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Estimation of manufacturing development costs of cell-based therapies: a feasibility study

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ABSTRACT

Background aims: Cell-based therapies (CBTs) provide opportunities to treat rare and high-burden diseases. Manufacturing development of these innovative products is said to be complex and costly. However, little research is available providing insight into resource use and cost drivers. Therefore, this study aimed to assess the feasibility of estimating the cost of manufacturing development of two cell-based therapy case studies using a CBT cost framework specifically designed for small-scale cell-based therapies.
Methods: A retrospective costing study was conducted in which the cost of developing an adoptive immunotherapy of Epstein-Barr virus-specific cytotoxic T lymphocytes (CTLs) and a pluripotent stem cell (PSC) master cell bank was estimated. Manufacturing development was defined as products advancing from technology readiness level 3 to 6. The study was conducted in a Scottish facility. Development steps were recreated via developer focus groups. Data were collected from facility administrative and financial records and developer interviews.
Results: Application of the manufacturing cost framework to retrospectively estimate the manufacturing design cost of two case studies in one Scottish facility appeared feasible. Manufacturing development cost was estimated at £1,201,016 for CTLs and £494,456 for PSCs. Most costs were accrued in the facility domain (56% and 51%), followed by personnel (20% and 32%), materials (19% and 15%) and equipment (4% and 2%).
Conclusions: Based on this study, it seems feasible to retrospectively estimate resources consumed in manufacturing development of cell-based therapies. This fosters inclusion of cost in the formulation and dissemination of best practices to facilitate early and sustainable patient access and inform future cost-conscious manufacturing design decisions.

Introduction

Cell-based therapies (CBTs) are promising products bringing new opportunities for treatment of rare and high-burden diseases [1]. CBTs include cell therapy medicinal products and tissue-engineered products, which are part of an innovative group of pharmaceuticals in Europe formally defined as advanced therapy medicinal products [2]. CBTs contain autologous, allogeneic or xenogeneic cells and tissues, which have been substantially manipulated, resulting in a change in their biological characteristics [3]. Translation of CBTs from the laboratory setting to effective and safe treatments is a breakthrough in both medicine and biomedical science [4,5].

Since CBTs are regulated as medicinal products, they must comply with specific requirements set by regulatory bodies such as the European Medicines Agency in Europe or the Food and Drug Administration in the United States [2,3]. Overall, these regulations aim to

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ensure patient safety, product quality, data validity and reproducibility and, eventually, effective medicinal products with a positive benefit–risk balance [6]. Like other medicinal products, CBTs are also required to be manufactured under Good Manufacturing Practice (GMP) conditions [7]. However, translating conventional medicinal product GMP requirements to CBTs is challenging for both regulators and developers [8]. To facilitate development, European regulators have issued several guidelines and directives specifically for advanced therapy medicinal products (which include CBTs) [7].

Each CBT, as well as its manufacturing process, can be considered unique. Design of manufacturing processes is not routine practice and is subject to rapid technical and scientific advancements [9,10]. In contrast to more conventional medicinal products, CBTs are more often developed by public institutions (such as academic centers and hospitals) or small- and medium-sized enterprises (SMEs) [11]. This is attributed to the highly innovative and technologically complex characteristics of these products. In addition, batches of products are often personalized for individual patients. To advance product manufacturing, diverse strategies are explored, such as centralized manufacturing, up- and out-scaling, automation and use of platforms and bioreactors [12–14]. Public facilities and SMEs are known to have strong innovator capabilities but demonstrate less experience in structural incorporation of regulatory and economic considerations [15,16]. Additionally, these types of developers have lower reserves of finance and product development experience at their disposal compared with large, established commercial companies [17].

Recently, experiences and best practices of CBT design and manufacturing have been appearing in the literature [18–21]. Thus far, these best practices are on a case-by-case basis and focus mainly on technical and quality aspects [22,23]. Alongside the technical experiences and challenges, developers mention that development is resource-intensive and emphasize the importance of including development costs in the design process [24,25]. They describe that investments are substantial, risks high and materials costly. Yet, to the authors' knowledge, thus far little or no literature is available quantifying the cost of manufacturing development or apparent cost consequences of design decisions.

Because of the complex and highly regulated CBT environment, design decisions in manufacturing development can substantially affect downstream product development [26]. Consequently, cost considerations in manufacturing design as well as insights into the financial consequences of design decisions are of importance in further facilitating translation of CBTs toward sustainable patient access to viable medicinal products [27]. Previous research provides several models and frameworks for costing the manufacturing of CBTs, specifically in academic and small-scale settings [8,28,29]. However, it seems that none describe costing of manufacturing development. Of the available frameworks, two have been developed specifically for CBTs across multiple facilities [8,28]. One in particular has the authors' interest, as it provides a ready-to-use costing tool [28]. Although the authors focus on costing of established manufacturing processes, exploration of the applicability of this framework in manufacturing development could aid and cater to the need to include cost in the design of CBT manufacturing development.

Therefore, the primary objective of this study was to assess the feasibility of estimating the cost of manufacturing development of two cell-based therapies in a publicly funded cell and tissue center in Scotland using a novel cost framework and methodology. The insights from these two case studies may be used to accommodate inclusion of cost in the design of CBT manufacturing development and inform cost-conscious decisions toward accelerated and sustainable clinical adoption.

