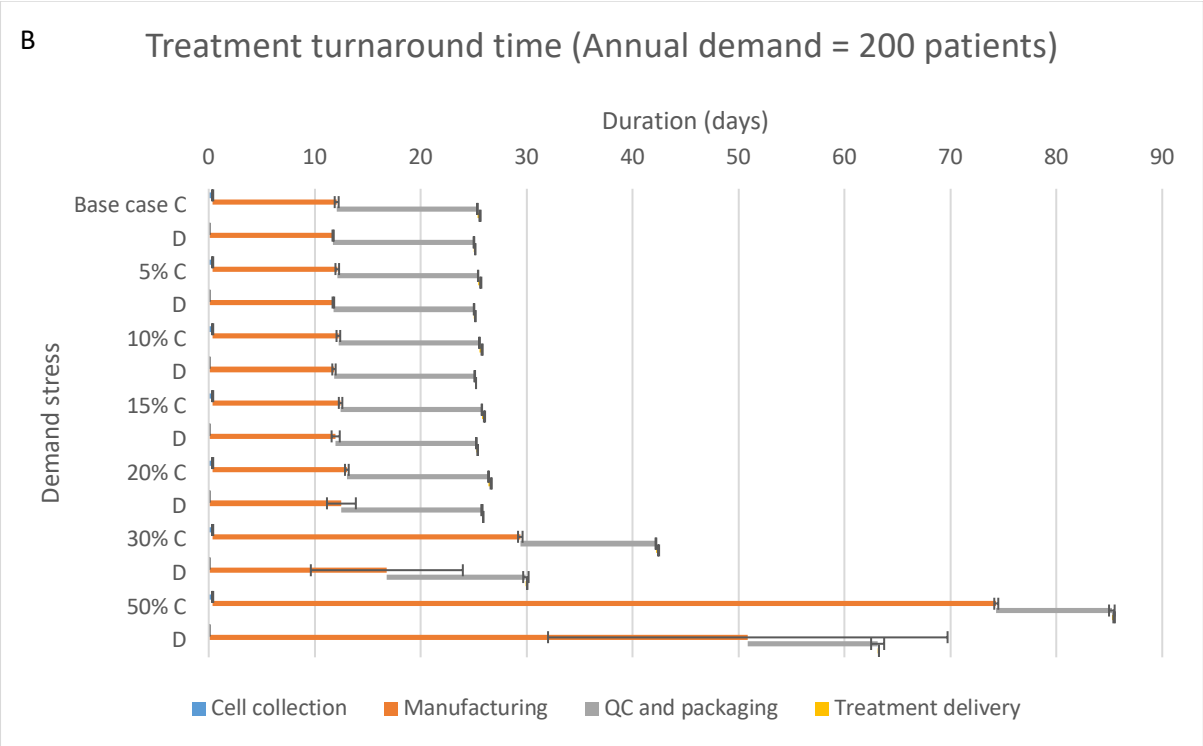
Cell collection
Manufacturing
QC and packaging
Treatment delivery


B
Treatment turnaround time (Annual demand = 200 patients)
Duration (days)
0
10
20
30
40
50
60
70
80
90
Demand stress
Base case C
D
5% C
D
10% C
D
15% C
D
20% C
D
30% C
D
50% C
D
Cell collection
Manufacturing
QC and packaging
Treatment delivery

