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FULL-LENGTH ARTICLE

Manufacturing

What does cell therapy manufacturing cost? A framework and methodology to facilitate academic and other small-scale cell therapy manufacturing costings

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ABSTRACT

Background aims: Recent technical and clinical advances with cell-based therapies (CBTs) hold great promise in the treatment of patients with rare diseases and those with high unmet medical need. Currently the majority of CBTs are developed and manufactured in specialized academic facilities. Due to small scale, unique characteristics and specific supply chain, CBT manufacturing is considered costly compared to more conventional medicinal products. As a result, biomedical researchers and clinicians are increasingly faced with cost considerations in CBT development. The objective of this research was to develop a costing framework and methodology for academic and other small-scale facilities that manufacture cell-based therapies.
Methods: We conducted an international multi-center costing study in four facilities in Europe using eight CBTs as case studies. This study includes costs from cell or tissue procurement to release of final product for clinical use. First, via interviews with research scientists, clinicians, biomedical scientists, pharmacists and technicians, we designed a high-level costing framework. Next, we developed a more detailed uniform methodology to allocate cost items. Costs were divided into steps (tissue procurement, manufacturing and fill-finish). The steps were each subdivided into cost categories (materials, equipment, personnel and facility), and each category was broken down into facility running (fixed) costs and operational (variable) costs. The methodology was tested via the case studies and validated in developer interviews. Costs are expressed in 2018 euros (€).
Results: The framework and methodology were applicable across facilities and proved sensitive to differences in product and facility characteristics. Case study cost estimates ranged between €23 033 and €190 799 Euros per batch, with batch yield varying between 1 and 88 doses. The cost estimations revealed hidden costs to developers and provided insights into cost drivers to help design manufacturing best practices.

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Conclusions: This framework and methodology provide step-by-step guidance to estimate manufacturing costs specifically for cell-based therapies manufactured in academic and other small-scale enterprises. The framework and methodology can be used to inform and plan cost-conscious strategies for CBTs.

Introduction

Recent technical and clinical advances with cell-based therapies (CBTs) hold great promise in the treatment of patients with rare diseases and those with high unmet medical need [1]. In Europe, CBTs include cell therapy medicinal products (excluding genetically modified cell therapy medicinal products) and tissue engineered products (TEPs) [2]. These technologies are not new, as they have been applied in a laboratory setting for many years [3,4]. Nonetheless, their recent translation to medicinal products for human use is considered one of the major breakthroughs in biomedical history [5–7].

Although classified as medicinal products, CBTs differ significantly from more conventional pharmaceutical agents, such as small molecules or monoclonal antibodies. CBTs consist of live tissue or cells and therefore require specific manufacturing, quality control and supply chain solutions [8]. Recently large pharmaceutical companies are showing increasing interest in CBTs, although a majority of products are developed and manufactured in specialized academic and public facilities [9–11]. This is mainly driven by the personalized nature, science and advanced technologies required to develop CBTs. In these specialized centers, the CBT specific supply chain, including tissue procurement, substantial manipulations and administration, require close collaboration among biomedical scientists, technicians, pharmacists, clinicians and administrators. New collaborations incite (re) definition of roles and responsibilities, including novel cost allocations and payment considerations. Although costs in general are a topic of debate in health care, this is even more the case for CBTs because of their perceived high cost compared with non-CBTs [7]. The continued expansion of CBT applications will progressively stress budgets. As a result, biomedical researchers and clinicians are increasingly faced with cost considerations, which are normally not a part of their routine activities [12].

Cost insights are of interest for multiple reasons. Accurate resource valuation helps determine budget allocation by administrators, payers and investors. Perhaps most important, understanding of resource use and cost drivers facilitates product maturation and institutional readiness [13]. CBT manufacturing often involves multiple hospital units, introducing internal cost-sharing questions. Additionally, CBTs are manufactured in facilities holding a Good Manufacturing Practice (GMP) license, adding to the complexity [14]. Consequently, it is not only direct operational costs that should be taken into account, but also personnel, equipment and materials needed for maintenance, quality management and training purposes. Not including these so-called hidden expenses can result in substantial undervaluation of resources.

The literature includes several CBTs costing studies; however, these are mainly cost-effectiveness analyses (CEAs) of cell-based products [15–17]. In these analyses, the aggregate price of a product and overall treatment cost proportionate to its effect is compared with a standard of care. Although informative for pricing and reimbursement decisions, these CEAs provide little to no information on (in-house) manufacturing costs itself. Looking outside CBT literature a few universal pharmaceutical frameworks are available, yet these focus heavily on pricing [18,19]. In 2013, Abou-El-Enein *et al.* were the first to describe a cleanroom technology assessment technique in which the detailed manufacturing costs of two cell products were calculated [12]. Despite interesting insights, their complex approach shows low external validity, which is confirmed by its scarce uptake in literature and practice. More generalizable is a tool developed by Boeke *et al.*, which is specifically designed for dedicated large-scale vector production facilities [14].

Thus, the aim of this research was to develop a costing framework and methodology specifically for academic and other small-scale developers who manufacture in-house CBTs. To do so, an international multi-center costing study was performed in which eight CBTs from four facilities acted as case studies. The framework and underlying methodology will guide facilities to more accurately estimate CBT manufacturing costs to inform and plan cost-conscious strategies.

Methods

Study design

We conducted an international multi-center costing study. First, we designed a costing framework. Thereafter, we developed a more detailed methodology to allocate specific cost items within this framework. The methodology was tested in eight case studies from four facilities in Europe. Last, we validated our framework and methodology with research scientists, clinicians, biomedical researchers, pharmacists, technicians and administrators (hereafter called developers). The starting point in this study is cell or tissue procurement, and the endpoint is release of end product for clinical use.