Methods

Study design

A retrospective costing study was conducted in which resources consumed in manufacturing development of two cell-based therapy case studies were estimated. Manufacturing development was defined as products advancing from technology readiness level (TRL) 3 to (and meeting all requirements of) TRL 6 [30]. The study was conducted at the tissues, cells and advanced therapeutics (TCAT) department at the Scottish National Blood Transfusion Service (SNBTS) in Edinburgh, Scotland. Cost estimates were obtained using a framework and methodology designed specifically for application in small-scale CBT manufacturing (hereafter referred to as CBT manufacturing cost framework). Detailed development and validation of this CBT manufacturing cost framework are described in the original CBT manufacturing cost framework publication [28]. Here the authors adhered to definitions and resource allocation guidance as depicted in that document.

Technology readiness levels

TRLs were first defined in the 1970s by the National Aeronautics and Space Administration as an indicator of the maturity level of evolving innovative technologies during early operational development [31]. Since that time, this framework has increasingly been applied outside of aeronautics. From 2011 onward, TRLs were implemented in European policies as a uniform

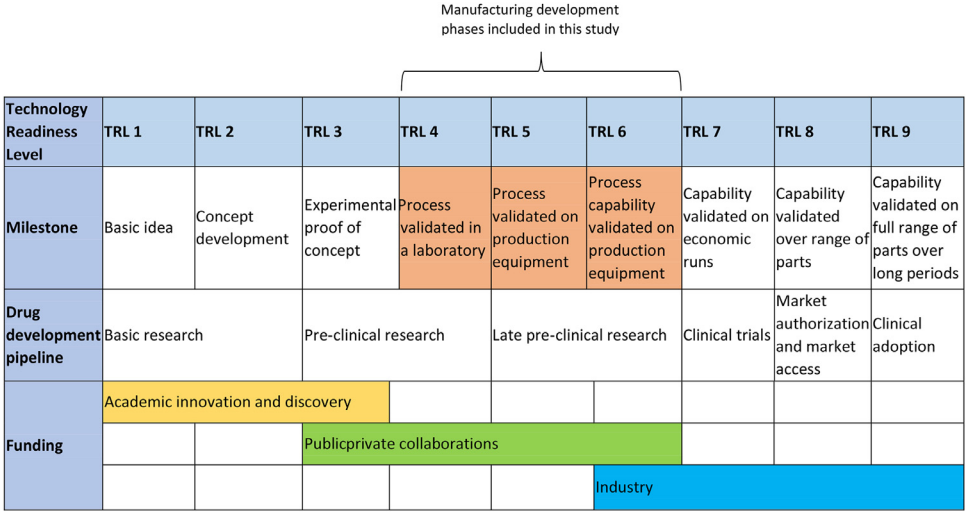

Figure 1. TRLs in CBT manufacturing development. Figure adapted from written evidence from Professor Chris Mason [17,32]. (Color version of figure is available online.)

Table 1
Case study characteristics.

Product description	Case study 1 Anti-EBV CTLs	Case study 2 PSCs
Indication	PTLD	Source of cells for metabolic, degenerative and inflammatory diseases
Cell/tissue procurement	Apheresis	–
Product origin	Allogeneic peripheral blood	Existing PSC lines
Manufacturing time	3 weeks	6 weeks + 2 months' extended testing
Development time (TRL 4–6)	45 months	10 months
Product developer	Public developer	Public developer

measure to compare development maturity of different technologies across sectors. An example is their use in the European framework program Horizon 2020 [30]. Figure 1 shows the TRL framework translated to regenerative medicines [17,32]. This figure visualizes the context of TRLs and CBTs in comparison to more traditional drug development milestones as well as differences in developer types and main funders [32]. Individual TRLs are defined as a product hitting a level-specific development milestone [30]. If a product has successfully achieved the milestone(s), it will advance to the next TRL.

Facility and case study characteristics

Data were collected within the TCAT department located at the Jack Copland Centre (JCC) in Edinburgh, Scotland [33]. TCAT is a specialized unit of the SNBTS that has development facilities and Medicines and Healthcare Products Regulatory Agency and Human Tissue Authority-licensed GMP manufacturing facilities for cell and tissue products [33]. TCAT is one of several directorates of the SNBTS (e.g., blood manufacturing and testing), which is a National Health Service-funded organization. TCAT performs internal research and development. It also offers expertise and development services to academics and early-stage cell and gene therapy developers with the overall aim of developing safe, effective, scalable and affordable products [33]. This expertise includes scientific, analytics and process development, quality, regulatory and clinical. Externally developed products have usually reached TRL 4 when brought to TCAT for further development and support.

The true origin of a research idea is often difficult to trace back, as many products are built on pre-existing techniques or theories. Combining this limitation with the normal practice of the JCC facility to undertake development of external products from TRL 4 onward resulted in exclusion of TRLs 1–3 in this research.

Continuing down the product pipeline, a product reaching TLR 6–7 will transition into pre-clinical testing and manufacturing or will form the basis of an application for additional funding. The initial research and development phase is considered complete. At this point, TCAT is contracted to manufacture the product or the process is transferred. This results in products often leaving JCC facilities and moving to larger (commercial) facilities or contract manufacturing organizations, or the developer may opt for industry acquisition. The authors therefore excluded TRL 7 and above (i.e., animal studies, clinical trials, etc.).

Case studies were selected based on the following criteria:

(i) Manufacturing development (TRL 4–6) occurred at the SNBTS TCAT department.
(ii) Manufacturing steps and decisions are documented and available.
(iii) Costs associated with these manufacturing steps and decisions are documented and available.
(iv) People involved in the manufacturing development are still associated with JCC or are prepared to contribute to this research.