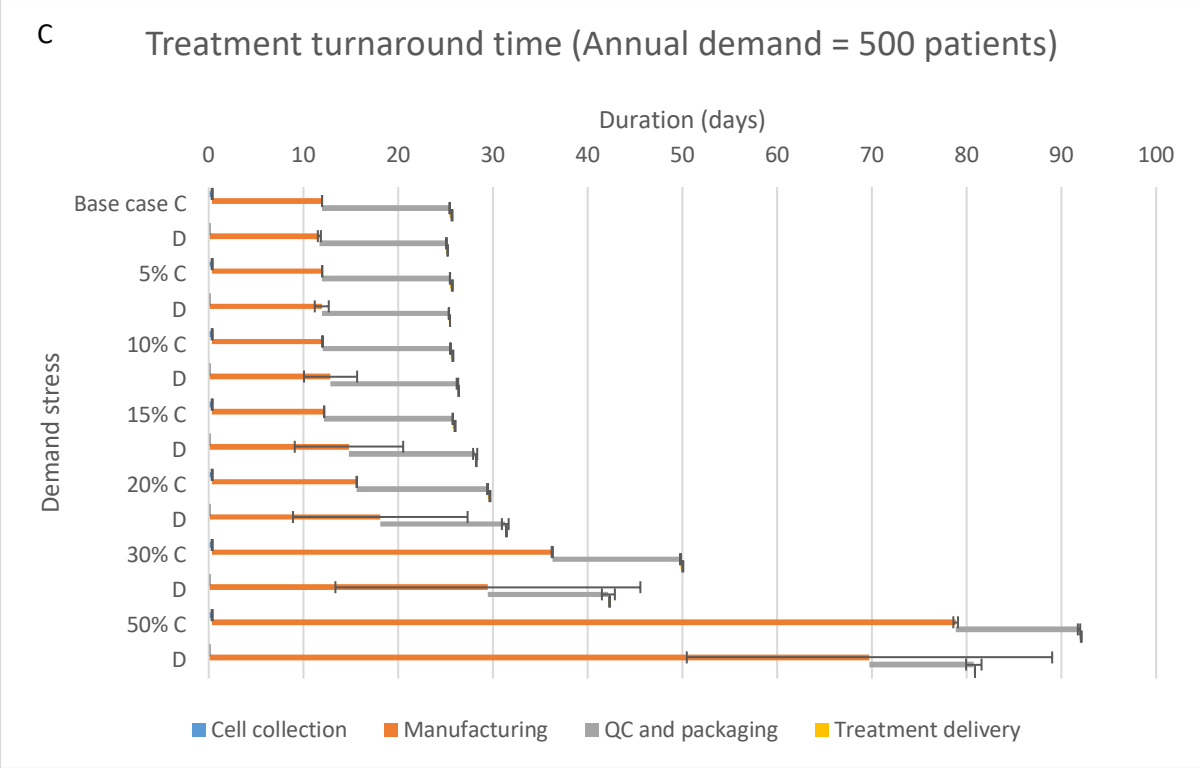


Figure 6 Duration breakdown for centralised vs decentralised manufacturing at various annual demands. (A) 100 treatments per year; (B) 200 treatments per year; (C) 500 treatments per year.

System Throughput and resource utilisation

For centralised manufacturing, sharing of resources meant the overall manufacturing capacity (number of equipment and shift patterns) can be more tightly designed to meet the particular demand level. Consequently, as shown in Figure 7A-F, the centralised scheme can cope with less demand fluctuations. For lower nominal annual demand levels (Figure 7A, B), the drop-in system throughput is due to over-utilisation of equipment as demand stress increases from 20% to 30%. For higher nominal demand level (Figure 7C), the quality control facilities start to become a constraint and hence the drop in system throughput occurred at lower demand stress (between 10-20%).

For the decentralised scheme, for low demand level (Figure 7D, E), the drop in system throughput only occurred between 30-40% while for high demand level (Figure 7F), the drop in system throughput occurred much earlier. This is due to the better utilisation of resources at higher demand decentralised scheme as shown in the previous section (Figure 3).

