Overcoming Challenges in Cellular Therapies:
A Systems Engineering Approach for Equitable Access

By

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Abstract

Cellular and gene therapies have ushered in a new era of medical treatment, promising cures previously thought unattainable. Technologies like CRISPR/Cas9 enable precise genome manipulation, yet challenges persist in therapy delivery, prompting the rise of ex vivo approaches. Despite the promise of adaptive cell therapies, high development costs, manufacturing complexities, and regulatory hurdles hinder widespread adoption. The lack of agreement in the field with respect to centralized versus decentralized manufacturing models and the choice between autologous and allogeneic cell sources pose additional challenges. Equally as critical for global access to these therapies, personnel shortages and specialized expertise requirements must be addressed. A systems engineering approach offers a framework for overcoming these barriers, facilitating comprehensive bioprocess design analysis. Ultimately, developing a descriptive model for analyzing therapeutic delivery is crucial for ensuring equitable access to these transformative therapies worldwide.

Thesis supervisor: Joan Rubin

Title: Executive Director, System Design and Management Program

Acknowledgements

I become saturated with gratitude when I think of my MIT journey – It did not have to be, yet it was. As the journey ends, I would first have to recognize my thesis advisor Joan Rubin for encouraging, guiding, and mentoring me from start to finish. I will forever value how Joan always placed my well-being and career first, providing sensible and timely advice when I needed it the most. I hope you will allow me to return for the selfish exchange of dark chocolate for timeless advice.

In the Statement of Objectives I submitted as part of my MIT SDM Masters application I wrote about the mission I inherited from my parents Jorge and Reneta. In that statement I explained how they "leveraged their careers to give back to less fortunate communities and have inspired me to adapt this blueprint and use it to drive innovation between the most and least developed economies." This thesis is directly tied to that mission so as I conclude this voyage I thank them again for the drive and values they inculcated in me. As if that weren't enough, I have always counted with an endless well of love and encouragement from my siblings Ceci and Jorge. This core group of four makes me believe anything is possible.

All the challenges in the past few years have always felt a little lighter around my friends; those abroad, in different states, here in Boston, and the those I've made while completing this program – the most valuable jewels I found at MIT. I am particularly grateful for my friend Paulo Garcia who supported my MIT journey before it even started and continues to provide the highest example of excellence across all aspects of life.

To my colleagues at Kytopen, I thank you for having been excellent sources of energy and wisdom that helped me navigate some of the challenges this MIT journey presented.

Isabella, my dream-turned-reality. I appreciate your patience, value your support, and most importantly, admire the way you walk this world. I look forward to the life we have ahead and believe we have not lived our best years together yet.

Lastly, I thank my 16 years-old self, for having the courage to leave his known world behind in search of a chance to make the world a better place for others. The journey has been wonderful, with every challenge stealthily hiding an incredible opportunity.

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Introduction

The last decade witnessed the birth of cellular and gene therapy products and with it an elusive treatment paradigm, cures. The rapid evolution of genome-editing technologies such as CRISPR/Cas9 systems have allowed precise manipulation of the genome in mammalian cells to become a reality. These technologies have enabled scientists and medical professionals to modify deleterious genetic sequences or integrate foreign sequences to the genome that enhance the function of a cell for the benefit of patients. Some of the commercially available therapies such as Luxturna can restore the vision of patients that had completely lost sight to a congenital disorder named Leber congenital amaurosis (LCA)(Darrow, 2019). Gene therapy, however, presents delivery challenges for dividing cells and the delivery vehicles are not well established, which has led to the development of *ex vivo* gene therapies or adoptive cell therapies (ACTs). Here, primary human cells can be engineered outside the body where appropriate controls can be put in place and the editing processes is targeted to the cells of interest (Finck et al., 2022).For example, patients suffering from sickle cell disease can have their hematopoietic stem cells retrieved via blood collection, edited, and reintroduced into the bone marrow for major clinical benefits (Kanter et al., 2023). But just as the promise of these new therapeutic modalities is large, so too are the challenges associated with their implementation and worldwide adoption.

At present, it is estimated that the costs associated with the development of cell and gene therapies average ~$2.5B (Sabatini & Chalmers, 2023). This places a significant economic burden for pharmaceutical organizations to turn these therapies into profitable opportunities. The personnel and raw materials required for the development of the drugs are a big cost driver for early research, process development, and preclinical stages. Once a therapy has been approved for commercialization, the costs for raw materials alone can range from tens of thousands to hundreds of thousands of dollars; the reported manufacturing costs for Novartis' Kymriah remains at $40,000 (Sagonowsky, 2018) making it a distant dream for acute lymphoblastic leukemia patients in developing nations. These costs don't include other ancillary costs associated with therapy delivery, treatment

for the amelioration of adverse reactions, or patient conditioning just to name a few (Potnis et al., 2023; Ring et al., 2022).

The structure of manufacturing and supply chains for cell therapies remains challenging. Centralized vs. decentralized manufacturing and supply chain is major source of ambiguity with respect to where the field is heading (Analysis, 2018). In a centralized manufacturing system, all production activities take place in a single or few locations. By consolidating operations, centralized models line up with the common advantages of economies of scale such as standardization, lower costs of production, but large upfront investments. This approach could also accelerate industry-wide convergence on best practices, tools, and equipment. However, they place a lot of stress on transport and logistics systems given the “living” nature of these products. In contrast, a decentralized model imposes distributed production sites, which in the context of cell therapies means production happens closer to the point of care. A decentralized approach could decrease the need for complex cryopreservation steps and increases production capacity flexibility, but consistent scale up of any one therapy becomes challenging and places a significant burden on an already-overtaxed regulatory system. While a decentralized system increases flexibility, it may not economically feasible to deploy the infrastructure required for cell therapy manufacturing at the municipal level. One approach to overcome these barriers is by implementing automated, closed manufacturing systems such as the Miltenyi CliniMACS Prodigy system (Miltenyi Biotec, North Rhine-Westphalia, DE) or the Lonza Cocoon platform (Lonza Group AG, Basel, CH) but these tend to be rigid on production processes and can struggle to adapt to the variability of raw materials (Harrison et al., 2017).

Studies looking at cost drivers for cell therapies estimate that batch costs are primarily driven by materials and personnel costs at comparable contributions (ten Ham et al., 2020). Similar to the intense debates around centralized vs. decentralized manufacturing, autologous vs. allogeneic cell sources have their own lists of advantages and disadvantages. In both cases raw materials remain expensive and inconsistent (ten Ham et al., 2020). Issues with patient-patient variability present a substantial issue for

autologous and allogeneic products (Baguet et al., 2024; Levine et al., 2017). The lack of small-scale models can force cell therapy manufacturers to troubleshoot at scale, adding significant variable costs to the manufacturing process (Rameez et al., 2014).

Skilled personnel are scarce and expensive throughout the entire fulfillment of these therapies (Shah et al., 2023). In manufacturing, the added costs and process variability of complex tasks managed by skilled personnel presents opportunities for automation and standardization (Mikhael et al., 2022). In the administration of these novel therapies, personnel with deep expertise in the disease state that are also able to address the host of adverse events such as cytokine release syndrome (CRS), graft vs. host disease, and immune effector cell-associated neurotoxicity syndrome (ICANS) are required (Bailey et al., 2023). Beyond manufacturing and logistics challenges, addressing this latest challenge in less developed healthcare systems remains a major barrier for worldwide adoption (El-Galaly et al., 2020).