These criteria yielded two CBTs that acted as case studies: (i) adoptive immunotherapy of Epstein-Barr virus (EBV)-specific cytotoxic T lymphocytes (CTLs) [34,35] and (ii) pluripotent stem cell (PSC) master cell bank [36]. Case study 1 is an adoptive immunotherapy of EBV-specific CTLs indicated for post-transplant lymphoproliferative disease (PTLD) [35]. EBV-specific CTLs are isolated from leukapheresis donations of healthy EBV-seropositive donors and subsequently expanded *in vitro* to generate multiple patient doses [34]. CTLs from multiple donors with different HLA types are manufactured as an allogeneic bank and are issued on demand for one PTLD patient at a time on a partially HLA-matched basis. For this product, TRL 7 and further costing data were retrievable. However, to increase comparability between case studies, only TRLs 4–6 were included in this study.

Case study 2 is a manufacturing intermediate master cell bank of PSCs. PSCs may be either embryonic or induced and are expanded in the form of stable cell lines. From these established lines, seed lots or master cell banks can be established, enabling PSCs to be transported to other facilities or companies for differentiation into various tissues [36]. The manufacturing process was developed for up to 400 vials. Table 1 shows case study characteristics. Non-proprietary technical and scientific details are described in detail elsewhere [21,34–37].

Data collection and analysis

Data were collected within the TCAT department located at JCC in Edinburgh, Scotland, between February and July 2019. First, for each case study, a focus group was organized in which participants together aimed to reconstruct a timeline for each product describing milestones and to collectively recollect development decisions. Focus group participants were SNBTS employees directly involved (current and past) in the manufacturing development of each product. The reconstructed timelines were drafted by an author (JN) based on focus group input and circulated among the developers to ensure content and face validity [38,39].

Next, costs were collected. In line with the CBT manufacturing cost framework, development activities were matched with resources consumed [28]. Costs were collected per TRL and divided into four domains (materials, equipment, personnel and facility) [28,40]. Cost and resource use were collected using the costing tool template in Excel (Microsoft Corporation, Redmond, WA, USA) provided by the CBT manufacturing cost framework. Utilized data sources were manufacturing flowcharts; facility purchase, payroll and contracting administration; quality management system documentation; supplier catalogues; floor plans and billing documents. Additionally, data were collected via developer interviews. Historical versions of quality management system documents were used to trace back changes in manufacturing development activities and both refine and validate reconstructed product timelines.

For materials and equipment, list prices were used. Personnel costs were derived from SNBTS wage agreements. Facility costs were calculated using fixed and variable facility costs allocated per square meter [28].

In this study, the authors applied an opportunity cost approach [41]. This means the authors costed all time and resources spent in developing the manufacturing process, which therefore could not be used for other purposes. For example, the cost of partially used materials with limited shelf life that exceeded their expiration date was allocated fully to the case study; although perhaps only partially used, these materials (e.g., peptides or buffers) had to be discarded.

Costs were expressed in 2019 pounds sterling (£). Costs obtained in different years were adjusted for inflation to 2019 prices using price index numbers [42]. This adjustment is in line with guidelines for economic evaluation in health care [43,44].

Results

Product development and timelines

The focus groups yielded detailed product development roadmaps. Figure 2 shows a condensed summary of these roadmaps for case study 1 (Figure 2A) and case study 2 (Figure 2B).

In case study 1, initial research to generate EBV-specific CTLs using newer technology by way of interferon gamma selection was done in-house (Table 1). The first step of manufacturing development in TRL 4 entailed a proof-of-principle of interferon gamma isolation at small scale using buffy coats and development of flow cytometric quality control (QC) assays. In TRL 5, platform technology (CliniMACS Prodigy; Miltenyi Biotec, Bergisch Gladbach, Germany; GatheRex and G-Rex flasks; Wilson Wolf Corporation, Saint Paul, MN, USA) was introduced using multiple buffy coats mixed together as starting material to mimic full-scale processes (instead of leukapheresis) to minimize starting material costs. Introduction of this platform automated isolation of virus-specific cells from starting material. In TRL 6, platform use and manufacturing were optimized using a commercial leukapheresis product.

Since the final EBV CTL product is cryopreserved until it is issued to the patient, many of the bagged doses generated are used not only in the final product quality release testing but also at regular time points in an ongoing stability program to ensure that frozen cell products are still viable and efficacious years after manufacture. Therefore, it is crucial to fully optimize the full-scale expansion such that a single