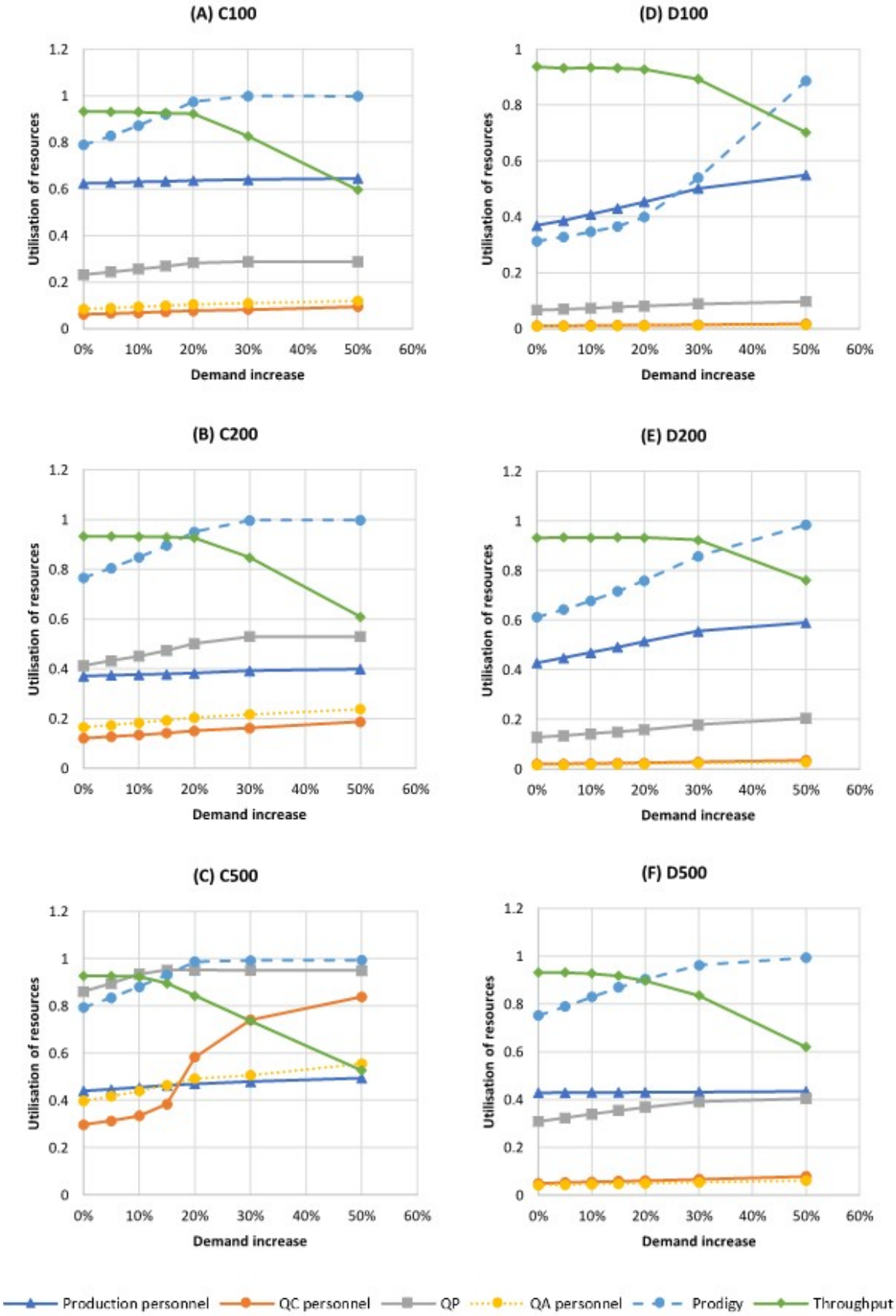


Figure 7 Resource utilisation with demand stress. A-C: Centralised manufacturing for annual demand of 100, 200 and 500 treatments per year; D-F: Decentralised manufacturing for annual demand of 100, 200 and 500 treatments per year.

Discussion

Operational pain points for autologous cell therapy manufacturing

One of the most critical steps in the production of CAR-T therapy is genetic modification and cell processing. In currently active clinical trials registered on clinicaltrials.gov that have reported their gene-editing method, 167 out of 179 trials employ a lentiviral or retroviral vector. The currently approved products Kymriah and Yescarta employ lentiviral and retroviral vectors respectively. In Table 5, it is shown that raw material and consumables costs are consistently significant costs, of which the reagents for lentiviral transduction costs account for over one-third of the raw material costs. Improvement in large-scale virus production processes [51,52] and cheaper CAR-gene insertion technologies such as electroporation and CRISPR/Cas systems can greatly lower the per unit treatment cost.

Quality control has shown to be a bottleneck for the delivery time for CAR-T treatments[53,54]. The current pharmacopoeia requirement for sterility testing takes around 14 days for incubation[55,56], although regulatory authorities such as US FDA and EMA allow use of sterility test results from 3 days pre-harvest, the QC process still take over 10 days to complete (Figure 6).
Currently approved CAR-T products are cryopreserved for improved flexibility in scheduling, shipping delays[12] and release testing. However, as CAR-T products consist of live cells, the quality of the product (viability of cells) may be compromised while being refrigerated or cryopreserved where the freeze-thaw cycle have quality implications on the cells[57]. Whilst cryopreserved CAR-T cells have been shown to be comparable to fresh CAR-T cells and have demonstrated safety and efficacy[58–60], studies have also shown that cryo-thawed CAR-Ts demonstrate elevated expression of apoptotic and cell cycle damage pathways compared with fresh CAR-Ts[57]. A point-of-care manufacturing approach allows better access to patients and less logistics delays and may allow fresh and better quality products to be used on patients[60]. Under circumstances where the benefits of providing a treatment that has not been fully tested outweighs the risks, it may be possible for the product to be used before completion of sterility testing. Under such circumstances, the rationale should be detailed in the risk assessment and strategies to assure sterility such as testing of media or intermediate products should be considered[23]. Non-culture, quick-detection methods such as gram staining[61] or acridine orange staining in addition to sterility tests of in-process samples can be a possible solution subject to full validation[62]. Innovation in shortening the sterility testing turnaround time has shown promising results, reducing the length of test to 2 days[63].
Due to the autologous nature of CAR-T therapies, there are multiple handover points where mix-ups can occur. From the simulation results, due to the limited number of total treatments, the effect of mix-ups (estimated based on blood bag mix-up probabilities[49]) was shown to be minimal. In reality, regulatory authorities impose strict track-and-tracing requirements to ensure full proof of chain of identity[23]. On top of this, sensitive patient data is subject to HIPAA (US) or GDPR (EU) regulations[64]. Streamlining data management and proper handling of patient data have proven to be a challenge in CAR-T delivery[65].
The QC bottleneck has led to various discussions over the possibility of release by exception. Release by exception means to release a product automatically if the production process had no deviations from the characterised and documented manufacturing process[66]. This can potentially shorten the turnaround time of autologous cell therapies by over 50%. To facilitate release by exception, better in-process sensors by capturing the critical process parameters are required and other in-process

testing methods such as Raman spectroscopy for monitoring molecular profiles and cell microenvironment will be of great importance[67].

Operational pain points for decentralised manufacturing

This hypothetical case study serves to understand whether there is a case for point-of-care manufacturing of CAR-T products within the UK.