Development of framework

To design the framework, for each case study, we started with dissemination of the manufacturing process using flow charts and investigational medicinal product dossiers (IMPDs). The rationale for the bottom-up approach was to start with documents familiar to developers [20]. Across facilities and case studies, we identified three high-level and generalizable steps: (i) procurement, (ii) manufacturing and (iii) fill & finish. Thereafter, we defined four cost categories across these steps: materials, equipment, personnel and facility. Within these categories, a distinction was made between fixed and variable costs [12,21–23]. Additionally, manufacturing steps and cost categories were required to be mutually exclusive preventing double counting or overlooking of costs [24]. The sum of costs acquired per step provides total manufacturing cost (or aggregated cost). To check internal validity, the aggregated cost should be equal to the sum of the cost categories.

Development of methodology

An accepted approach of identifying activities within an organization and assigning costs to each activity employed to produce a product or service is activity-based costing (ABC)[25]. The ABC method is especially helpful in the identification of cost drivers and possible inefficiencies as well as in its applicability to manual and small-scale processes [25]. In traditional cost accounting, resources are directly allocated to products or services [23]. With ABC, products and services are translated into activities (here, manufacturing steps) and traced back to resource drivers (here cost categories) [25]. This makes ABC more accurate compared with direct cost allocation, especially

when allocating indirect costs, which are thought to account for a considerable proportion of CBT manufacturing [10,26].

Per cost category, for both fixed and variable cost, we defined a method to best identify and allocate cost. These methods are based on the campaign and day rate model by Boeke *et al.* and Abou-El-Enein's manufacturing cost algorithm [12,14]. Our methodology ought to be applied for each manufacturing step defined in the framework.

This study takes the developer perspective. This means only costs incurred during the manufacturing process by the CBT developer are included [24]. Excluded are transportation costs, storage and medical costs (e.g., patient pretreatment, admission or follow-up care). We assumed that in each of the case studies manufacturing took place on a routine basis in established facilities. Therefore, we did not include learning effects including product specific training of (new) employees, product development costs, validation runs and costs such as IMPD or standard operating procedure (SOP) writing. The outcome is cost per batch. We assumed one batch yields one treatment. If this framework and methodology are applied for products that yield more than one treatment per batch or a different outcome (e.g., cost/dose, cost/treatment) is preferred, the outcome should be adjusted accordingly. Costs are reported in 2018 euros (€) because this was the most recent full financial year at time of data collection. Our method is also applicable for other currencies (e.g., U.S. dollar, English pound, yen). Costs obtained in different years were adjusted for inflation to 2018 prices using price index numbers [27]. Purchasing power Parity (PPP) was used to convert difference in currency by taking gross domestic product differences into account [28]. These adjustments are in line with the *Dutch Manual for Costing: Methods and Reference Prices for Economic Evaluations in Healthcare* [29].

Data collection and cost definitions

Data were collected within the facilities between June 2018 and September 2019. Sources used were IMPDs; manufacturing flowcharts; internal purchase, payroll and contracting administration; and developer interviews. We used material and equipment list prices. For personnel cost, we used collective labor agreement wages.

Fixed cost

A cost is fixed if it does not increase as the number of products or services provided increases [14]. The sum of the fixed cost categories (fixed material, equipment, personnel and facility cost) is considered the facility running cost and calculated per year [12,22]. These facility running costs are consumed to ensure operability of the facility, independent of whether products are manufactured. The multi-layered and continuously monitored GMP environment in which CBTs are manufactured makes allocating these shared costs to individual products impossible [9]. Therefore, we have chosen to divide the annual facility running cost by the annual number of batches (all products) manufactured in each facility, taking the same approach as the Campaign model described by Boeke *et al.* [14].

In the equipment category, we included all non–product-specific equipment present in the facility (e.g., microscopes, pipettes, centrifuges, fridges, freezers, water baths). Fixed equipment costs are calculated as the sum of annual depreciation cost plus annual maintenance fees [30]. The annual depreciation per apparatus is calculated by division of purchase price by an annuity factor [29]. This annuity factor takes into account the equipment life time and a 4.5% interest rate [29]. For example, using the formula provided by Kanters *et al.*, a pipette with a lifetime of 5 years is assigned an annuity factor of 4.39. For larger equipment (e.g., cell manufacturing platforms, flow cytometers) we applied a 10-year lifetime (annuity factor 7.91) [29]. When an item was still in operation but had exceeded its lifetime, it was removed from the costing template and considered amortized [29]. Annual maintenance fees should continued to be included in the costings after amortization. For fixed material cost, we took a similar approach. In this study, fixed material cost is defined as the sum of all non–product-specific materials purchased per annum. Examples are stock materials and consumables, such as gloves, pipettes, pipette tips, tubes and cleanroom suits, but also demi water, ethanol, etc. Fixed personnel cost includes personnel with dedicated administrative, research, (project) management and quality positions (e.g., quality assurance [QA], quality person [QP], project managers). For personnel with hybrid responsibilities, we estimated (in percent) their time spend on routine non–product-specific (quality) duties such as GMP training and quality management (e.g., environmental monitoring, setting up and maintaining quality management system [QMS]). Their annual salary was adjusted proportionally to this estimate and added to the fixed personnel cost. Last, the fixed facility cost includes annual housing and maintenance cost—such as mortgage or lease, non–product-specific cleaning, environment control contracts, storage and inventory depreciation—of the facility excluding the cleanrooms [29].

Variable cost

If a cost changes proportionally to the quantity of delivered good or services provided, the cost is considered variable [12]. When allocating variable cost items, we took an opportunity cost approach [24]. This means we costed all time and resources that were spent manufacturing the product of interest and therefore could not be used for other purposes.