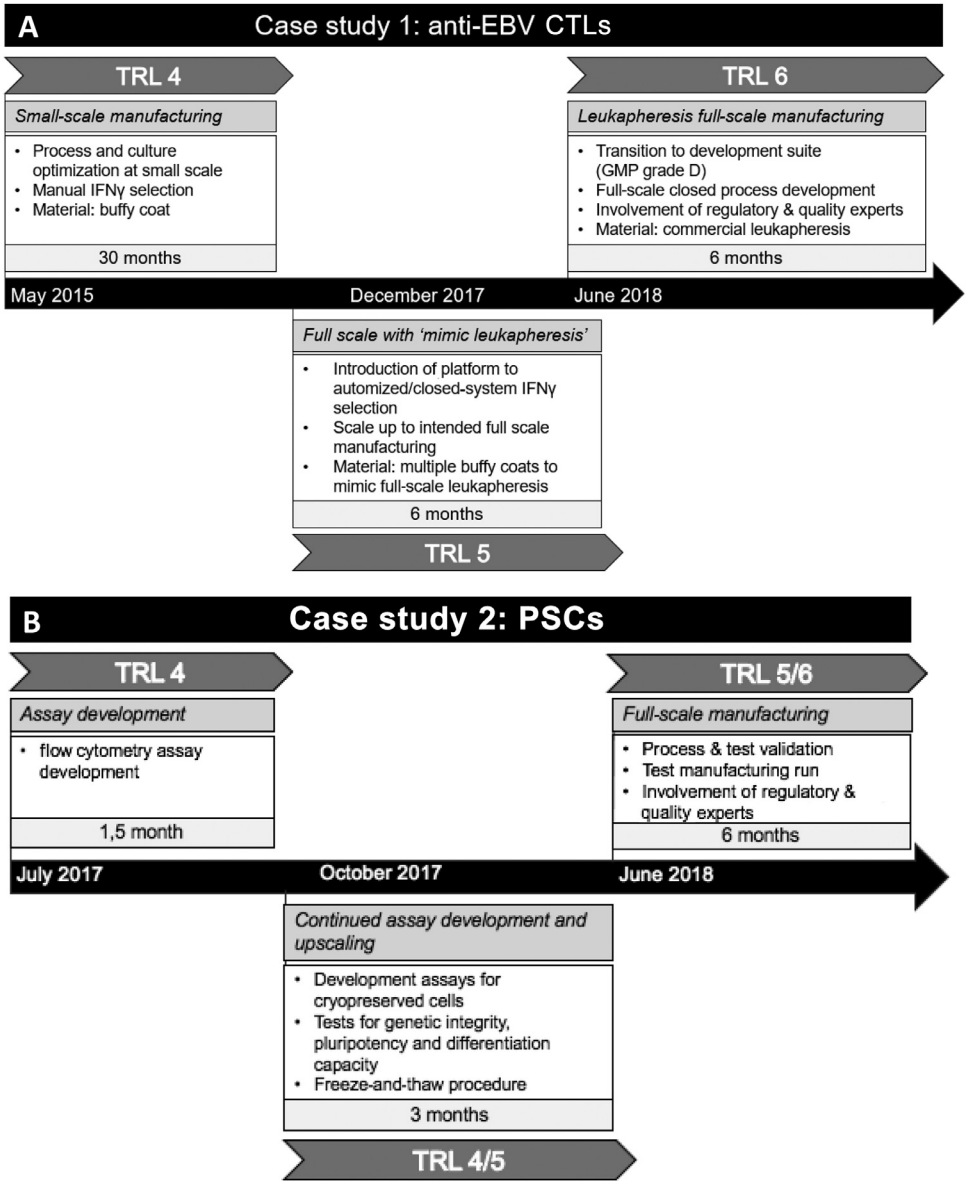

Figure 2. Product development timeline summary of (A) anti-EBV CTLs and (B) PSCs displayed per TRL. IFNγ, interferon gamma.

Table 2
Cost estimates of manufacturing development in case study 1 (anti-EBV CTLs) and case study 2 (PSCs).

Case study 1				Case study 2			
	TRL 4	TRL 5	TRL 6		TRL 4	TRL 5	TRL 6
Materials	£48,527	£88,786	£94,523	Materials	£4,083	£10,893	£61,647
Equipment	£18,408	£13,326	£15,276	Equipment	£1,697	£2,399	£5,254
Personnel	£117,823	£53,897	£72,722	Personnel	£17,409	£31,594	£108,039
Facility	£458,444	£109,642	£109,642	Facility	£37,269	£62,992	£151,180
Total cost/TRL	£643,202	£265,651	£292,163	Total cost/TRL	£60,458	£107,878	£326,120
Total manufacturing development cost			£1,201,016	Total manufacturing development cost			£494,456

Cost estimates are reported per TRL and cost domain in 2019 pounds sterling.

manufacturing process can generate enough cells for all analytical testing as well as treating numerous patients, with final stage development typically generating 100–150 doses at 1.5×10^8 CTLs/dose. Given that the dosage regimen for PTLD is four doses over a monthly period per patient and accounting for doses used in analytical testing, a single manufacturing process would therefore aim to treat 20–30 patients.

In TRL 6, the development was moved from a research (non-GMP) laboratory to a development suite for the development of a process under GMP (closed system in a grade D environment). Additionally, in TRL 6, quality and regulatory experts were involved in the development process. These experts co-developed, among other things, standard operating procedures, risk assessments, supply chain maps and microbial control strategies. At the end of TRL 6, case study 1 was considered "GMP-ready," meaning the product was in accordance with GMP guidance and ready to advance to TRL 7 [7]. TRL 7 entails manufacturing process validation runs in a GMP environment, after which (TRL >7) routine manufacturing (e.g., clinical studies) can commence [17,32].

The manufacturing development time of case study 1 was approximately 42 months (Figure 2A). This was mainly driven by TRL 4. Although previous iterations of EBV-specific CTL products had been developed at SNBTS many years prior, introduction of new technology and comprehensive contemporary characterization assays to meet current regulatory requirements was time consuming and described as the main driver in the development time of this product. Additionally, between TRL transitions, developers changed starting materials (from buffy coat to leukapheresis-mimic product and commercial leukapheresis product), which required some adjustments. When composing the development timeline, it was possible to clearly distinguish when one TRL was complete and the next started because most of the development was done by one researcher.