With the substantial variability and uncertainty in the production of gene therapies, this work aims to improve the process by identifying and validating figures of merit that can be used to assess potential for patient access within the boundaries of the therapy delivery cycle and help guide the industry towards widespread access. This is largely accomplished by rethinking the system architectures of the cell therapies. Considerations are given towards establishing manufacturing systems that minimize the downside and maximize the upside with respect to known uncertainties (e.g., gene therapy vs. cell therapy, autologous vs. allogeneic). As the field elucidates these uncertainties, other architectures may become more valuable which is demonstrated in a trade space analysis. Lastly, a set of architectures are proposed under an assumed theoretical target performance that would pave the way towards cell and gene therapy access in developing countries.

The problem with how we evaluate success

While the field of cell therapies, including CAR-T cell therapy, has traditionally focused on evaluating cost-effectiveness and quality-adjusted life years (QALYs) gained, there are

significant system-level issues that prevent many eligible patients from receiving these transformative treatments. Factors beyond just the clinical and economic value of the therapy such as affordability, transportation, caregiver support, and regulatory/manufacturing challenges, can create major barriers to patient access.

Taking a systems engineering approach to the delivery of cell therapies, from manufacturing to administration, could empower stakeholders across the healthcare ecosystem - including regulators, providers, and biopharma companies - to invest resources and address these systemic access barriers. This work aims to develop a multi-attribute utility (MAU) framework that can be used to analyze various bioprocess designs from collection through infusion in cell therapy. As new technologies evolve, this approach would help highlight the impact across its interfacing components, and how outputs may be affected. Lastly, the work would aid design processes for different disease stages considering all aspects of CAR-T cell therapy fulfillment by understanding the sensitivity to desired outputs.

Literature Review

1. The state of cell therapy

As of December of 2023, there are currently over 30 gene and cell therapy products approved by the FDA for the treatment of various indications (FDA, 2023). Six of these therapies fall under the realm of Chimeric Antigen Receptor T-cell (CAR-T cell) therapies for the treatment of blood cancers such as leukemia and multiple myeloma. These therapies are possible by using genetic engineering tools to modify a patient's own immune cells such that a cancer-targeting protein – a CAR protein – is now produced on the T-cells of the patient. Once the cells are back in the patient's bloodstream, these CAR proteins will help T cells recognize and eliminate cancer cells.

While not all patients respond equally to the administration of CAR-T cell therapies, the results are outstanding and widely considered paradigm shifting. For instance, in the case of patients diagnosed with Mantle-Cell Lymphoma, CAR-T cells targeting CD19 receptors

on cancer cells can induce a complete response for 67% of patients treated (M. Wang et al., 2020). For a study looking at the use of CD19 targeting CAR-T cells for treatment of B-cell acute lymphoblastic leukemia (ALL), an impressive 93% of patients treated had no evidence of disease 1-month after treatment (Maude et al., 2016).

Table 1. *Approved CAR-T cell therapies as of December 2023 (Cappell & Kochenderfer, 2023)*

Therapy Name	Company	Indication	Year*
ABECMA (idecabtagene vicleucel)	Bristol-Myers Squibb	Multiple myeloma	2021
BREYANZI (Lisocabtagene maraleucel)	Bristol-Myers Squibb	Mantle cell lymphoma	2021
CARVYKTI (ciltacabtagene autoleucel)	Janssen Biotech	Multiple myeloma	2022
KYMRIAH (tisagenlecleucel)	Novartis Pharmaceuticals	Acute lymphoblastic leukemia, diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, follicular lymphoma	2017
TECARTUS (brexucabtagene autoleucel)	Kite Pharma (Gilead Sciences)	Mantle cell lymphoma	2020
YESCARTA (axicabtagene ciloleucel)	Kite Pharma (Gilead Sciences)	Diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, DLBCL arising from follicular lymphoma	2017

**Year of approval for 1st indication approved*

The success of these initial therapies has encouraged many in the scientific and finance communities to look for other applications for CAR-T cell therapies. As of late 2023 more than 1000 clinical trials have been launched globally, despite the challenges of implementing these therapies (Joy et al., 2023). Some centers with enough infrastructure and subject matter experts such as the Mayo Clinic are housing as many as 16 CAR-T cell clinical trials at once. While it is difficult to predict the number of CAR-T cell therapies that will be approved in the coming years, a recent statement by the FDA stated that they expect to approve more than 10 therapies per year by 2025 (Scott Gottlieb, 2019). This rapid pace of review and approval will require significant regulatory and manufacturing

infrastructure and is fundamentally going to change the way the American healthcare system provides cancer care.

Specifically for adoptive cell therapies, there are two approved by the FDA for the treatment of cancer, which are CAR-T Cell Therapies: Axicabtagene ciloleucel (Yescarta®) and Tisagenlecleucel (Kymriah®).

2. Baseline model for CAR-T cell therapy fulfillment

Cell therapies can come in different formats. For the purposes of evolving a systems level framework and applying to this evolving field, a CAR-T cell therapy standard model will be explored. A CAR-T cell therapy cycle (seen in **Fig 1.**) can be condensed into the following 4 functions: 1) Collection, 2) Processing (Activation-Editing-Expansion), 4) Controls and Characterization, and 4) Infusion.