Due to the niche indications and low demand levels, the general utilisation rates of facilities can be low as shown in the D100 scenario where resources were under-utilised and hence the per treatment cost was very high. Moreover, quality control testing equipment costs are shared amongst a very small number of treatments, making the system economically not viable.

At higher demand levels, decentralised manufacturing proved more and more cost competitive as shown in Table 5. The difference in resource utilization between the centralised and decentralised scenario reduce as demand increases, allowing equipment and personnel to be better utilised at local facility levels (Figure 3). As shown by the greater standard deviation in treatment turnaround time for the decentralised scenario (Figure 6), better scheduling of patient demand at hospitals and hence job dispatching can allow more efficient resource and equipment investment and utilisation within each decentralised facility.

At lower demand levels for the decentralised manufacturing scheme, each hospital only has one integrated processing platform (Miltenyi Prodigy), hence equipment failure can have a greater impact on manufacturing. However, it is noted that the common practice for equipment maintenance in GMP setting for direct system impact equipment is to have a 24-hour service replacement contract in place. The replacement equipment will have to go through the installation and operational qualification (IQ/OQ) and a deviation report for equipment change should be raised. Subject to risk assessment of individual facilities, they may need additional performance validation prior to being used.

In this case study, the end-to-end process is assumed to be completed in the United Kingdom. Harrison et al looked at the impact of offshore manufacturing, including the evaluation of resource cost discrepancies [68]. It is also important to note that import and export processes across borders can add to the time required for the overall treatment. Extra personnel work hours may have to be allocated to preparing associated paperwork for Human Tissue Act compliance (for equivalent in other countries) [69]. Such extensions could well alter the comparison between the centralised and decentralised schemes. In addition, extra costs incurred due to transhipment are not considered.

Merits of decentralised manufacturing

Within the UK, as transportation networks are well established, the effect of decentralisation has a relatively low impact on the overall turnaround time of treatments (Figure 6). However, when looking at regional centres where cell products may have to go through import and export procedures and airfreight, the impact of transportation, transhipment and associated costs with maintaining the ultra-cold chain during transportation will be more apparent.

If autologous CAR-T treatments are approved for less niche indications such as solid tumours[70], the overall demand level for autologous treatments will be increased greatly. The effect of having greater flexibility and communication between the hospital and facility was not simulated in this study but was previously cited as one of the key merits of the decentralised paradigm[71]. As there is no need for freezing and thawing for products produced at the point-of-care, this can allow better quality product, better communication between patient's medical team and the manufacturer and an overall more streamlined treatment experience.

Using discrete event simulation for comparing centralised and decentralised manufacturing

As shown in this study, discrete event simulation combined with scenario analysis allows the granularity of resource allocation to be studied. It could be particularly useful in planning parallel GMP production activities and understanding the production personnel requirement for optimisation. Scenario analysis allowed the study of various input variables for process optimisation for finding the process pain points and bottlenecks.

Limitations

This article provides insights on the operational pain points of centralised and decentralised manufacturing paradigms using closed, automated equipment to tightly control the manufacturing process and ensure comparability across facilities. Product quality impacts introduced in cell collection, freeze-thaw cycle of raw material and the reduced need of transportation are considered to a certain extent in the turnaround time attribute, which however is not able to capture all important aspects of production quality in this operation simulation model.

The per treatment cost ($C_{treatment}$) can be overestimated as cost of treatments that are still being processed at the cut-off time of one year are included in the total cost (Eq 11). The ramp-up period was considered relatively insignificant over the simulation duration of a year in this work and therefore not modelled specially. However, consideration of this period can become important for shorter simulations.

As cost data for commercialised products are not publicly available, the model could not be validated with real world data. However, the results were benchmarked with other published models and have shown comparable results.

Conclusions

This article employed discrete event simulation to investigate and compare operational issues of centralised and decentralised manufacturing of autologous CAR-T therapies. As shown by the simulation, centralised manufacturing is a preferred option for lower demand levels (annual demand of 100-200 patients per year) due to better utilisation of resources which in turn provides cost savings. However, as the anticipated demand increases, the per-treatment cost between centralised and decentralised schemes converges, and the decentralised model becomes more comparable cost-wise. The decentralised model shows greater demand stress resilience and, as the demand level increases, resource utilisation improves within individual facilities and provides opportunity for economies of scale. Quality control lies on the critical path for both centralised and decentralised schemes, more investigation in the potential of release by exception based on risk-benefit assessment should be conducted to shorten the time needed for testing.

Considering both cost and treatment turnaround time, point-of-care manufacturing does not show great advantages over centralised manufacturing due to the relative short amount of time for product transportation required within the country. However, further studies on cross-border product manufacturing and treatment delivery may show greater promise for decentralised manufacturing.

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Author contributions

CL conceptualized and carried out the modelling work and wrote the manuscript. AY and ZFC provided supervision to model construction and simulation studies. EM, AY and ZFC provided comments to the manuscript for better relevance and clarity. All authors approved the final manuscript.