In case study 2, manufacturing development in TRL 4 started with assay development (cell characterization and cell count) (Table 1). Moving to TRL 5, assay development was continued (i.e., surface marker expression flow cytometry, stem cell differentiation, single-nucleotide polymorphism analysis for genetic integrity). The freeze-and-thaw process was also designed. Similar to case study 1, regulatory and quality experts were involved in TRL 6. Their involvement entailed process review, validation and documentation. TRL 6 completion yielded PSCs, which are an intermediate product. TRL 4–6 development took place in a research and development laboratory. Development was not dependent on specific equipment or conditions, so could thereafter go straight to cleanroom validation. Development in the research suite was not needed.

Manufacturing development time of case study 2 was considerably shorter (± 11 months) compared with case study 1. Although several assays needed to be developed, the time needed to do so was also shortened, as multiple researchers worked simultaneously on manufacturing development. Consequently, more people involved in the development of concurrent work streams led to less clear distinction in TRLs over time, as can be seen in Figure 2B.

The case study 2 product is somewhat different from the case study 1 product, as the manufactured product is a master cell bank composed of stocks of cells that will be used for further manufacturing, not direct clinical use. This PSC product is therefore categorized as a manufacturing intermediate, but the level of process control is equivalent to that of a final product. Also, as the master cell bank may be used as starting material that may be used to treat large numbers of people, the testing demands are high, requiring analysis for an extensive panel of human and animal viruses and other adventitious agents. Given the scope and specialist nature of this testing, which would be outsourced to a contract laboratory rather than developed internally alongside other QC testing, costs for this testing are not incorporated here.

Manufacturing development cost estimates

Following the methods outlined by the CBT manufacturing cost framework, fixed and variable costs were collected and allocated across pre-defined domains: materials, equipment, personnel and facility. The estimates of consumed resources per domain to elevate case studies 1 and 2 from TRL 4 (research-grade) to TRL 6 (GMP-ready) are shown in Table 2.

The total estimated manufacturing development cost of case study 1 was £1,201,016, and the total estimated manufacturing development cost of case study 2 was £494,456. The cost estimate for case study 1 is considerably higher than the cost estimate for case study 2. Relative resource use per TRL is 54% (TRL 4), 22% (TRL 5), 24% (TRL 6), 12% (TRL 4), 22% (TRL 5) and 66% (TRL 6) for case studies 1 and 2, respectively. These are crude estimates, taking no development variances into account. In case study 1, cost seems to decrease from TRL 4 to TRL 6, whereas in case study 2, an opposite trend is seen. Taking time into account, the authors observe that time per TRL decreases for case study 1 (Figure 2A) and increases for case study 2 (Figure 2B). In addition to time, other factors are likely to influence resource consumption, such as product characteristics, techniques applied, supplier choice, available techniques, costs of safety testing (in-house or contracted) and scientific advances. Because of high case study variance, the effect of these characteristics could not be examined.

The relative distribution of consumed resources per cost domain is displayed in Figure 3. Although the case studies differ significantly, trends in relative resource consumption are observed. In both cases, the facility is most resource-intensive, at 56% (38–71%) in case study 1 and 51% (46–62%) in case study 2. Equipment seems to consume the least costs, with 4% (3–5%) of costs allocated to this domain in case study 1 and 2% (2–3%) of costs allocated to this domain in case study 2. In between were personnel costs, at an average of 20% (18–25%) in case study 1 and 32% (29–33%) in case study 2. This was followed by materials, at 19% (8–33%) and 15% (7–19%) in case studies 1 and 2, respectively.