Variable materials include all consumables and (raw) materials directly used to manufacture a batch. To prevent double counting, these materials may not be part of the facility stock. The cost of these materials is identified and allocated per manufacturing step. Variable equipment cost includes specialized equipment only. This is equipment specifically purchased for production of the CBT of interest. We allowed equipment to be shared by multiple projects with a maximum of five (project share 20%). When equipment was shared by more than 5 products, it was considered fixed equipment. To translate equipment purchase cost to a variable cost, the cost was translated to an annual cost using an annuity factor (similar to fixed equipment cost), adjusted for project share (in %) and corrected for annual production volume (APV). APV corresponds with the number of CBT batches manufactured per year.

Variable personnel and facility costs are calculated using the day-rate model [14]. This implies cost is allocated based on time rather than share. Variable personnel cost includes all personnel directly involved in product manufacturing (e.g., technicians, QP, QA). A day rate is calculated by correcting annual salary by full-time equivalent (FTE) and, if applicable, estimated time spent on QMS (as specified under fixed personnel cost). This day rate is multiplied by days spent on product manufacturing. Taking the opportunity cost approach, this includes time spent on preparation, administration, in-process and release testing. The variable facility day rate is determined by dividing the annual cleanroom-specific cost—including maintenance, control and cleaning expenses—by facility active days (FAD). FAD is defined as number of days the cleanroom can be used for manufacturing. This excludes days the cleanrooms are inoperable (e.g., due to recertification, inspections, maintenance or non–product-specific cleaning activities) or not in use (holidays and, if applicable, weekends). Similar to variable personnel cost, this facility day rate is multiplied by the number of days cleanrooms were used for product manufacturing. Pro rata adjustment is needed when a facility has multiple cleanrooms and/or cleanrooms with multiple workstations.

Framework and methodology validation

We conducted multiple rounds of semi-structured interviews with developers. First, to understand the product manufacturing processes and the resources used. Second, the framework and underlying methodology were translated into a Microsoft Excel

Table I
Case study characteristics.

Product ID	A-1	A-2	A-3
Product description	Peptide pulsed tolerogenic dendritic cells	pp65-specific T cells	*Ex vivo*–expanded mesenchymal stromal cells
Indication	Type 1 diabetes mellitus	Refractory cytomegalovirus infection	Immunomodulation and tissue regeneration
Procurement	Apheresis	Apheresis	Bone marrow aspirate
Product origin	Allogeneic peripheral blood	Allogeneic peripheral blood	Allogeneic bone marrow
Specialized equipment	Yes	Yes	Yes
Runtime	7 days	2 days	28 days (range 21–35)
Batches per year	2	6	14
Dose yield per batch	2	1	2
Dose per treatment (avg/pt)	2	1	2

Product ID	B-4	B-5	C-6
Product description	Peptide-loaded natural dendritic cell vaccine	Stem cell–derived natural killer cells	Monocyte-derived macrophages
Indication	Stage III melanoma	Acute myeloid leukemia, ovarian carcinoma	Hepatic cirrhosis
Procurement	Apheresis	Umbilical cord blood	Apheresis
Product Origin	Autologous peripheral blood	Allogeneic umbilical cord blood	Autologous peripheral blood
Specialized equipment	Yes	Yes	Yes
Runtime	4 days	35 days	8 days
Batches per year	55	9	9
Dose yield per batch	9	1	1
Dose per treatment (avg/pt)	9	1	1

Product ID	C-7	D-8
Product description	*Ex vivo*–expanded limbal stem cells	Anti-viral cytotoxic T lymphocytes
Indication	Ocular surface disorders	Post-operative lymphoproliferative disease
Procurement	Tissue extraction	Apheresis
Product origin	Allogeneic corneal tissue	Allogeneic peripheral blood
Specialized equipment	Yes	Yes
Runtime	15 days	21 days
Batches per year	10	6
Dose yield per batch	1	88
Dose per treatment (avg/pt)	1	4

(Microsoft Corp. 2018) costing template and developers were asked to use the template and provide feedback. Changes were made accordingly. Last, within each facility, developers were asked to validate collected data, resource allocation and assumptions for each case study.

Facility and case study characteristics

The study was conducted in four specialized cell manufacturing facilities in the Netherlands (facilities A and B) and Scotland (facilities C and D). Facility A (case studies 1–3) is an academic center with a dedicated GMP advanced therapy medicinal products (ATMPs) development and production facility. The facility has an in-house chemical peptide synthesis facility and several cleanrooms of which one is dedicated to gene therapy production. Facility B is a dedicated GMP cell facility, which is integral part of the pharmacy department of a Dutch large academic center. The GMP cell facility is considered an independent organizational unit. Costs of this facility are borne pro rata by two hospital departments developing cell therapies. Each department contributed one case study, in which the first department fully manufactures the product (case study 4) in the GMP facility, and the other department conducts procurement and a few manufacturing steps in a JACIE (Joint Accreditation Committee ISCT-Europe & European Group for Blood and Marrow Transplantation [EBMT]) [31] environment before moving to the hospital's GMP cell facility (case study 5). Facility C is a shared GMP cell therapy and tissue repair facility. This center of excellence houses scientists and clinicians from a university and hospital and aims to facilitate scientific knowledge to the clinic and industry. Facility D is part of a large and recently opened (2016) blood transfusion, cell and tissue center. This facility contributed case study 8.

Case study inclusion criteria were as follows:

1. products are manufactured under GMP conditions,
2. products are routinely manufactured at time of inclusion,
3. developer (academic group, facility, clinical researcher, biomedical scientist or other) can provide detailed manufacturing information, and
4. developer can provide access to detailed financial information.

Table I provides case study characteristics. In case studies 1 to 7, one batch corresponds to one treatment. In case study 8, one batch yields 88 doses corresponding with 22 treatments. The included case studies are manufactured under Hospital Exemption, compassionate use program or in clinical trial setting.