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Declaration of Interests

No relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Appendix 1: Distribution of treatment centres in the United Kingdom

Name	Type	Location	
		x-coordinate	y-coordinate
Catapult Cell and Gene Therepy	Manufacturing centre	-0.200701298	51.8851217
Great Ormond Street Hospital	Treatment centre	-0.1207462	51.5218626
University College London Hospital	Treatment centre	-0.1229515	51.5219385
King's College Hospital	Treatment centre	-0.0943969	51.4679288
University Hospitals Bristol NHS Foundation Trust	Treatment centre	-2.5944794	51.4599695
The Christie NHS Foundation Trust	Treatment centre	-2.2304081	53.4299659
Royal Manchester Children's Hospital	Treatment centre	-2.2249666	53.4601835
Manchester Royal Infirmary	Treatment centre	-2.2261188	53.462879
Queen Elizabeth Hospital	Treatment centre	-1.944448	52.450565
Great North Children's Hospital	Treatment centre	-1.6179465	54.979611
Newcastle Freeman Hospital	Treatment centre	-1.5929456	55.0030284

Appendix 2: Cost and production duration data

2a. Cost data in USD

$$Cost\ per\ year = Capital\ cost * depreciation\ factor$$

Resource type	Resource Name	Cost per year	Cost per hour	Cost per use	Cost per day	Cost per item
Consumables	Liquid nitrogen			10		
Consumables	Liquid nitrogen		0.5			
Consumables	Sepax consumables kit			100		
Consumables	Mycoplasma detection kit					31.55
Consumables	Clinimacs reagent					2156.76
Consumables	Leukapheresis kit					2000
Consumables	Expansion media				28	
Consumables	Transduction kit					627.9
Consumables	T-cell activation kit					2156.76
Consumables	Prodigy kit					3179
Consumables	Aseptic gowning					7.5
Equipment	Shipping container	63.5				

Equipment	Sepax	5000				
Equipment	Clinimacs Prodigy	20000				
Equipment	Barcode reader	120				
Equipment	Peltier block	180				
Equipment	Microscope	1100				
Equipment	Vi-cell	6550				
Equipment	Flow cytometer	6550				
Equipment	PCR	5898				
Equipment	ELISA plate reader	5000				
Equipment	Isolator-2 glove	23834				
Equipment	Incubator	2300				
Equipment	Endosafe	1214.5				
Equipment	BacT-alert	3250				
Equipment	Refridgerator	720				
Equipment	Barcode reader	120				
Equipment	Freezer (-20)	720				
Equipment	freezer (-80)	720				
Equipment	Peltier block	180				
Equipment	Isolator-2 glove	23834				
Equipment	CRF (facility)	1600				
Equipment	Cryogenic freezer	3000				
Equipment	Autoclave	28000				
Facility	Annual revalidation	25000				
Facility	Utility cost (per m^2)		0.00588			
Facility	EMS – handheld portable particle counter	300				
Facility	EMS – annual calibration and maintenance cost	5000				
Hospital	Operation theatre cost		1562.03			
Hospital	Emergency and intensive care		125			
Hospital	Lymphodepletion jabs			1562.03		
Personnel	Nurses		30.24			
Personnel	Chief surgeon		167.92			
Personnel	Pharmacist		33.3			
Personnel	Logistics technicians		25			
Personnel	Clinical support worker		28.64			
Personnel	QC personnel	35000				
Personnel	Production personnel	35000				
Personnel	QP	80000				
Personnel	QA personnel	35000				
Transport	Transportation cost		20			

Facility EMS assumptions

The cost of facility environmental monitoring system is dependent on the type of data monitored, number of equipment requiring temperature monitoring (e.g. incubator, fridges), humidity monitoring, pressure and particle monitoring.

As the process modelled is a closed automated system, it is assumed that only temperature and pressure monitoring is required for the Grade D cleanroom. A portable particle sensor is used for monitoring particle count within the Grade D rooms.

An example quote for an EMS system with software, validation documents and system commissioning for a Grade D room with room sensors (temperature and pressure) and temperature sensors for the following 11 equipment is £13,000/$16,000 (provided by Pharmagraph (United Kingdom)) and an installation cost of £2,000/$2,500:

2 x incubators

2 x Fridges

2 x -20 Freezers

2 x -80 Freezers

1 x Controlled rate freezer

2 x Cryofreezer

Ongoing calibration and maintenance cost contract would be around £4,000/$5000 per year.