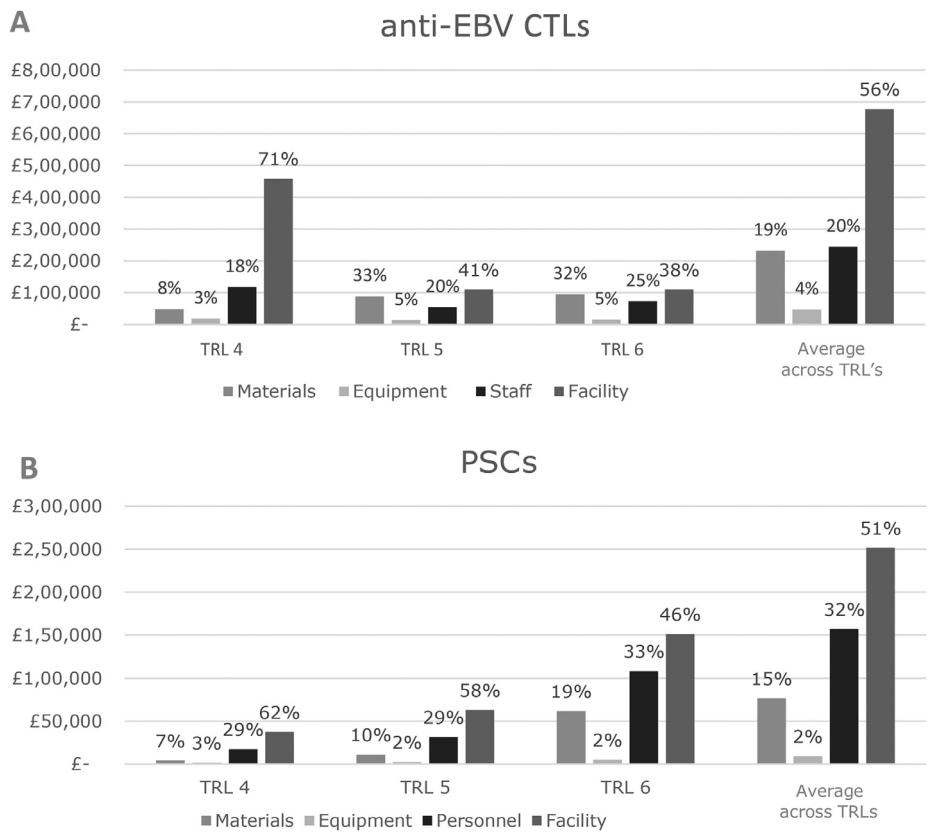

Figure 3. Relative distribution of consumed resources per cost domain for (A) case study 1 and (B) case study 2.

Materials

The main cost drivers in the material cost domain for case study 1 were tissue culture materials (88% of material cost) such as specialized reagents, peptides and media. This seemed partially to be influenced by the use of a (commercial) platform. To operate, the platform-specific buffers, and also consumables, had to be purchased from the platform vendor. In case study 2, substantially less specialized materials were used in culture, and the material cost drivers were components for QC (90% of material cost). Also, more assays needed to be developed for case study 2, resulting in more material consumption.

Another cost driver was thought to be material wastage. For CTL development, highly specialized materials were acquired. Because of short expiration dates and changes in manufacturing design, these materials could not be reused or allocated elsewhere. As mentioned before, CBTs differ widely, as do their manufacturing processes. Therefore, the opportunity to purchase specific reagents and proteins in bulk in general is often not possible. This is partially because bulk offerings of complex materials are not supplied by vendors but mostly because only small amounts are needed by developers. Non-platform consumables were bought in bulk; however, these materials were not found to be a cost driver.

Equipment

Equipment costs absorbed a relatively small percentage of manufacturing development costs (on average, CTL = 5% and induced PSCs = 2%). In this domain, a differentiation was made between product-specific and non-product-specific equipment. In line with the costing framework, equipment purchased specifically for manufacturing and/or not shared with five or more other products was deemed product-specific. After introduction of a platform in case study 1 TRL 5, no clear increase in the absolute cost in the equipment domain was observed. Although the aggregated equipment cost distribution seems constant across TRLs, the distribution between product-specific and non-product-specific equipment within the cost domain shows a shift. Product-specific costs in case study 1 are 11% for TRL 4, 72% for TRL 5 and 63% for TRL 6. SNBTS already had the specialized equipment (i.e., Miltenyi Biotec CliniMACS Prodigy platform and Wilson Wolf Corporation GatheRex) used in this study, and therefore the cost of purchase was not met only by this project; however, the initial capital outlay for such equipment would be a significant factor (e.g., an SME developing a single product).

In case study 2, the equipment used was all non-product-specific, such as pipettes, microscopes, refrigerators, freezers and incubators. Following the applied costing method, the equipment in case study 2 was shared between more than five products and was considered a fixed cost. In both cases, these low equipment costs reflect the relatively artisanal, handcrafted nature of CBTs, in contrast to the largely automated processes that are normal for, for example, small-molecule drugs.

Personnel

Personnel cost was the second largest domain in manufacturing development (on average, CTL = 20% and induced PSCs = 32%). Examining cost drivers within this domain, it was observed that the main driver was developer salary, followed by manager salaries. From TRL 6 onward, quality and regulatory personnel were systematically involved. Regulatory and quality experts periodically allocated a few hours or days of their time, whereas researchers and line managers often worked full time on development. However, the involvement of these experts accounted for 10% and 12%

of personnel costs for CTLs and PSCs, respectively, because of higher wages or tariffs.

In these case studies, deployment of personnel seemed to influence development time. In case study 1, most work was done by one researcher. This resulted in sequential execution of development milestones. In case study 2, multiple researchers conducted development in parallel. Although not all products or assays allow parallel development, the results of this research suggest that allocating more full-time equivalents could help shorten development timelines, which does not necessarily translate into lower costs due to high personnel time/time units.

Facility

The facility domain absorbed the most cost in manufacturing development for both case studies (on average, CTL = 56% and PSCs = 51%). As mentioned before, the facility cost seems to display a time-dependent factor, with longer development time resulting in higher facility cost, as was expected. In compliance with GMP guidelines, manufacturing of medicinal products occurs under strictly controlled conditions [7]. Different levels of GMP environments and associated environmental control were found to be reflected in the facility costing. TRL 4 and TRL 5 development of both case study 1 and case study 2 occurred in a research laboratory environment. In TRL 6, development was allocated to a development suite (GMP grade D environment). The research laboratory was estimated to cost 75% of the development suite. In turn, the grade D environment cost approximately 74% of a grade C cleanroom and 69% of a grade B cleanroom. In line with the CBT manufacturing costing framework, this converted cost/day included fixed facility running cost and variable operational cost. In the facility domain, approximately 70% of costs across TRLs were fixed facility running costs. This included building mortgage and life cycle, utility and hard facility management costs. JCC is a relatively new facility (opened in 2017), which may result in high depreciation costs in the first years after occupation in comparison to other facilities (here a 30-year linear depreciation model). SNBTS is also the sole occupier of the facility. This is also common in the private sector, such as companies and contract manufacturing organizations. However, in the public sector, such as hospitals and academic facilities, facilities are often shared, resulting in shared facility (maintenance) costs or contributions. For example, the overhead of the JCC facility is shared with other directorates within the organization. This suggests that facility costs for a standalone facility may be higher than estimated here.