Results

Visualization of framework and methodology

The developed framework is visualized in Figure 1. This figure outlines high-level steps to calculate an aggregate per batch manufacturing cost as well as step- and category-specific costs. To start CBT costing, the manufacturing process of an individual product is categorized in mutually exclusive steps 1 to 3. For each step, we identified both fixed and variable costs for given resources and determined the quantity of consumed resources and associated costs in each category.

After the framework is populated, the cost for each case study is calculated using the methodology described in Methods of this article. This methodology is visualized in Figure 2 as a per step cross-section of the framework shown in Figure 1. When manufacturing took place in one location/facility, steps 1–3 were bundled for the fixed costs. For the manufacturing taking place in multiple locations, facility running cost were determined for each location separately and

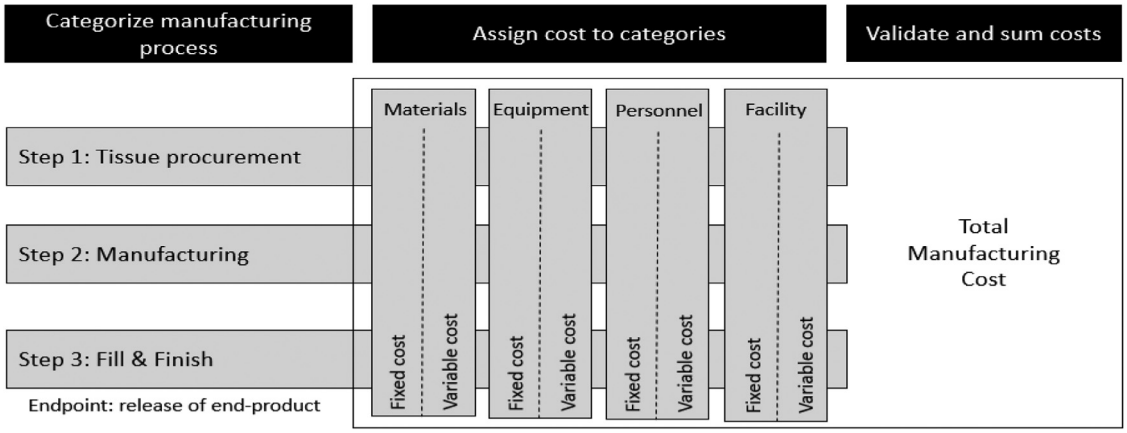

Figure 1. Cell-based therapy manufacturing costing framework. Cost categories present both fixed and variable cost.

combined as presented in Figure 1 and 2. Based on developer interviews, we assumed a 5% failure rate (% failed batches) across case studies. This assumption is based on the average failure rate observed across facilities. We noticed failure rates were higher for manufacturing processes new to facilities and that these decreased over time. If a cost estimation is made for processes with different failure rates, this should be adjusted accordingly. If one batch yields multiple treatments or doses, post hoc adjustment is needed to translate these costs into a desired output (e.g., cost/treatment, cost/dose).

Availability and use of costing template

We generated a costing template (in Microsoft Excel), which is available as Supplementary Material (Costing_Template_blanc.xls) accompanying the online version of this article. The provided template by default applies the costing framework and methodology as described in this research and assumes that the full manufacturing process takes place in one facility. The authors waive responsibility and liability for use, application and maintenance of the provided costing template.

Facility running cost

The sum of fixed cost categories per year was calculated as the annual facility running cost [12,21]. These resources are consumed regardless of whether or not CBTs are produced. Figure 3 shows fixed costs per facility stratified by category, as well as absolute costs and percentage of the cost category compared with total facility running costs. Although absolute facility running cost varied, cost category ratios showed similarities between facilities. Note that facility C did not show the fixed material or personnel cost because these could not be separated from the facility costs because of a lumpsum payment agreement between developers and facility C. In this agreement, a fixed annual rate is payed and includes facility, materials, QMS, equipment and maintenance. Therefore, the proportional comparison of facility C gives somewhat of a distorted image compared with the other facilities. Across facilities, fixed material cost account for 8–10% of total facility costs. Equipment accounts for 6% of annual running cost of facility B (both departments) and D, with facilities A and C having higher proportional equipment cost of 21% and 23% respectively. Personnel cost is the main driver in facilities A (41%), B-4 (46%) and B-5 (53%), but not in facility D (4%). A similar pattern is seen within the facility-category, where facility