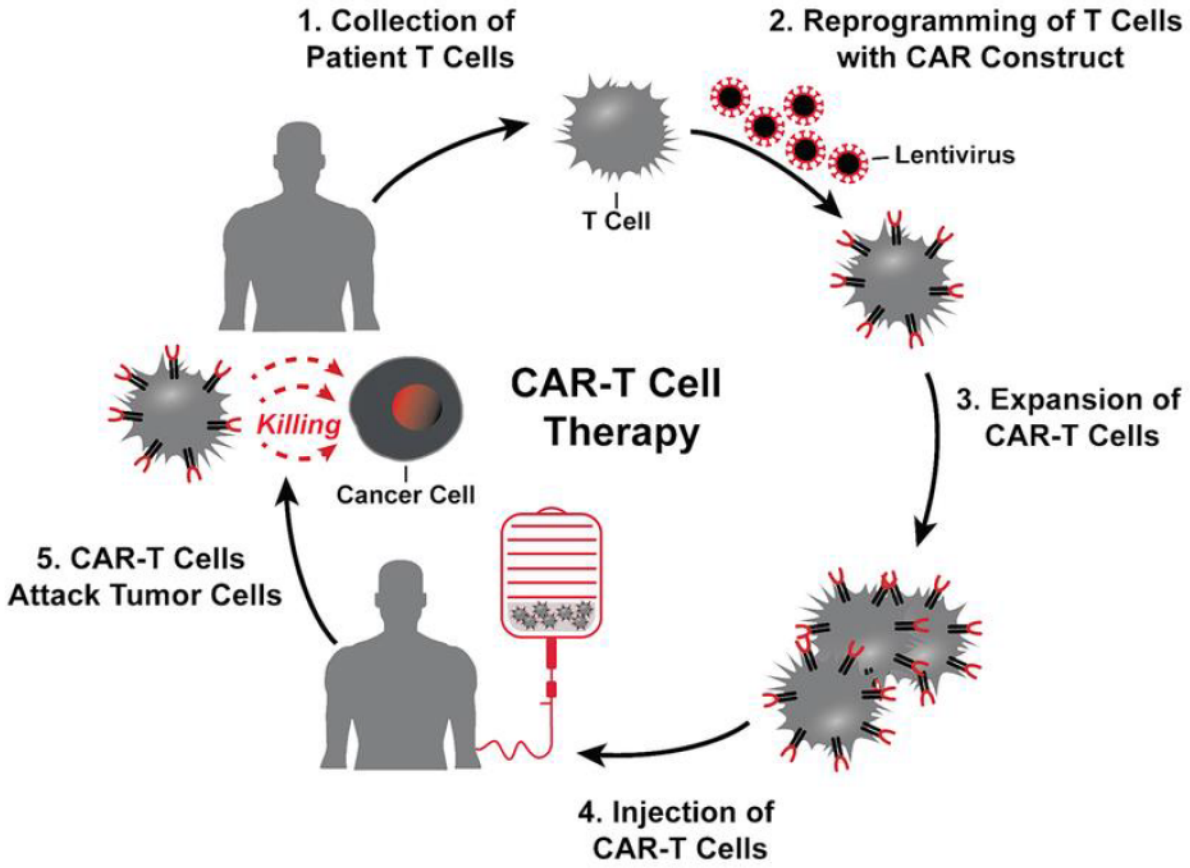

Figure 1. *General CAR-T cell therapy lifecycle highlighting the journey towards autologous CAR-T cell product (Dario et al., 2020).*

We now investigate how these functions are achieved and what some of their biggest challenges are:

Collection

At present, all commercially approved CAR-T therapies are based on an autologous process (Cappell & Kochenderfer, 2023) in which the patient's own immune cells are collected via leukapheresis and typically followed by cryopreservation. Of note, most of these therapies are approved as third, fourth, or fifth line of treatment which results on the patient's immune cells receiving significant stress prior to apheresis. There exists, however, several CAR-T cell therapy products under development that would be produced under an allogeneic process, using donor cells from a healthy subject (Y. Zhang et al., 2023).

Processing

It is important to note that processing can include three major sub-functions that have been the subject of much research: Activation, Gene Editing, and Expansion.

- Isolation & Activation: During the activation stage, the apheresis material is processed to remove red blood cells, platelets, and other contaminants in a series of washes and fractionation steps (X. Wang & Rivière, 2016). Additional steps may be taken to isolate or select specific subsets of T cells that may be preferred for a specific therapy. Once the appropriate cell population is achieved, cells are stimulated to enter the cell cycle via an activation step. The activation requires T cells to detect 2 signals which can be achieved by a combination of interactions with other cells such as dendritic cells, exposure to synthetic stimulating reagents, and/or antibodies.
- Gene Editing: At present, CAR-T cell therapies are primarily developed by taking activated cells and exposing them to viral vectors carrying the gene of interest. While the molecular machinery of viruses can be leveraged to produce high levels of stable expression of the CAR of interest, there are significant regulatory, financial, and processing challenges with this approach. There are significant efforts in the field to address these challenges via non-viral gene editing

approaches such as pulsed-electric field technologies, lipid nanoparticles, among others.

- Expansion: To achieve the right dosage amount for CAR-T cell therapy, the population of cells available for infusion is increased by culturing the activated and edited T cells. This step is critical to set the appropriate metabolic state of the cells which is directly tied to the efficacy and persistence of the therapy (M. Zhang et al., 2021).

Controls and Characterization

As in any biomanufacturing process, the drug product must be carefully monitored to ensure the engineered cells meet the safety, purity, potency, and identity criteria (Lipsitz et al., 2016; X. Wang & Rivière, 2016). This is currently achieved by a series of in-process and release tests involving killing assays, off-target genome edits, and other tests that typically involve manual handling of drug product by highly skilled personnel. This is one of the most significant cost-drivers in CAR-T cell therapy manufacturing, which can account for nearly half the cost of goods and services (COGS) of the drug product (Lopes et al., 2023). To overcome some of the personnel-related costs, automation-oriented initiatives are considered to be a mid- to near-term requirement for the economic success of these therapies (Tomtishen, 2023).

Once the drug product is characterized, the newly engineered cells are frozen for future use. At present, this cryopreservation step requires that cells are suspended in an optimized medium with cryoprotectants to minimize cell damage and then they are frozen using specific protocols that maximize the number of cells available for infusion at the clinical site. Optimal cryopreservation materials and protocols are necessary to sustain the appropriate number of viable cells of the intended identity and potency. This step is critical for preservation of the drug product from the point of manufacturing to the bedside and has been shown to preserve the CAR-T cell product critical attributes (Panch et al., 2019).

Infusion

This is a complicated part of the process where logistics and post-treatment morbidities introduce significant variability. To account for the variability introduced by patient cells in the manufacturing process hospitals need to make a range of dates available for infusion as the exact data for arrival of the CAR-T cell drug product is variable. This uncertainty presents a significant challenge for hospital administrators to overcome as patients must go through a preconditioning step one week prior to the arrival of the CAR-T cell product (Papathanasiou et al., 2020). The drug product is typically transported by specialized couriers at a temperature -150C with a high degree of visibility (e.g., GPS trackers, wireless thermometers).

If the timing from leukapheresis to infusion is not properly managed, the consequences are dire for all stakeholders. Some research has estimated that ~40% of patients fail to receive the CAR-T cell they were expecting due to a combination of health deterioration and delays from payers and other stakeholders (Wayment, 2022). In addition to the horrific consequences for patients, hospitals and pharmaceutical manufacturers face financial losses from the systemic issues.

Typically, pharmacists with training specific to the handling of CAR-T cell products manage preparation of the frozen product prior to infusion – The product is frozen in infusible medium (Levine et al., 2017; Nezvalova-Henriksen et al., 2023). Once the patient receives the treatment, a high number of resources are required to oversee patient progression and manage some of the common side effects of the therapy such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) which often leads to lost wages for hospital staff (Mikhael et al., 2022).

3. Investment and research

The markets have recognized both the potential benefits and challenges of the technology and as a result, have made substantial investments. The cell and gene therapy space experienced exponential growth in first-time investments from 2014 when ~$100 million were invested in the field to 2018 when >$1 billion were invested (Lohr, 2023). Companies

such as Johnson & Johnson, Astra Zeneca, and Bayer, to name a few, have demonstrated their commitments to the technology by placing large bets (>$100 MM) in manufacturing facilities with the hopes of creating efficiencies and addressing manufacturing bottlenecks that exist in the present (Font et al., 2023; Liu, 2022; McEvoy, 2024).

4. Cell therapy metrics

Historically, oncology-oriented therapies have been evaluated under various metrics for cost to the healthcare system as well as effectiveness such as time progression-free, time under remission, and quality of life to name a few. Quality-adjusted life years (QALYs) is a common model that captures the utility of a therapy over some period of time. The model includes no considerations to the costs of the therapy and assumes that a 1 unit of QALY is equivalent to a full year of perfect health (Prieto & Sacristán, 2003). Studies looking to understand the cost-effectiveness of a novel therapeutic have applied an incremental cost-effectiveness ratio (ICER), which presents the ratio of the cost per QALY of the current standard of care to the cost per QALY of novel therapeutic intervention (Carrera & IJzerman, 2016). One study looking at the use of CAR-T cell therapies for the treatment of follicular lymphoma as a third-line option found that while an incremental clinical benefit was evident, this would come at an ICER of $183k/QALY, which is unlikely to be defined as cost-effective (Potnis et al., 2023).