Discussion

This study demonstrates the feasibility of retrospectively estimating the cost of manufacturing development of two cell-based therapies using a CBT manufacturing cost framework. The original framework was designed and validated for use in small-scale routine manufacturing of cell-based therapies. By demonstrating the feasibility of its use outside its initial context, broader application of this framework may be possible. However, it is highly recommended that extensive validation of this framework be undertaken before adoption in costing of CBT manufacturing development. Replication of this study in other facilities, across countries, prospectively and with different CBTs will provide more insights into its applicability and possible necessary adjustments. Additionally, in general, cost reduction should not be the primary objective when applying cost estimate frameworks, as their use lies in facilitating inclusion of cost considerations in quality and safety considerations in product development.

To be able to conduct this study, access to historical administrative records as well as technical and cost data was a prerequisite. This was partially facilitated by the development of manufacturing case studies occurring in one facility. The authors were able to extract data from databases supplemented by interviews. It is not uncommon for medicinal products, especially during manufacturing development, to be relocated, outsourced or acquired. This scatters data over multiple locations and owners. Meticulous recordkeeping may overcome some of these barriers to cost estimation. Additionally, the retrospective design of this study allowed reflection on past manufacturing design choices and their cost consequences. These lessons can be applied in future cases.

Development costing could be conducted alongside development to manage budgets and spending. This can be useful for investors and funding bodies or help substantiate business models. An increase in a variety of publicly available costing models and tools is seen in the literature [8,29,45,46]. Experience in costing of CBTs in any context will contribute to more accurate cost predictions. The authors therefore encourage others to explore the use of the framework applied here as well as others. Additionally, the authors stress that the cost estimates presented here are strictly the consumed resources and should not be confused with the prices of products or services. Also, the authors' estimates represent the cost at a specific time point and context. Moreover, if development of these case studies were started anew today, experience may shorten timelines, but additional increases can be expected in material and equipment costs as well as wages. Costing of the included case studies in other facilities and at a different time point will undeniably yield different estimates, as CBT development is subject to rapid technological and scientific advances.

Based on the aggregated cost estimate, in this study, the facility domain absorbed the most cost, indicating that the development environment affected cost, with more controlled environments being more costly. Therefore, developers tried to utilize a lower grade environment as much as possible. Additionally, in this study, developers had access to a grade D research development suite. Acces to a development suite was found to be helpful because the environment closely replicated the equipment and processes used for manufacturing in a GMP-environment. Also, it increased understanding of logistics of taking in process samples from controlled environments to accredited QC laboratories, and therefore tested suitability of the process to move to full GMP in the cleanroom.

In addition, of the facility costs, on average, 70% were fixed. Fixed costs are resources consumed regardless of the products or services being delivered [47]. In a CBT context, these fixed costs include air particle control, periodic cleaning, certification and recertification. Therefore, it is recommended to reduce facility downtime as much as possible [28]. This could be achieved by facility sharing, leasing vacant space or considering the possibility of more developers working in one space by adapting staff scheduling and product or facility design.

Personnel consumed the next largest part of the budget, at 20% (CTLs) and 32% (PSCs). PSC manufacturing was developed as a mostly manual process, whereas in case study 1, a commercial cell processing platform was introduced. Commercial platforms may not reduce costs during development but claim to reduce manual labour during manufacturing up to 70%, improving reproducibility and better accomodaing scalability [48]. This may warrant their inital investment but on further investigation may become more compelling [46]. The specialized manufacturing of CBTs also requires highly skilled personnel, who are increasingly in high demand [33]. Allocation of these personnel elsewhere may contribute to a more effective use of resources.

In both case studies, regulatory and quality experts were involved from TRL 6 onward. This was considered by the developers to be optimal because processes were likely to change in TRL 4 and TRL 5 and input was required sufficiently early to avoid the necessity of redoing critical and costly work if regulatory requirements were not met. Prior to TRL 6, developers managed quality requirements and reporting. As previously stated, timely involvement of regulatory and quality experts contributed greatly to development timelines. In the focus

groups, it was estimated that timely involvement of regulatory and quality experts could shorten manufacturing development timelines up to 50%. In this study, the authors were not able to directly substantiate this claim, as alternative strategies were not available for comparison. Moreover, when addressing the regulatory requirements, experts recommended including local, national and international guidance early in process development, as regulatory requirements may differ across jurisdictions. Developers were advised to be considerate of these variances, keeping in mind the intended use of the product [49].

Scarcity and high cost of raw materials are often mentioned as cost drivers in CBT development [49,50]. In this study, the case studies showed an average of 19% (CTLs) and 15% (PSCs) of costs absorbed by the material domain. Cost drivers here were specialized and low-volume materials. In case study 1, developers intentionally used a single buffy coat (TRL 4) and multiple buffy coats during development to mimic full-scale leukapheresis (TRL 5) from internal sources (with ethical approval). Because of the high cost of this starting material, a commercially sourced leukapheresis product was not used until the final full-scale development stage (TLR 6). In clinical manufacture (TLR 7 onward), leukapheresis starting material was then procured from internally sourced donors (with ethical approval), which may have reduced upfront material costs but also incurred other costs due to extensive testing to determine suitability for clinical use. Another material domain cost driver appeared to be platform-specific buffers and consumables. Also, essential reagents are usually platform-specific and can only be purchased via the platform vendor. Moreover, in the literature, it is suggested that QC and regulatory requirements are cost drivers [49]. In this study, the authors aimed to categorize material costs in tissue culture and QC categories. The large disparity between case studies did not allow in-depth inter- and intra-case study comparison. Further research is needed to explore this hypothesis. Additionally, resources consumed for regulatory, testing and quality proceedings may spill over into personnel, facility and equipment cost domains.