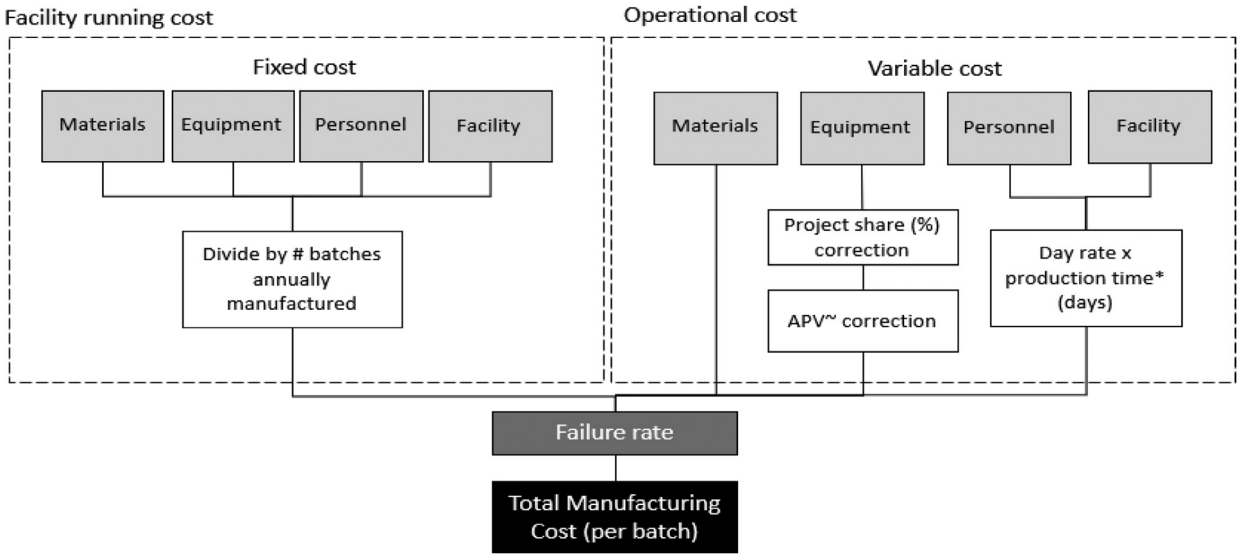

Figure 2. Costing methodology model of fixed and variable cost per cost categories to calculate manufacturing cost per batch. This analysis ought to be applied for each step in the Cell-Based Therapy Manufacturing Costing Framework. *Production time is corrected for FAD, that is, the number of days the facility is available for production. When a batch yields >1, post hoc adjustment is needed to calculate per treatment or per dosing cost.

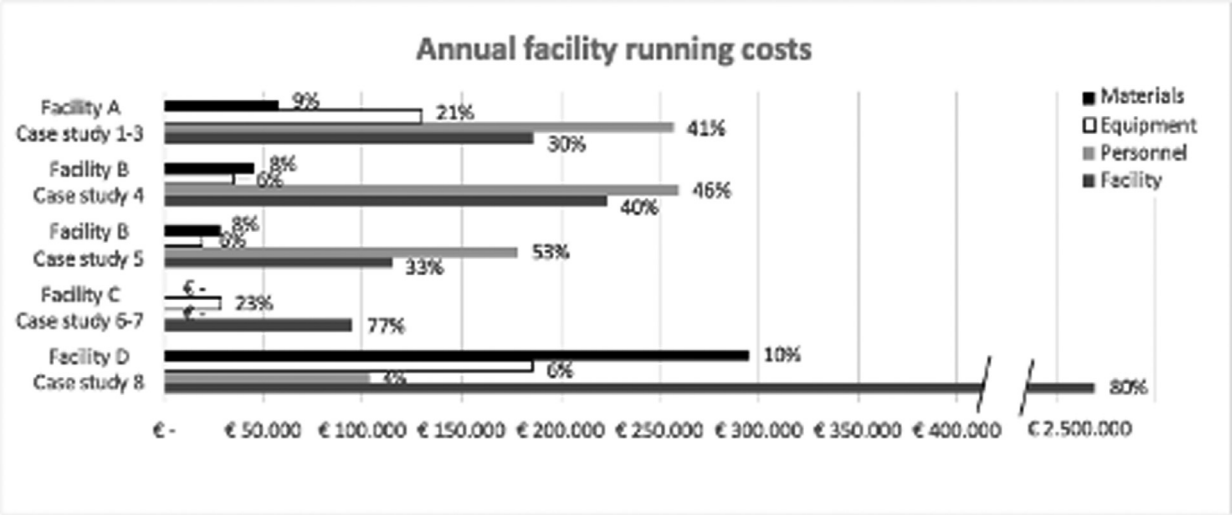

Figure 3. Annual facility running cost per facility. Percentages are proportion of total running cost per facility. Costs are presented in 2018 euros. Numbers presented are direct measures, meaning they not adjusted for failure rate or doses/batch (post hoc adjustment).

A (30%), facility B-4 (40%) and B-5 (33%) allocate similar percentage of resources to fixed facility cost. Facility D (80% fixed facility cost) is a more costly facility, both absolute and proportionally. This 80% facility cost however is similar to facility C (77%), but direct comparison between C and D cannot be made due to the specific payment agreement. The high fixed facility cost for facility D can partially be explained by its novelty. The facility was built in 2016, which results in higher annual depreciation in the first few years after opening. Also, facility D is the only standalone facility in this study. This means the cell facility is not part of a complex but a detached building. When costing facility D, proportionally more square meters were allocated to office space, reception room, technical areas and the cost; for example, the cafeteria was included. In contrast, facilities A, B-4 and B-5 are departments within a larger building complex. Facility A seemingly has the lowest facility costs, but it should be pointed out that annual mortgage and utilities were not included because these costs are absorbed by the academic center and not charged to the facility and developers. In facility C, only cleanrooms, supporting areas and a small office were included.

Operational cost

The sum of variable cost is the product specific operational cost per batch. Total operational and variable cost per category for each case study are shown in Figure 4.

Both absolute and proportional results in Figure 4 show large differences between case studies. This variance can partially be explained by product and facility characteristics. For example, case studies 1, 2, 4, 6 and 8 use specific antigenic peptides, which appear to be a major driver of material costs. Another emerging material cost driver is hypothesized to be the use of platforms (e.g., CliniMACS or CliniMACS Prodigy). Use of such platforms requires specific and costly consumables (e.g., cell selection reagents, tubing sets, bags) and buffers purchased from the platform provider. These buffers and consumables are more costly than generic or homemade buffer solutions. Use of these platforms and other specialized equipment (e.g., flow cytometer, closed system harvest device) were also cost drivers in the equipment section. Specialized equipment was used in all case