5. Systems Engineering and Cohesion in the field

The evolution of monoclonal antibody (mAb) therapeutics offers learning opportunities for new therapeutic modalities such as cell therapies. Dating back to the 1980's, mAbs have its manufacturing titers from <0.1mg/L to titers nearing 10 g/L in recent years (Rader & Langer, 2015; Xu et al., 2020). Since the 1st mAb-based therapy was approved by the FDA in the late 1980's, not only has production increased but so has the complexity of the antibodies to improve on the therapeutic potential (Gera, 2022). In an industry review by Bader and Langer, the authors present data around titer and yield for biomanufacturing of approved products. Interestingly, while titer (upstream) has, on average, improved ~15X, yield (downstream) which is a constrained (0-1) has increased from ~40% to ~70%

(Langer & Rader, 2015). This alone offers some insights into how the CAR-T cell therapies may become current challenges; variables which are fundamentally constrained such as editing efficiency, step recovery, and cell viability may not offer long-term solutions for accessibility.

Bioprocess systems are complex and the industry has looked at systems engineering frameworks as a valuable approach to designing, integrating, modeling, and managing such systems (Helgers et al., 2022; Narayanan et al., 2020). From system-level interactions to agent-based modeling, and development of Process Analytical Tools systems engineering has provided a framework for progress in the space (Jackson et al., 2018; Luo et al., 2021). There are little-to-no efforts, however, in modeling the last stages of fulfillment for biologics – likely because until C&GT this stage was not a major factor in therapy access. Additionally, while cell therapy remains largely unstable and grappling with fundamental technological barriers such as off-target gene edits, feasibility of allogeneic products, and regulatory frameworks, the field is still working to converge on process data that could be used for decision-making.

A Systems Engineering Approach to Cell Therapy Delivery

1. Introduction

Typically, the calculation of Quality-Adjusted Life Years (QALYs) for CAR-T cell therapy involves assessing several key components that collectively assess the impact of the therapy on both the quantity and quality of a patient's life. These components include:

- Life-Years Gained: This fundamental component of QALYs assessment measures the increase in survival time attributable to CAR-T cell therapy compared to standard treatments or no treatment (Gribben et al., 2022; Mark G. Kuczewski, 2019).

- Health State Utilities: These are numerical values that reflect the quality of life associated with different health states, ranging from 0 (death) to 1 (perfect health).

Health state utilities are used to adjust the life years gained by the quality of life experienced during those years (Gribben et al., 2022).

- Adjustment for Side Effects and Morbidity: The calculation of QALYs takes into account the negative impact of any side effects or morbidity associated with CAR-T cell therapy (Gribben et al., 2022; Mark G. Kuczewski, 2019). A specific example for CAR-T cell therapy would be adjusting for the severity and duration of adverse effects such as cytokine release syndrome (CRS), which commonly affects the patient's quality of life.

Most groups include a Cost-Effectiveness Analysis (CEA) alongside QALY estimates to assess the economic value of a therapy. This involves comparing the incremental cost-effectiveness ratio (ICER) of CAR-T cell therapy to standard of care or other treatments, considering both costs and QALYs gained (Gribben et al., 2022). For a particular therapy to be considered cost-effective, ICERs must remain below a certain threshold, which is typically $100k/QALY.

This approach, however, leaves room for interpreting the real value of therapy to the patient population. The patient journey presented in **Figure 2** illustrates some of the challenges that lead to patient dropout. For example, QALY calculations do not account for uncertainties in timeline and failures in manufacturing, which not only present additional costs to the patient via bridge therapy but sometimes renders the patient ineligible. If a CAR-T cell manufacturing cycle fails one could argue that the value of the therapy is negative given that other approaches are likely to be put on hold while the hospital waits to receive the CAR-T cell product from the manufacturer. While this work assumes all patients receiving the therapy benefit equally, independent of the transient nature of oncological disorders, it is well documented that disease burden increases over time.

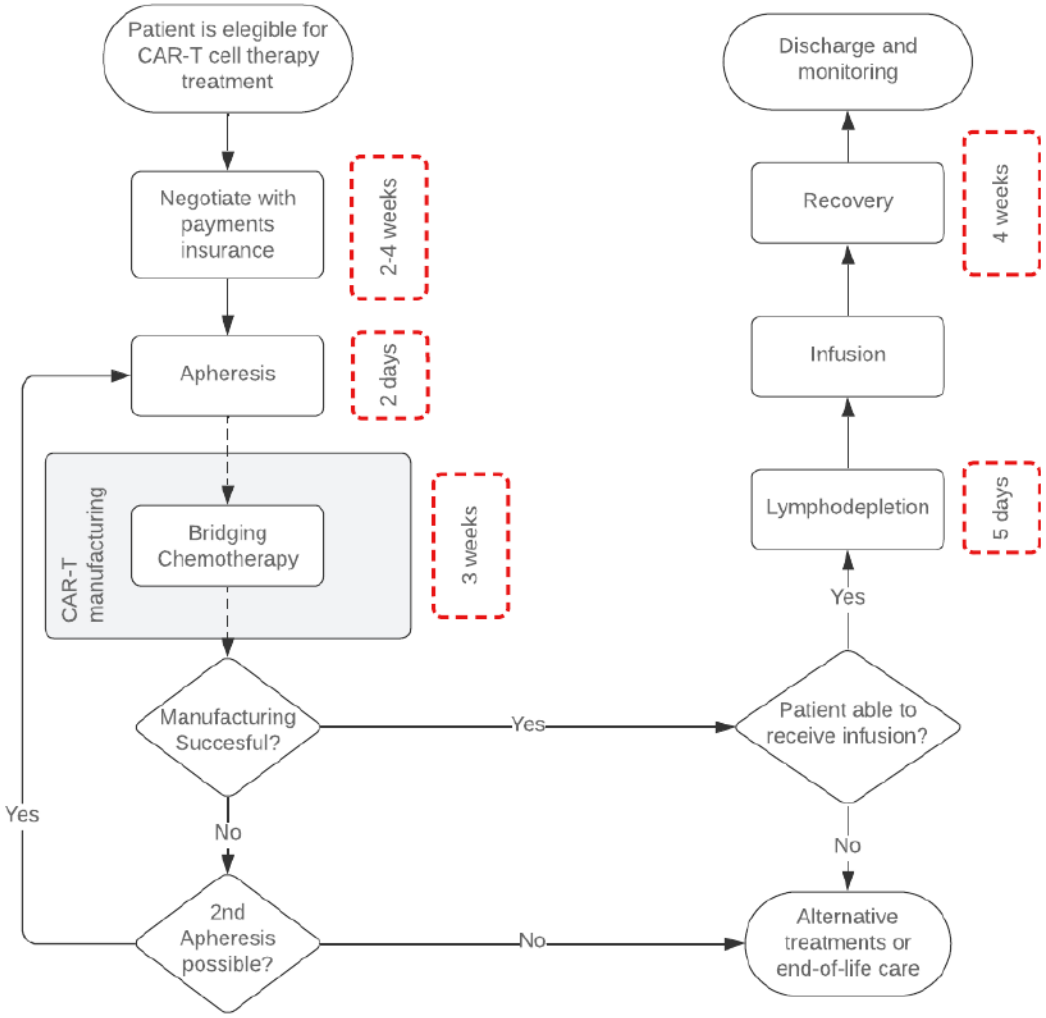

Figure 2. *Patient journey after determining eligibility for CAR-T cell therapy treatment. Flow diagram highlights 2 possible patient dropout points related to manufacturing success and duration of the treatment. These patients are unlikely to receive other therapies after dropping out due to highly advanced disease stage or death (Ayala Ceja et al., 2024).*

Here, we present an approach to further assess the value of CAR-T cell therapies to patients beyond QALYs. A multi-attribute utility (MAU) model is used to assess the value of the therapy that can be used as a multiplier or in conjunction to QALYs. Architectural decisions with an impact to patient access as portrayed in **Figure 3** are explored. Additionally, the cost estimate for cell therapy delivery is considered beyond the cost of a CAR-T cell product dose. This tool could be used by different stakeholders in the CAR-T

cell therapy space to assess the impact of changes to different elements in the value chain from apheresis to patients returning home after treatment.