As a rough guide, the "0.6 rule" usually used for production processes scale economies is applied for scaling up the EMS system[72]:

$$EMS\ Capital\ cost = 18500 * (\#\ of\ equipment - 11)^{0.6}$$

2b. Process duration data

Location	Activity	Value	Unit
Hospital	Leukapheresis	30	minutes
Hospital	Documentation of collected cells	Tr(20,30,45)	minutes
Hospital	Controlled rate freezing of collected cells	Tr(4,5,6)	hours
Hospital	Lymphodepleting therapy (prep)	10	minutes
Hospital	Lymphodepleting therapy (Day 1)	Tr(1,1.5,2)	hours
Hospital	Lymphodepleting therapy (Day 2)	Tr(1,1.5,2)	hours
Hospital	Lymphodepleting therapy (Day 3)	Tr(1,1.5,2)	hours
Hospital	Lymphodepleting therapy (Day 4)	Tr(1,1.5,2)	hours
Hospital	Product preparation before transplant	Tr(1,1.5,2)	hours
Hospital	Transplant	Tr(1,1.5,2)	hours
Transportation	Transportation	(dependent on location)	hours
Manufacturing	Visual inspection	Tr(0.1,0.2,0.5)	hours
Manufacturing	Batch record creation	Tr(0.1,0.2,0.5)	hours
Manufacturing	Patient cell sample prep	Tr(0.1,0.2,0.5)	hours
Manufacturing	Patient cell thaw	Tr(0.5,0.75,1)	hours
Prodigy	Prodigy set up	30	minutes
Prodigy	Tubing set priming	30	minutes
Prodigy	Sample and reagent prep for Prodigy	30	minutes
Prodigy	T cell selection	Tr(1.5,2,2.5)	hours
Prodigy	Activation (program)	20	minutes
Prodigy	T cell activation	Tr(0.5,0.75,1)	days
Prodigy	Transduction (program)	10	minutes
Prodigy	Transduction	Tr(0.9,1,1.1)	days

Prodigy	Sampling post-transduction	Tr(0.2,0.35,0.5)	hours
Prodigy	Expansion check	10	minutes
Prodigy	Expansion	9	days
Prodigy	Sampling in expansion phase	Tr(0.2,0.35,0.5)	hours
Prodigy	Formulation (program)	15	minutes
Prodigy	Formulation	2	hours
Prodigy	Remove product	15	minutes
Prodigy	Remove kit	15	minutes
Manufacturing	Controlled rate freezing of product (prep)	10	minutes
Manufacturing	CRF of product	Tr(4,5,6)	hours
Manufacturing	Batch record check	Tr(1,2,3)	hours
Manufacturing	QP sign off	Tr(1,2,3)	hours
QC	Virology screening (prep)	Tr(1.5,2,2.5)	hours
QC	Virology screening	Tr(11,12,13)	hours
QC	Virology report documentation	Tr(0.25,0.4,0.5)	hours
QC	Viability, cell count	0.18	hours
QC	Flow cytometry (phenotype)	0.18	hours
QC	Mycoplasma PCR (prep)	Tr(0.4,0.5,0.6)	hours
QC	Mycoplasma PCR	Tr(2,2.5,3)	hours
QC	Mycoplasma PCR (report)	Tr(0.25,0.4,0.5)	hours
QC	ELISA (surface protein testing)	2	hours
QC	Sterilty testing sample prep on agar	Tr(0.3,0.5,0.7)	hours
QC	Sterilty testing (incubator)	Tr(13.9,14,14.1)	days
QC	Sterility testing report	Tr(0.15,0.2,0.25)	hours
QC	Endosafe	Tr(0.4,0.5,0.75)	hours

Appendix 3: Definitions of terms introduced in equations

A_{CNC}	Number of required air changes per hour for CNC cleanroom
A_{D}	Number of required air changes per hour for Grade D cleanroom
c_{gown}	Cost per aseptic gown ($)
c_{HVAC}	Air change cost per m3 per hour ($)
C_{CNC}	Capital cost per m^2 of CNC clean rooms($)
C_{D}	Capital cost per m^2 of Grade D clean rooms ($)
$C_{treatment}$	Cost per treatment ($)
d	Depreciation factor (over 10 years)
$D_{m,CNC}$	Depth of manufacturing equipment in CNC areas (m)
$D_{m,D}$	Depth of manufacturing equipment in Grade D areas (m)
$D_{qc,CNC}$	Depth of QC equipment in CNC areas (m)
E	Capital/equipment cost per year ($)
E_{h}	Total hospital equipment cost ($)
$E_{m,D}$	Total manufacturing equipment in Grade D cleanroom cost ($)
$E_{m,CNC}$	Total manufacturing equipment in CNC cleanroom cost ($)
$E_{qc,CNC}$	Total QC equipment in CNC cleanroom cost ($)
E_{t}	Total transportation equipment cost ($)
F_{H}	Facility costs for hospitals per year ($)
F_{M}	Facility cost for manufacturing per year ($)
F_{QC}	Facility cost for QC per year ($)
$f_{m,CNC}$	Manufacturing floor space Controlled not classified (CNC)
$f_{m,D}$	Manufacturing floor space (Grade D) (m^2)
$f_{qc,CNC}$	QC floor space Controlled not classified (CNC)
g	GMP working space multiplier
h_{t}	Transportation hours per year (h)
h_{m}	Height of cleanroom (m)
h_{OT}	Operating theatre cost per hour ($)
H_{OT}	Hours spent in an operating theatre (h)
Lf	Lang factor for cell therapy facilities
L_{h}	Hospital labour costs per year ($)
$L_{h,nurse}$	Hours worked by nurses per year (h)
h_{nurse}	Hourly rate of nurses ($)
$L_{h,pharmac}$	Hours worked by pharmacists per year (h)
$h_{pharmacis}$	Hourly rate of pharmacists ($)
$L_{h,doctor}$	Hours worked by doctors per year (h)
h_{doctor}	Hourly rate of doctors ($)
$L_{h,support}$	Hours worked by support staff per year (h)
$h_{support}$	Hourly rate of support staff ($)
L_{t}	Transportation labour cost per year ($)
L_{lt}	Hours worked by logistics technician per year (h)
h_{lt}	Hourly rate of logistics technician ($)
L_{m}	Manufacturing labour costs per year ($)
L_{p}	Annual salary of production personnel ($)
L_{QC}	Annual salary of QC personnel ($)
L_{QA}	Annual salary of QA personnel ($)