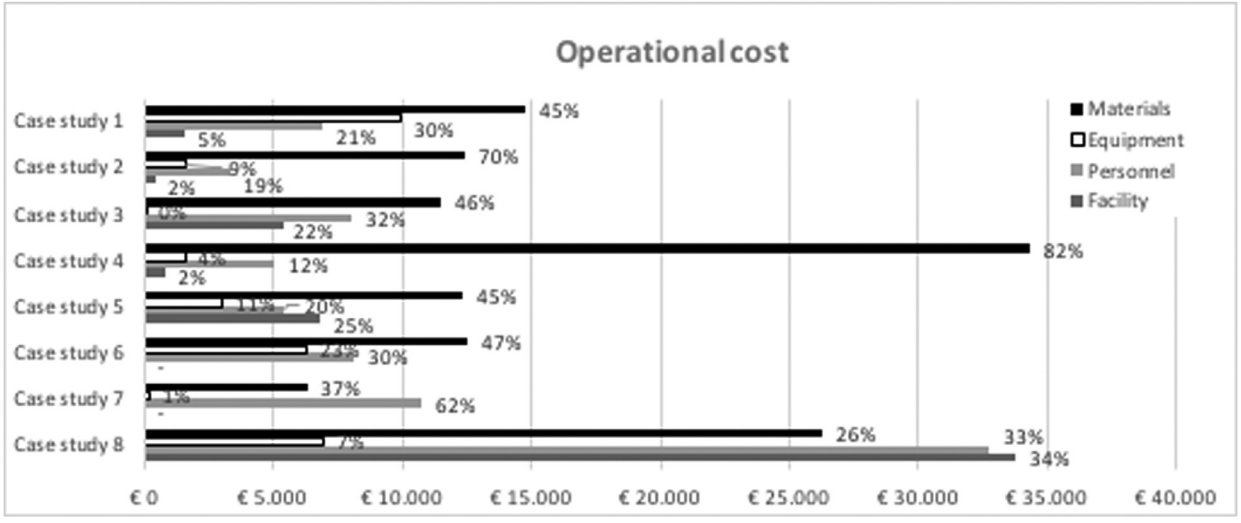

Figure 4. Operational cost presented per case study (per batch). Percentages are proportion of total running cost per facility. Costs are presented in 2018 euros. Numbers presented are direct measures, meaning they are not adjusted for failure rate or dose/batch (post hoc adjustment).

Table II
Total cost per batch and treatment, adjusted for failure rate (assumed 5%) and treatment yield per batch (post hoc adjustment).

	Facility A			Facility B		Facility C		Facility D
Case study	1	2	3	4	5	6	7	8
Materials	€15 171 (46%)	€12 801 (58%)	€11 897 (41%)	€35 096 (69%)	€13 916 (30%)	€12 542 (39%)	€6287 (28%)	€34 695 (19%)
Equipment	€5862 (18%)	€2506 (11%)	€904 (3%)	€2150 (4%)	€4063 (9%)	€7521 (23%)	€1604 (7%)	€12 247 (7%)
Personnel	€9202 (28%)	€ 4997 (23%)	€9747 (33%)	€9384 (18%)	€15 296 (33%)	€8147 (25%)	€10 754 (47%)	€35 723 (20%)
Facility	€2801 (8%)	€1632 (7%)	€6674 (23%)	€4496 (9%)	€13 162 (28%)	€4167 (13%)	€4,167(18%)	€99 047 (54%)
Total/batch	€33 036	€21 936	€29 221	€51 126	€46 437	€32 376	€22 812	€181 713
Fixed	€4206 (13%)	€4,206 (19%)	€4,206 (14%)	€ 9389 (18%	€18 908 (41%)	€5419 (17%)	€5598 (25%)	€81 958 (45%)
Variable	€28 830 (87%)	€17 730 (81%)	€25 016 (86%)	€41 738 (82%)	€27 529 (59%)	€26 957(83%)	€17 214 (75%)	€99 756 (55%)
Failure rate adjustment								
Failure rate	5%	5%	5%	5%	5%	5%	5%	5%
Total/batch	€34 688	€23 033	€30 682	€53 683	€48 759	€33 995	€23 952	€190,799
Fixed	€4416 (13%)	€4416 (19%)	€4416 (14%)	€9858 (18%)	€19 854 (41%)	€5690 (17%)	€5877 (25%)	€86,055 (45%)
Variable	€30 272 (87%)	€ 18 617 (81%)	€26 266 (86%)	€43 825 (82%)	€28 905 (59%)	€28 305 (83%)	€18 075 (75%)	€104 743 (55%)
Post hoc adjustment								
Treatment yield/batch	1	1	1	1	1	1	1	22
Total/treatment	NA	NA	NA	NA	NA	NA	NA	€8673
Fixed	NA	NA	NA	NA	NA	NA	NA	€3912
Variable	NA	NA	NA	NA	NA	NA	NA	€4761

Total costs are presented in fixed and variable cost, €(%). One treatment can consist of more than one dose.

studies with the exception of cost study 7 in which equipment cost accounted for 1% of operational cost, respectively. Although costly, the impact of the purchase of such specialized equipment seems to be associated with APV and project share. It seems that sharing cost of expensive specialized equipment over multiple projects (or routine diagnostics and insured health care in case study 5) reduced the impact on the total operational costs. Another example is center-wide equipment sharing in facility A. Here, departments have a fee-based arrangement to use flow cytometers of a centralized fluorescence-activated cell sorting (FACS) unit. Whether project share or APV has more impact cannot be derived due to high case study and facility variability. Although purchasing a platform is a large investment for a small-scale developer, it is also thought to reduce labor and facility costs [32].

In the next category, personnel costs seem to correlate with both manufacturing time and the level of manipulations. Resource-intensive products with longer manufacturing times (case studies 7 and 8) show higher personnel costs than products with shorter manufacturing timelines and little manual manipulations (case studies 2 and 4). However, caution is warranted in this comparison because 10-day runtime does not necessarily correspond with 10 cleanroom days. Whether sharing of specialized equipment or manufacturing time has more impact cannot be derived from these case studies because of high heterogeneity. In the facility cost category, the variable costs correlate mostly with manufacturing time. This is seen in facility A with case studies 1, 2 and 3, where manufacturing time is 7, 2 and 28 days, respectively. This result is not a surprise because variable facility and personnel costs are both based on a day rate model. Case study 8 from facility D shows the highest absolute and proportional cost, similar to the fixed cost results. This facility is also the largest facility, both in absolute surface area and square meters per cleanroom compared with other facilities.