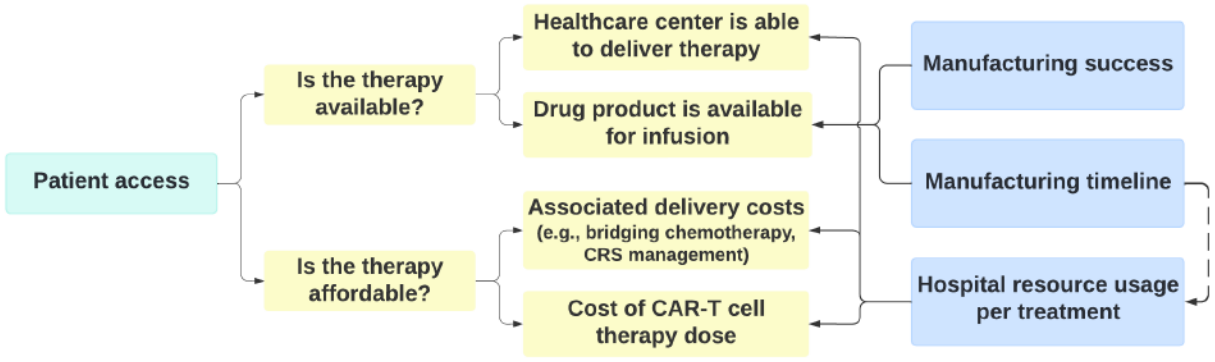

Figure 3. *Factors influencing patient access to a therapy assuming regulatory agencies have approved the therapy for commercialization. Two fundamental questions influence patient access to most therapies: "Can I receive it?", "Can I afford it?". These questions are largely influenced by three factors: the manufacturability of said therapy, the availability (i.e., can the demand be met in a timely manner), and the availability of healthcare resources needed for therapy delivery (e.g., trained personnel, hospital beds).*

2. Methodology

System decomposition for analyses

As a system of systems, the CAR-T cell therapy fulfillment system can be decomposed into 4 functional modules: collection, processing, controls & characterization, and infusion. In **Figure 4**, we can observe at Level 2 how some of the sub-functions are currently achieved at the point-of-care or hospital for the existing autologous-based therapies.

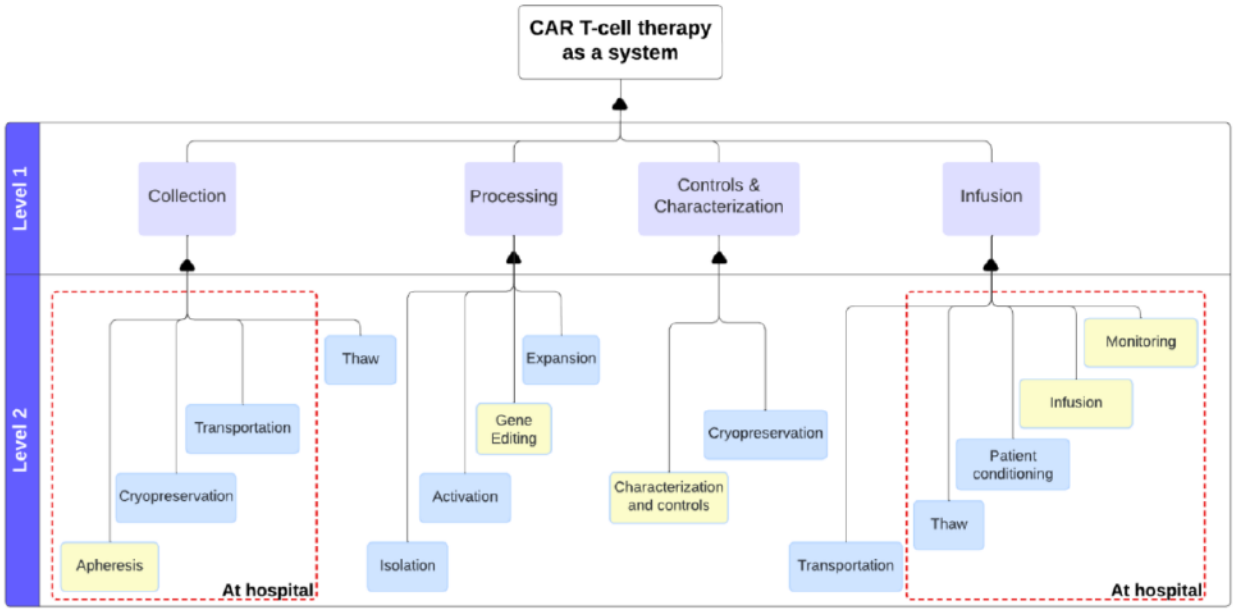

Figure 4. *CAR-T cell therapy delivery as a system and its functional decomposition. At Level 2 of the functional decomposition functions owned by hospitals can be observed. Functions in yellow are directly related to architectural decisions evaluated in the multi-attribute utility model.*

Framework

In creating a multi-attribute utility (MAU) model a set of architectural decisions must be established. The utilities, metrics, and the distribution of performance vs. utility must be developed as a function. Then an approach for how all the decisions converge towards impact on utility can be established and a weight is assigned towards each utility. Lastly, the impact on cost for each of the decisions is established.

Utility 1 – Manufacturing Success: Even after patients have secured insurance coverage and jump from the queue into CAR-T cell process, the vein-to-vein time can take over 1 month. Studies have reported that anywhere between 10-25% of patients never receive the CAR-T dose after apheresis for various reasons including manufacturing failures, multiple rounds of bridging therapies, and/or death (Baguet et al., 2024; Westin et al., 2021). This figure could be higher if we consider the number of patients who received doses considered to be safe but not meeting the manufacturing specifications. To understand the aggregate impact of all decisions, the product of all of them is calculated as observed in **Figure 5**.

Utility 2 – Hospital Usage: A study led by Ring *et al* evaluated over 1000 CAR-T treatments and estimated an overall treatment time of 30 days. This estimate includes an estimated 20 days of in-patient hospital days (Ring et al., 2022). While the estimate for in-patient stays post-treatment is in good agreement with other studies (Kenzik et al., 2022), it does not account for the weeks (>3) patients need to wait for insurance approval and for the engineered cells to arrive for infusion. As observed in **Figure 5**, the total sum of days added or subtracted from the median timeline is based on all individual architectural decisions.

Utility 3 – Vein-to-vein Timeline: At present, it takes on average 5-7 weeks for patients to be considered suitable for undergoing a CAR-T cell therapy treatment and receiving a dose of the drug product. It can take more than 3 weeks from the moment apheresis is sent to the manufacturing to the arrival of the genetically modified T-cell product back at the healthcare center. Chen *et al.* have looked at the impact these long timelines can have on patient access (Chen et al., 2022). To account for the value of drug access at the time of patient enrollment, we will introduce a utility function based on a Kaplan-Meier curve generated with synthetic data.