$L(QP)$	Annual salary of QP ($)
M	Maintenance costs per year ($)
$M(m)$	Maintenance costs for manufacturing per year ($)
$M(qc)$	Maintenance costs for QC ($)
ms	Maintenance and service rate
$n(m, D)$	Number of equipment for manufacturing in Grade D areas
$n(m, CNC)$	Number of equipment for manufacturing in CNC areas
$n(qc, CNC)$	Number of equipment for quality control in CNC areas
R	Raw material costs per year ($)
$R(h)$	Raw material cost for processes in hospital per year ($)
$R(m, D)$	Raw material cost for manufacturing processes in Grade D cleanroom per year ($)
$R(m, CNC)$	Raw material cost for manufacturing processes in CNC cleanroom per year ($)
$R(qc, CNC)$	Raw material cost for QC processes in CNC cleanroom per year ($)
$R(t)$	Raw material cost for transportation per year ($)
$s(p)$	Number of shifts of production personnel per day
$s(QC)$	Number of shifts of QC personnel per day
$s(QA)$	Number of shifts of QA personnel per day
$s(QP)$	Number of shifts of QP per day
TR	Transportation cost per year ($)
$TR(t)$	Transportation cost per hour ($)
TC	Total cost ($)
$T(treatment)$	Total number of treatment
v	Annual revalidation cost (HEPA recertification) ($)
$W(m, CNC)$	Width of manufacturing equipment in CNC areas (m)
$W(m, D)$	Width of manufacturing equipment in Grade D areas (m)
$W(qc, CNC)$	Width of QC equipment in CNC areas (m)

Appendix 4: Patient arrival schedule Triangular distribution of number of days in between patient arrival.

4a. Annual demand of 100 patients

Hospital	1			2			3			4			5		
Triangular Distribution	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely
Base Case	20.0	48.0	32.0	30.0	50.0	44.0	24.0	40.0	36.0	20.0	40.0	30.0	30.0	80.0	48.0
5%	19.0	45.6	30.4	28.5	47.5	41.8	22.8	38.0	34.2	19.0	38.0	28.5	28.5	76.0	45.6
10%	18.0	43.2	28.8	27.0	45.0	39.6	21.6	36.0	32.4	18.0	36.0	27.0	27.0	72.0	43.2
15%	17.0	41.0	27.2	25.5	42.5	37.4	20.4	34.0	30.6	17.0	34.0	25.5	25.5	68.0	40.8
20%	16.0	38.4	25.6	24.0	40.0	35.2	19.2	32.0	28.8	16.0	32.0	24.0	24.0	64.0	38.4
30%	14.0	33.6	22.4	21.0	35.0	30.8	16.8	28.0	25.2	14.0	28.0	21.0	21.0	56.0	33.6
50%	10.0	24.0	16.0	15.0	25.0	22.0	12.0	20.0	18.0	10.0	20.0	15.0	15.0	40.0	24.0

Hospital	6			7			8			9			10		
Triangular Distribution	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely
Base Case	30.0	46.0	38.0	30.0	48.0	40.0	24.0	54.0	42.0	20.0	50.0	26.0	20.0	52.0	40.0
5%	28.5	43.7	36.1	28.5	45.6	38.0	22.8	51.3	39.9	19.0	47.5	24.7	19.0	49.4	38.0
10%	27.0	41.4	34.2	27.0	43.2	36.0	21.6	48.6	37.8	18.0	45.0	23.4	18.0	46.8	36.0
15%	25.5	39.1	32.3	25.5	40.8	34.0	20.4	45.9	35.7	17.0	42.5	22.1	17.0	44.2	34.0
20%	24.0	36.8	30.4	24.0	38.4	32.0	19.2	43.2	33.6	16.0	40.0	20.8	16.0	41.6	32.0
30%	21.0	32.2	26.6	21.0	33.6	28.0	16.8	37.8	29.4	14.0	35.0	18.2	14.0	36.4	28.0
50%	15.0	23.0	19.0	15.0	24.0	20.0	12.0	27.0	21.0	10.0	25.0	13.0	10.0	26.0	20.0