Total batch cost, failure rate and post hoc adjustments

Following the presented methodology in Figure 2, the sum of the fixed and variable category cost adjusted by failure rate results in the aggregated per-batch manufacturing cost. Results of the application of the framework and methodology to the case studies are presented in Table II. In case studies 1 to 7, batch cost is equal to per-patient CBT treatment cost, whereas case study 8 needs post hoc adjustment because one1 batch yields 88 doses and can thus can treat 22 patients.

Batch cost is presented as total, fixed and variable cost. Fixed cost in our case studies account on average for 24% (13–45%) of total cost and variable for 76% (55–87%) of total cost. Total batch costs varied between €21 936 and €181 713. When adjusted for failure rate and treatment yield cost varied between €8,673 and €53,683 per treatment. Although facility D and case study 8 proved throughout the research to be most resource intensive, after post hoc adjustment, the treatment cost result was the lowest. This may imply that increase of treatment yield per batch could reduce treatment costs; however, this is not feasible for all products and indications (e.g., autologous products and rare indications).

Discussion

In this article, we have described the development of a uniform and transparent framework and methodology to facilitate costing of small-scale cell-based therapy manufacturing. This will help to advance the cell-based therapy field as this is the first method, to our knowledge, that shows demonstrable applicability for estimating costs of CBTs in different facilities with different products [12,14]. Our method showed sensitivity to differences in manufacturing time and resource use. The use and application of the framework and methodology was validated by developers in four types of facilities across Europe. To facilitate the uptake or our framework and method, we provide a Microsoft Excel costing template as a supplemental document accompanying the online version of this research.

Although not exhaustive, we are confident that the types of facilities included in this study are representative of the majority of facilities currently manufacturing small-scale CBTs in Europe [11,33]. Even in facilities where not all information was available, application of our method still yielded insights. For example, in facility C, a payment arrangement was in place that aggregates the fixed materials, personnel and facility costs. Such arrangements are not uncommon. Applying our methodology to this payment agreement, resulted in “empty” cost categories, meaning we have not been able to estimate the true breakdown of costs of CBT production in this facility. Moreover, our study takes the developer perspective. This resulted that for facility A partially and in facility C all overhead costs of the building are borne in full by the owner of the building. We have not been able to retrieve these costs, but it is likely that facilities A and C incur more facility cost than included in this analysis. This is confirmed when roughly comparing facility running costs of facilities A and C with facility B. By applying our methodology, we were able to provide this insight to the developer and created awareness that if

manufacturing of case studies 1, 2, 3, 6 and 7 were to be relocated, a cost increase should be expected.

Specialized materials and equipment are an important driver of operational cost. Peptides are often custom-made in low volume. The low demand corresponding with the novelty of the CBT field means that few vendors are active in the market [10]. Perhaps when demand for specialized raw materials increases, the specialized material costs will decrease because of an increase in competition and supply [23]. Regarding specialized equipment, the majority of the included facilities use platforms. Such platforms allow for partially automated material inputs and manipulations previously performed manually by technicians [34]. Additionally, the use of closed-circuit platforms allows for simultaneous manufacturing of multiple and different CBTs in the same room [9]. With the use of open systems, GMP regulation prohibits manufacturing of more than one CBTs in the same environment to avoid cross contamination [9]. Use of platforms could also decrease facility downtime. Therefore, although the capital investment in platform is significant, the impact on the aggregated manufacturing cost is suggested to decrease when project share and APV increased. To confirm this hypothesis, our framework and methodology can be used in future research to quantify the impact of factors such as platform use, project share and APV to inform best practices.

Another important cost driver we identified was personnel cost (18–47%). This observation is supported by findings in the literature [35,36]. Small batch sizes combined with manual manipulations make automation economically unattractive. Where possible, the development of modular approaches to CBT manufacturing, exploration of the possibility of allogenic material use instead of or in addition to autologous cells and the multipurposing of existing specialized equipment within the facility could offer opportunities to increase volume throughput [34]. Another option would be to share facilities, equipment and other resources (e.g., bioreactors) to reduce cleanroom downtime, as is done in facilities A and B. Facility A is available for all hospital departments and has access to a centralized FACS unit. Costs are primary borne by the hospital and pharmacy. Departments compensate for the services used. In facility B, the GMP facility is shared by two departments, which results in substantial cost and risk sharing. For case study 5 at facility B, tissue procurement occurs in a large stem cell processing facility. Whether this substantially lowers costs cannot be concluded due to product and facility heterogeneity. In general, however, when developing and planning manufacturing processes developers should strive to minimize equipment and facility down time.

It is important to realize that the timing of expenses and income differ substantially. The cost estimates presented in this research suggest that operational costs are incurred at time of production and that facility running costs are spread on an annual basis. However, a majority of costs are often incurred far before manufacturing in the form of substantial capital investments needed to build GMP facilities and purchase equipment. Also, the highly skilled personnel required to develop and manufacture CBTs needs to be hired upfront and are most often not occupied full-time by product manufacturing or development. These high upfront investments are considerable, especially for small developers. As mentioned earlier, increasing production volume and batch yield could reduce facility running costs considerably, but not all products or indications allow or require upscaling. An example of an initiative of a shared public–private expert center facility is the Cell and Gene Therapy Catapult in the United Kingdom [37], providing infrastructure and expertise for translation and early-phase manufacture to help overcome development challenges (e.g., safety, effectiveness, scalability). Institutions like these could help small scale developers advance their products without having to make speculative and substantial high upfront investment.