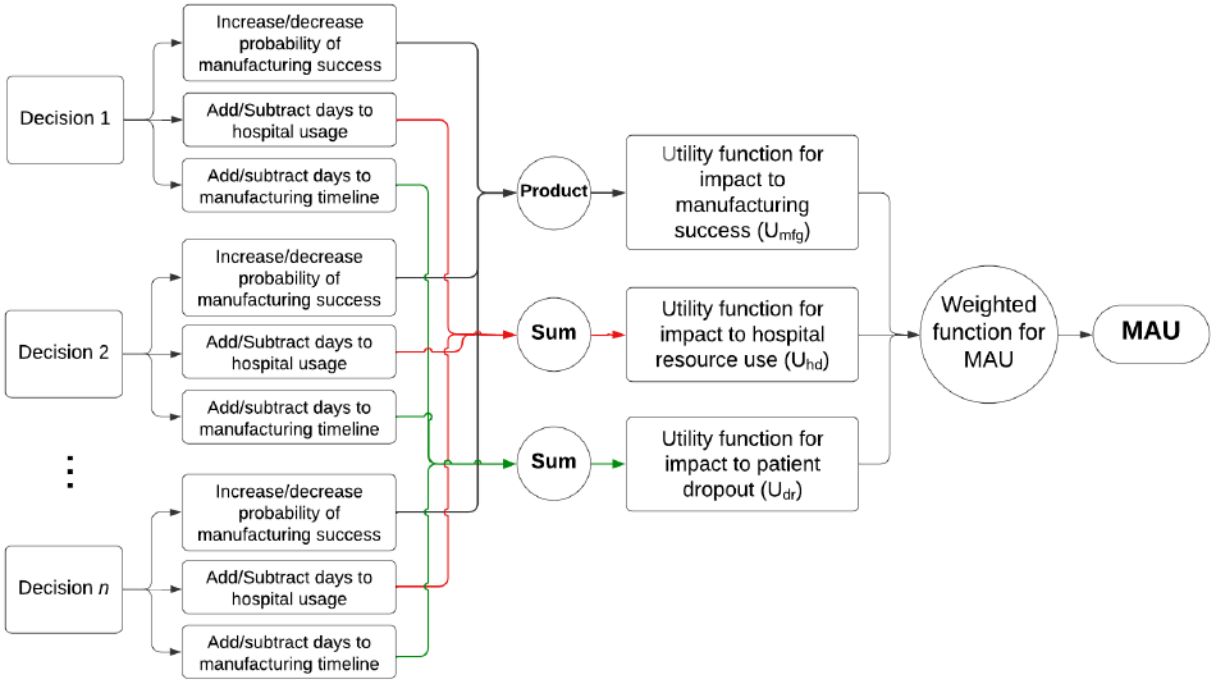

Figure 5. *Utility model flow diagram*

Patient costs: The costs associated with the therapy can be estimated to be around $450k for each dose. Here, we will assume that each decision will introduce a multiplier to these costs that will either increase or decrease costs for the patient. Additionally, the use of hospital resources will also be accounted for as a factor of $10k per day of hospital use (Saenger et al., 2022).

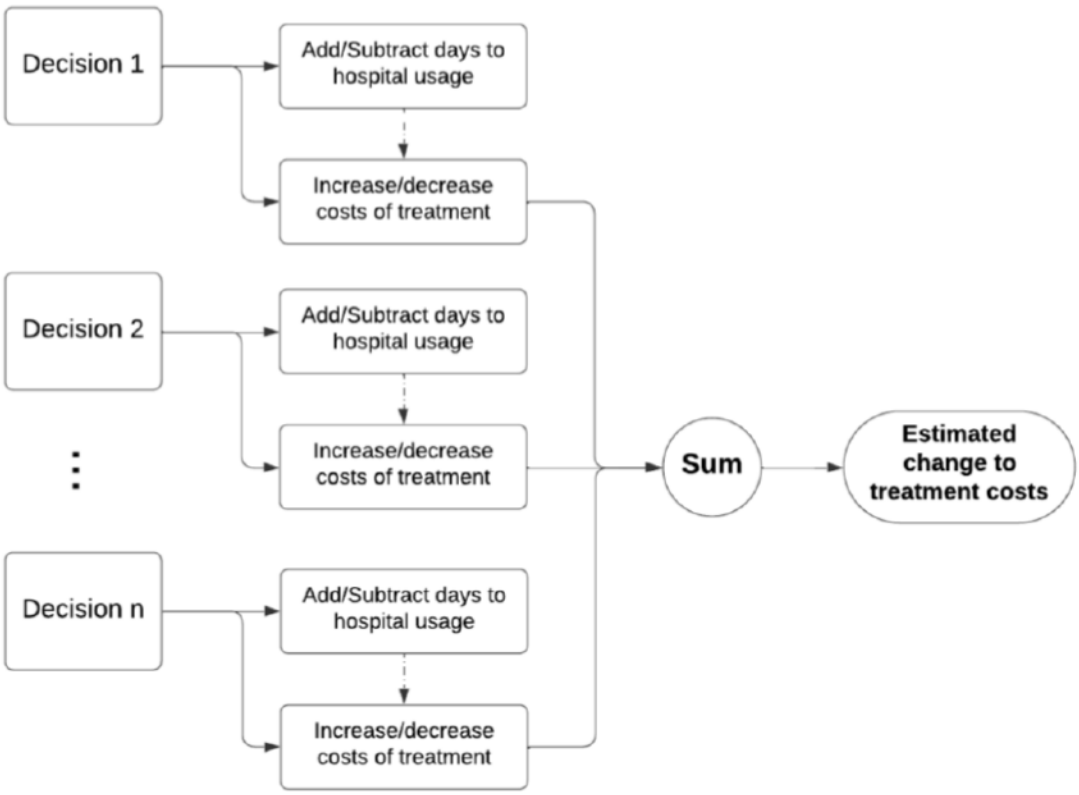

Figure 6. *Logic for impact of costs of each architectural decision. Each decision may increase or decrease manufacturing costs for the therapy. Additionally, hospital usage will accounted for independently with respect to its impact on overall costs of the treatment.*

Decisions to be considered in MAU:

- Cell Source: Today, all commercially approved CAR-T cell therapy products are based on autologous cell therapies. Allogeneic options are expected to increase the availability of this fundamental raw material in the supply chain. Matched donors have already been explored and is an option that could increase the availability of cells (i.e., apheresis is now performed on a healthy subject) and reduce lead times. A cell bank made up of “chassis” cells that are known to be hypoimmune could be considered the ultimate raw material given that availability

could be scaled and batches for could be much larger for each patient – leading to redundancies that don't exist today (Gribben et al., 2022). The latter option is also expected to substantially reduce costs for raw materials and other aspects of the manufacturing process through standardization.

- Gene editing approach: At present, all commercial options are based on viral transfection approaches. Moving forward, the field of cell and gene therapies is investing substantial resources towards non-viral gene editing approaches to lower the burden on costs. As of today, most non-viral gene editing approaches have struggled to meet the technical requirements necessary to produce a CAR-T cell therapy which will be reflected by a negative impact on manufacturing utility when considering non-viral approaches in the model.