The equipment domain consumed on average 5% (CTLs) and 2% (PSCs), with little variance per TRL, a finding that was surprising to CTL developers. It was expected that introduction of a platform would display a financial impact given purchase and maintenance of specialized equipment. Platforms may also replace other machinery, such as incubators and biological safety cabinets [48]. However, it cannot be concluded from a single case study whether equipment and cost substitutions were equivalent. One reason for the relatively little consumption of equipment costs could be the size of the facility in which this study was conducted. JCC is a large blood and tissue establishment aimed at both production and development. This makes it possible to allocate multifunctional equipment costs to multiple projects. For a smaller facility, the purchase and maintenance of specialized equipment are likely to have a larger financial impact that is exacerbated by the proliferation of highly specialized new equipment that has been designed for individual products rather than flexible platform technologies. In addition, similar to the facility domain, specialized equipment downtime should be avoided as much as possible. Methods of achieving this could involve sharing equipment or considering availability and flexibility of machinery during manufacturing development.

As previously mentioned, the CBT field is very dynamic, with technologies and scientific advances occurring during manufacturing development in the authors' case studies. Here the authors briefly discuss two trends mentioned by developers that are thought to significantly impact the CBT field. The first trend is more automation via increased uptake of platforms. Both developers and the literature mention a move toward automated and closed systems [24,46,51,52]. To address indication expansions, it is expected that manufacturing processes will be required to move from being open and manual to closed and automated. Early introduction of such systems may save time and costs downstream. However, if changes are made in a manufacturing process, revalidation and reporting to authorities are often required. With increased uptake of platforms, authorization of the platform could be a solution [7], which is a trend also described outside of the CBT field [53].

The second trend is the use of centralized expert development centers. Combining technical, scientific, regulatory and quality expertise in one place is expected to result in a more efficient use of resources, which could decrease development timelines. Furthermore, the upfront investments that are substantial for SMEs and academic developers could be spread or mitigated in a shared facility.

Study limitations

Despite the authors' best efforts, this study has limitations. First, the authors' feasibility testing was limited to a small part of the CBT product life cycle. In this study, the authors explored costing of products from TRL 4 to TRL 6 only. Not included are early discovery research and pre-clinical and clinical research. The reason for this is that various aspects of early research and development and pre-clinical testing may occur elsewhere. Therefore, the authors did not have access to all of these data. For example, in the focus groups, developers mentioned that CBT animal studies are highly resource-intensive and are expected to contribute substantially to development costs. Nevertheless, the highest costs are traditionally expected to be incurred in later phases of development (i.e., large-scale clinical-grade manufacturing, clinical trials and regulatory procedures). Future costing studies could aim to include a broader spectrum of the CBT life cycle for more accurate estimates.

Second, product timelines and data were collected in a retrospective interview setting. This may have caused information and recall bias, resulting in over- or underestimation. By combining triangulation (conducting interviews with multiple people asking the same questions) and focus groups, the authors aimed to appeal to collective memory and increase validity of qualitatively collected data. Additionally, prospective data collection would increase accuracy.

Third, some developers may not be familiar with the TRL framework. Although the use of TRL classification is gaining traction in health and biomedical sciences, it is mostly used in the innovative technology and policy context [30]. However, the benefit of this uniform classification system is that development stage and progress can be compared with other health and non-health interventions. If researchers prefer to use other classifications, definitions of TRLs are publicly available and can be translated to the preferred terminology.

Finally, this study included two case studies in one facility. This limits generalizability of the findings and lessons. However, the primary objective of this research was to test feasibility of the CBT manufacturing cost framework. Now that feasibility is demonstrated in one facility, the authors encourage exploration of its reproducibility and generalizability.

Conclusions

This study demonstrates the feasibility of using a novel costing framework and methodology, originally designed and validated for the costing of small-scale manufacturing of cell-based therapies, to estimate the cost of CBT manufacturing development in two case studies. The next step is more widespread application and validation of this framework and methodology for use in CBT manufacturing development cost estimations. This can be done in multiple facilities, across jurisdictions, prospectively and should include different products. The results from this study should be considered a cross section in time and in the context of this facility. The cost estimates revealed drivers and insights from which the authors aimed to derive lessons. The generalizability of these findings remains to be examined. To do so, the authors advise structural inclusion of cost considerations in

CBT manufacturing design. Costing can be done in retrospect to derive lessons and compose best practices or prospectively alongside development to track spending. Additionally, more informal sharing of experiences among developers will contribute to knowledge dissemination and facilitate CBT development.

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Declaration of Competing Interest

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

Author Contributions

Conception and design of the study: RtH, JH, GF, OH, HO, MH, JM and MT. Acquisition of data: JN, RC, JM, MT and JN. Analysis and interpretation of data: JN, RC, JM, MT and JN. Drafting or revising the manuscript: RtH, JN, RC, JH, GF, OH, HO, JM and MT. All authors have approved the final article.

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