4b. Annual demand of 200 patients

Hospital	1	2	3	4	5

Triangular Distribution	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely
Base Case	10.0	24.0	16.0	15.0	25.0	22.0	12.0	20.0	18.0	10.0	20.0	15.0	15.0	40.0	24.0
5%	9.5	22.8	15.2	14.3	23.8	20.9	11.4	19.0	17.1	9.5	19.0	14.3	14.3	38.0	22.8
10%	9.0	21.6	14.4	13.5	22.5	19.8	10.8	18.0	16.2	9.0	18.0	13.5	13.5	36.0	21.6
15%	8.5	20.4	13.6	12.8	21.3	18.7	10.2	17.0	15.3	8.5	17.0	12.8	12.8	34.0	20.4
20%	8.0	19.2	12.8	12.0	20.0	17.6	9.6	16.0	14.4	8.0	16.0	12.0	12.0	32.0	19.2
30%	7.0	16.8	11.2	10.5	17.5	15.4	8.4	14.0	12.6	7.0	14.0	10.5	10.5	28.0	16.8
50%	5.0	12.0	8.0	7.5	12.5	11.0	6.0	10.0	9.0	5.0	10.0	7.5	7.5	20.0	12.0

Hospital	6			7			8			9			10		
Triangular Distribution	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely
Base Case	15.0	23.0	19.0	15.0	24.0	20.0	12.0	27.0	21.0	10.0	25.0	13.0	10.0	26.0	20.0
5%	14.3	21.9	18.1	14.3	22.8	19.0	11.4	25.7	20.0	9.5	23.8	12.4	9.5	24.7	19.0
10%	13.5	20.7	17.1	13.5	21.6	18.0	10.8	24.3	18.9	9.0	22.5	11.7	9.0	23.4	18.0
15%	12.8	19.6	16.2	12.8	20.4	17.0	10.2	23.0	17.9	8.5	21.3	11.1	8.5	22.1	17.0
20%	12.0	18.4	15.2	12.0	19.2	16.0	9.6	21.6	16.8	8.0	20.0	10.4	8.0	20.8	16.0
30%	10.5	16.1	13.3	10.5	16.8	14.0	8.4	18.9	14.7	7.0	17.5	9.1	7.0	18.2	14.0
50%	7.5	11.5	9.5	7.5	12.0	10.0	6.0	13.5	10.5	5.0	12.5	6.5	5.0	13.0	10.0

4c. Annual demand of 500 patients

Hospital	1			2			3			4			5		
Triangular Distribution	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely
Base Case	4.0	9.6	6.4	6.0	10.0	8.8	4.8	8.0	7.2	4.0	8.0	6.0	6.0	16.0	9.6
5%	3.8	9.1	6.1	5.7	9.5	8.4	4.6	7.6	6.8	3.8	7.6	5.7	5.7	15.2	9.1
10%	3.6	8.6	5.8	5.4	9.0	7.9	4.3	7.2	6.5	3.6	7.2	5.4	5.4	14.4	8.6
15%	3.4	8.2	5.4	5.1	8.5	7.5	4.1	6.8	6.1	3.4	6.8	5.1	5.1	13.6	8.2
20%	3.2	7.7	5.1	4.8	8.0	7.0	3.8	6.4	5.8	3.2	6.4	4.8	4.8	12.8	7.7
30%	2.8	6.7	4.5	4.2	7.0	6.2	3.4	5.6	5.0	2.8	5.6	4.2	4.2	11.2	6.7
50%	2.0	4.8	3.2	3.0	5.0	4.4	2.4	4.0	3.6	2.0	4.0	3.0	3.0	8.0	4.8

Hospital	6			7			8			9			10		
Triangular Distribution	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely
Base Case	6.0	9.2	7.6	6.0	9.6	8.0	4.8	10.8	8.4	4.0	10.0	5.2	4.0	10.4	8.0
5%	5.7	8.7	7.2	5.7	9.1	7.6	4.6	10.3	8.0	3.8	9.5	4.9	3.8	9.9	7.6
10%	5.4	8.3	6.8	5.4	8.6	7.2	4.3	9.7	7.6	3.6	9.0	4.7	3.6	9.4	7.2
15%	5.1	7.8	6.5	5.1	8.2	6.8	4.1	9.2	7.1	3.4	8.5	4.4	3.4	8.8	6.8
20%	4.8	7.4	6.1	4.8	7.7	6.4	3.8	8.6	6.7	3.2	8.0	4.2	3.2	8.3	6.4
30%	4.2	6.4	5.3	4.2	6.7	5.6	3.4	7.6	5.9	2.8	7.0	3.6	2.8	7.3	5.6
50%	3.0	4.6	3.8	3.0	4.8	4.0	2.4	5.4	4.2	2.0	5.0	2.6	2.0	5.2	4.0