- Process Controls: Moving away from the existing manual controls would significantly lower manufacturing costs. However, at some point, developing the technology for fully automated systems is likely to come at a cost increase for a CAR-T cell therapy dose rather than a decrease In the model presented in this study, automation will be assumed to improve manufacturing success by reducing the probability of user error.

- Logistics: The lack of coordination between drug manufacturers and hospitals eventually puts a significant burden on patients by extending the timeline to treatment and increasing hospital costs. A predictive logistics system is likely to lower costs per treatment while significantly reducing the time to treatment for most patients. However, in the case of cell banks, this is likely to be significantly less of an issue as most adaptive cell therapies could become "off-the-shelf."

- Post-intervention monitoring approach: As more medical centers gain experience with these novel therapies, the decision to send patients to a nearby residence observation becomes more salient (Kirby et al., 2022; Mikhael et al., 2022). This is

likely to increase patient access by reducing the usage of critical hospital facilities and staff per patient treatment, while also reducing costs.

- Infusion setting: A large debate across the community, it is known that for these therapies to scale the field must decide to either 1) expand the capacity of existing cell therapies centers of excellence, or 2) decentralize the infrastructure such that patients can receive treatment in smaller, specialized centers, within a reasonable proximity of their communities. While the latter could significantly increase access to patients, a monumental effort would be required to train all the relevant staff – a major challenge in the field – across that would run these operations in smaller, local centers (Myers et al., 2021).

Table 2. Summary of options for each decision. The existing architecture is underlined.

Decision	A	B	C
Cell source	Autologous	Allogeneic (Donor)	Allogeneic (cell bank)
Gene editing approach	Viral	Non-viral	-
Controls automation	Manual	Semi-automated	Automated
Logistics methods	Reactive	Predictive	-
Post-intervention monitor	On-site	Off-site	-
Infusion setting	Centralized	Decentralized	-

Constraints and assumptions

The model assumes that all presented architectures are generated by compatible decisions that are technologically feasible. It does not account for the probability of success that the architectural elements can be achieved within a reasonable timeline nor the costs required for development of these technologies. Additionally, the model assumes that each architectural decision exists in an independent domain but this is unlikely to be the case in practice. For instance, while viral and non-viral cell engineering approaches may appear as mutually exclusive, many researchers are exploring hybrid approaches for viral gene knock-in's and non-viral knock-outs. Lastly, the scope of

logistics for this model begins at procurement of raw materials (i.e., apheresis) and ends at infusion.

The model is created with the following assumed values taken from the literature:

- A baseline cost of $450k per treatment, which includes the cost of a CAR T-cell therapy dose(Mark G. Kuczewski, 2019; Potnis et al., 2023).
- A baseline for manufacturing success of 80% (Baguet et al., 2024).
- A baseline for hospital usage of 56 days (Ring et al., 2022). This assumes the time is distributed pre- and post-infusion and that some of the time is blocked by the hospital as they await for the drug product to arrive.
- A baseline vein-to-vein timeline of 21 days was assumed.

Lastly, some dependencies need to also be considered for model creation:

- Cell sources: An Allogeneic Donor option assumes the donor needs to be reached out to at the time of patient enrollment.
- Cell sources: An Allogeneic cell bank would negate the need for predictive logistic methods as it would become an off-the-shelf therapy

The utility functions are presented in **Figure 7** cover a space of negligible utility (~0) to the highest possible value add (~1). It assumes that existing architectures based on the design below provide 50% of the total utility to patients. Of note, as observed in **Figure 7** (Right), no utility is expected from a therapy that can only be successfully manufactured 50% of the time, which is based on the impact this failure rate could have on autologous therapies. Arguments could be raised in favor or against these assumptions, but this is beyond the scope of this thesis.

The following sigmoid function was used to represent the utility for varying levels of manufacturing success (U_{mfg}),

$$U_{mfg} = \frac{U_{mfg,max}}{1+e^{k(X_0-MS)}} \quad (1)$$

Where $U_{mfg,max}$ represents the maximum possible utility (set to 1), k defines the sharpness of the transition zone (set to 20), X_0 defines the midpoint for the transition zone (set to 0.8), and MS is the manufacturing success for a given architecture.

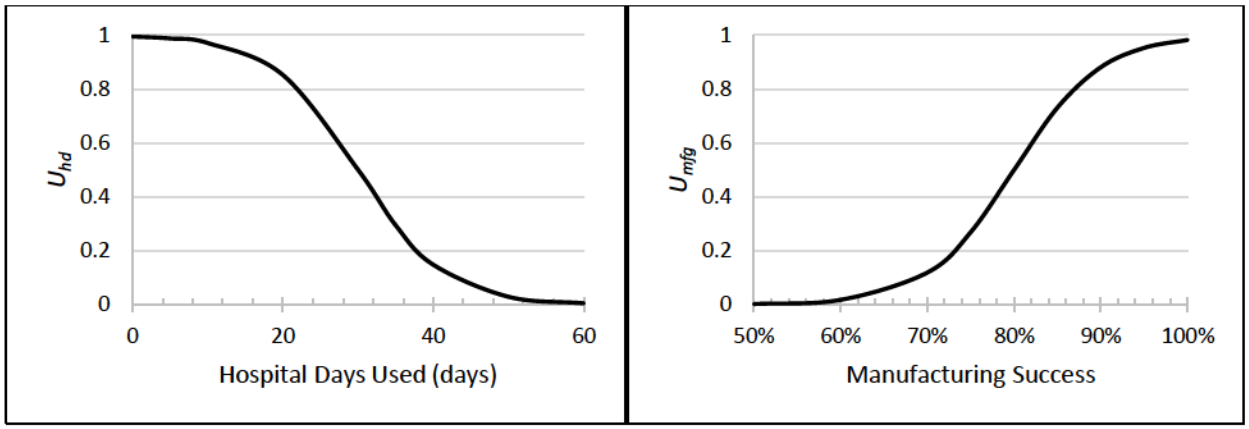

Figure 7. *Utility functions for* ***Left)*** *hospital resources used as measured by days in hospital, and* ***Right)*** *manufacturing success.*

The following function was used to represent the utility for the number of hospital days used (U_{hd}) in therapy fulfillment,

$$U_{hd} = \frac{U_{hd,max}}{1+e^{-k(HD_0-HD)}} \quad (2)$$

Where $U_{hd,max}$ represents the maximum possible utility (set to 1), k defines the sharpness of the transition zone (set to 0.175), HD_0 defines the midpoint for the transition zone (set to 30), and HD is the number of hospital days expected to be used by an architecture of interest.

The utility function for vein-to-vein timeline (U_{vtv}) is described by a Kaplan-Meiers curve in **Figure 8**.