Limitations of framework and methodology

Despite our best efforts, this study has limitations. First, by distributing the facility running costs over total batches manufactured per year, we assume that all batches consume similar resources. This may overestimate the fixed costs for products requiring limited manufacturing time or minimal manipulation. Similarly, this may underestimate the fixed costs for resource intensive products. However, in a GMP environment the manifold or shared quality assurance measures cannot be segmented as all are required to manufacture a CBT. This, combined with the aim of designing a workable methodology may rationalize this approach [14]. Second, use of day rates when estimating variable personnel and facility costs is known to somewhat underestimate resource use [14]. The day-rate approach assumes a facility is at full capacity, and any downtime is considered a loss. We partially corrected for this underestimation with an adjustment for FADs. The developers mentioned in the interviews that facility downtime was expected to decrease when experience and predictability of manufacturing process increased. Nonetheless, facility downtime should be minimized because the fixed running and maintenance costs account for a large percentage of total costs (13–45%). Third, in our study, we did not include the costs to recruit, hire and train personnel. Although beyond the scope of this research, one could argue that skills also experience some sort of depreciation, which require continuous training. Additionally, the most recent UK cell and gene therapy skills demand report foresees a shortage of highly skilled individuals [38]. The report expresses high concerns about education, recruitment and retention of skilled individuals, especially in process development and manufacturing. Fourth, in our framework, we distinguish three manufacturing steps. We specifically defined these steps, as they may occur in different environments, at different time points or are paid out of different budgets. When the steps defined in our framework are not applicable the provided costing template can be modified to fit the end-users needs. The same applies to the applied perspective, which in this research is a developer perspective. To facilitate application of our framework and method, the template can be modified to reflect a hospital or departmental perspective. However, we do not encourage this practice because modifications decrease the comparability of estimates between facilities and products. Also, the current framework and method are validated for the context as described in this research. Last, the heterogeneity of the included case studies in different facilities impedes direct comparison between products and reduces our learnings of cost drivers and best practices from this research. Ultimately, the main objective of this research was to develop a costing methodology. The heterogeneity of the case studies may reflect the large variety of CBTs currently applied in clinical practice. With our framework and methodology, future research may address identification of cost drivers and development of best practices across a broader range of examples. Other directions for future research could be exploration of the applicability of this framework and methodology toward (cell-based) gene therapies. Gene therapies are, together with CBTs, part of the advance therapy medicinal product group [2]. Expansion and validation of our framework and methodology would increase external validity.

We emphasize that the estimates given in our research only reflect manufacturing costs and under no circumstances should be confused with product price. We stress that this framework and methodology is designed and currently only validated for application in a routine manufacturing environment. Our estimates do not include costs incurred in other stages of medicinal product development, such as research and development, manufacturing setup, preclinical development, animal testing, clinical development and, if applicable, regulatory costs of applying for market authorization as well as clinical cost of the treatment. The price of a product includes more than the manufacturing costs alone [18,39,40].

Strengths of framework and methodology

The heterogeneity of included facilities and case studies can also be seen as a strength of our study. Our framework and methodology were deemed applicable across facilities and products and was validated by experts increasing the generalizability and potential uptake of our work. Another strength is use of the ABC-method. This bottom-up approach has proven particularly useful to estimate costs of the tailored, highly manual and small-scale manufacturing processes [10], which reflects the current state of CBT manufacturing. Via co-creation with biomedical researchers and clinicians, we aimed to develop a framework and methodology operable for developers with little or no experience in costing problems and also, we added a costing template to increase uptake. When using the template, it is important to realize that the cost estimate is a reflection of the manufacturing process at that point in time. This means that if changes occur in any of the cost categories, the cost estimate is outdated. However, the template allows the user to update items independently to address technical advances or change in the cost of goods without having to redo the complete analysis. Last, this research reiterates how developers and researchers can benefit from collaborations outside their specific field of research [14,41]. In this research, collaboration between biomedical researchers with regulators and health economists resulted in the described framework and methodology. The costing template was found to provide step-by-step guidance to CBT developers to cost their manufacturing process, as well as gain insights in cost drivers and efficiency gains. We observed that a majority of the developers undervalue their resources, leading to overly optimistic budgeting and low (external) price setting. In the short term, these unaccounted-for costs are likely to be absorbed in facility budgets or start-up subsidies. Long-term realistic costings are important to, for example, further facilitate sustainable translation of CBTs to the clinic and ensure financial stability of facilities. The latter is particularly relevant when quantity and volume of CBTs increase or when manufacturing locations are moved due to product scale-out or spinoff. Insights from this costing exercise have already been used by participating developers in grant applications and adjustments in individual facility service and product costings.

Conclusion

To our knowledge, this is the first study that aimed to develop a uniform and transparent framework and methodology to estimate the cost of cell-based therapy manufacturing. The framework and template have proven applicable in different facilities with different products and showed to be sensitive enough to capture differences in time and resources use. Developers found that the framework and methodology gave them step-by-step guidance in estimating the cost of CBTs. Manufacturing CBTs brings both technological and financial challenges. To advance the development and patient access to these promising products, resources should be efficiently allocated. This starts with insights in cost drivers and increasing efficiency. This research contributes to more accurate CBT manufacturing cost estimates to inform and plan cost-conscious strategies.

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Declaration of Competing Interest

The non-killer cell product of case B-5 is manufactured according to a proprietary protocol. The other authors have no commercial, proprietary, or financial interest in the products or companies described in this article.

Author Contributions

Conception and design of the manuscript: RtH, AH, JH, HO, JM, MT, GW, MH. Data collection and analysis: RtH, HO, JM, MT, GW, PM, AdG, GS, JdV, HD, IJ, TN, JJZ, SV, MvP, FL, MH. Revising or reviewing the manuscript: RtH, JH, GF, HL, OK, HO, JM, MT, GW, PM, AdG, GS, JdV, HD, IJ, MvP, JJZ, TN, MH. All authors have approved the final manuscript.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcyt.2020.03.432.

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