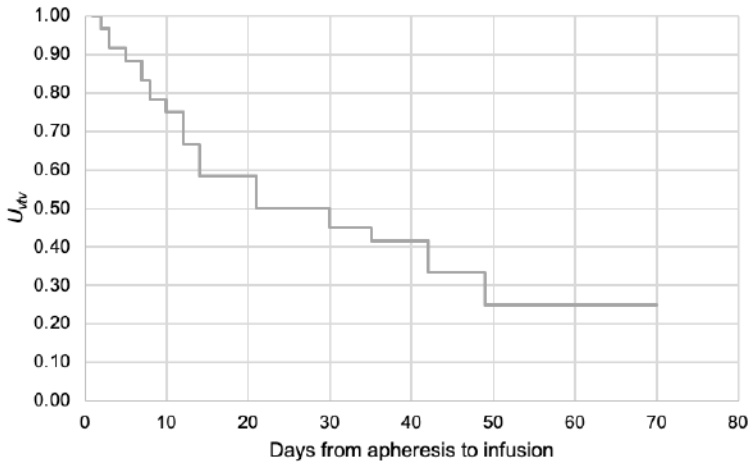

Figure 8. *Utility function for vein-to-vein timeline based on expected patient dropout.*

Table 3. *Percent Change in Manufacturing Probability of Success Associated with CAR-T Cell Therapy*

Decisions' Effect on: Manufacturing success (multiplier for baseline)						
Decision	**A**	**A-%**	**B**	**B-%**	**C**	**C-%**
Cell source	Autologous	1	Allogeneic (donor)	1.05	Allogeneic (bank)	1.2
Gene editing approach	Viral	1	Non-viral	0.9		
Process controls	Manual	1	Semi-automated	1.1	Automated	1.05
Logistics methods	Manual	1	Predictive	1.1		
Post-intervention monitor	On-site	1	Off-site	1		
Infusion setting	Centralized	1	Decentralized	0.95		

Table 4. *Changes in Hospital Resource Usage Based*

Decisions' Effect on: Hospital usage (Days for hospital stay + reserved beds)						
Decision	**A**	**A-%**	**B**	**B-%**	**C**	**C-%**
Cell source	Autologous	1	Allogeneic (donor)	-10	Allogeneic (bank)	-15
Gene editing approach	Viral	1	Non-viral	5		
Process controls	Manual	1	Semi-automated	-2	Automated	3
Logistics methods	Manual	1	Predictive	-3		
Post-intervention monitor	On-site	1	Off-site	-7		
Infusion setting	Centralized	1	Decentralized	10		

Table 5. Changes in manufacturing timeline

Decisions' Effect on: Vein-to-vein timeline (manufacturing timeline)						
Decision	**A**	**A-%**	**B**	**B-%**	**C**	**C-%**
Cell source	Autologous	1	Allogeneic (donor)	-10	Allogeneic (bank)	-15
Gene editing approach	Viral	1	Non-viral	5		
Process controls	Manual	1	Semi-automated	-2	Automated	3
Logistics methods	Manual	1	Predictive	0		
Post-intervention monitor	On-site	1	Off-site	0		
Infusion setting	Centralized	1	Decentralized	0		

Table 6. Expected change in costs associated with CAR-T Cell Therapy delivery as a multiplier

Decision	**A**		**B**		**C**	
Cell source	Autologous	1	Allogeneic (Donor)	0.9	Allogeneic (cell bank)	0.5
Gene editing approach	Viral	1	Non-viral	0.7		
Controls automation	Manual	1	Semi-automated	0.9	Automated	1.1
Logistics methods	Manual	1	Predictive	1.1		
Post-intervention monitor	On-site	1	Off-site	0.7		
Infusion setting	Centralized	1	Decentralized	0.9		

3. Results

A total of 119 different architectures were evaluated in the model. Most of the resulting architectures offer a combined cost and performance improvement in relation to the standard CAR-T cell therapy delivery system, which is presented as a triangle in **Figure 11**. With the set of assumptions and inputs presented in section 2, utility and cost outputs are most sensitive to the cell source decision (i.e., allogeneic donor cells, autologous cells). Of note, no architecture results as a worse trade off when compared to the standard CAR-T cell therapy architecture and no architecture has a utility of less than 0.25. Given the inputs and assumptions used in this model, one could conclude that no architecture

would result in patient costs lower than $150,000 (see **Table 7**), which means that none of the proposed architectures would become cost-competitive with an antibody therapeutic.

The sensitivity in **Figure 9** revealed that the choice of cell source, such as autologous versus allogeneic cells, had the most significant impact on the overall cost to the patient undergoing CAR-T cell therapy, with autologous cells being substantially more expensive due to the complex manufacturing process required for each individual patient. Additionally, the approach taken for post-treatment monitoring, whether inpatient hospitalization or outpatient monitoring, was identified as the second highest cost driver, as inpatient stays contribute substantially to the non-drug costs associated with CAR-T cell therapy administration.

Table 7. Summary of model results

Max costs (USD)	544,500
Lowest costs (USD)	163,296
Shortest timeline (days)	28
Longest timeline (days)	71
Shortest vein-to-vein timeline (days)	3
Longest vein-to-vein timeline (days)	26
Highest % Manufacturing Success (days)	1
Lowest % Manufacturing Success (days)	0.576

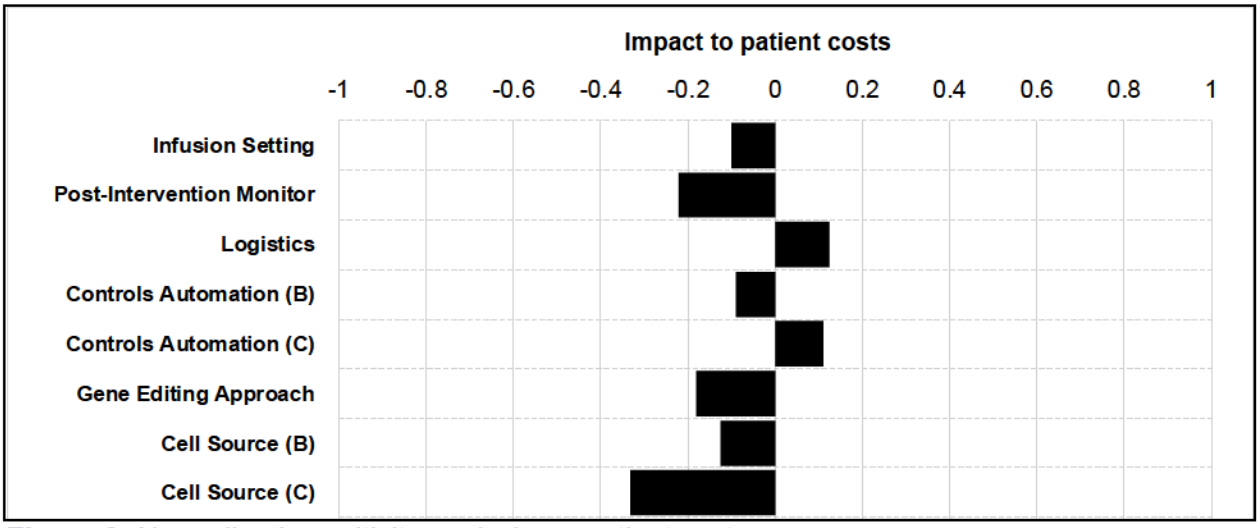

Figure 9. *Normalized sensitivity analysis on patient costs.*

The sensitivity analysis as presented in **Figure 10** indicated that the choice of cell source, whether autologous or allogeneic, had the most significant impact on the overall utility of CAR-T cell therapies to the patient population, with allogeneic cell products potentially

offering broader applicability and faster treatment turnaround times. Additionally, the gene editing approach utilized, such as viral vector transduction versus genome editing techniques like electroporation, emerged as the second most influential factor affecting patient utility, as different methods can impact factors like product yields and safety profiles. Furthermore, the logistics involved in managing the time-sensitive transportation and handling of patient cells and final CAR-T cell products played a crucial role in determining the feasibility and convenience of delivering these therapies to a wider patient population.

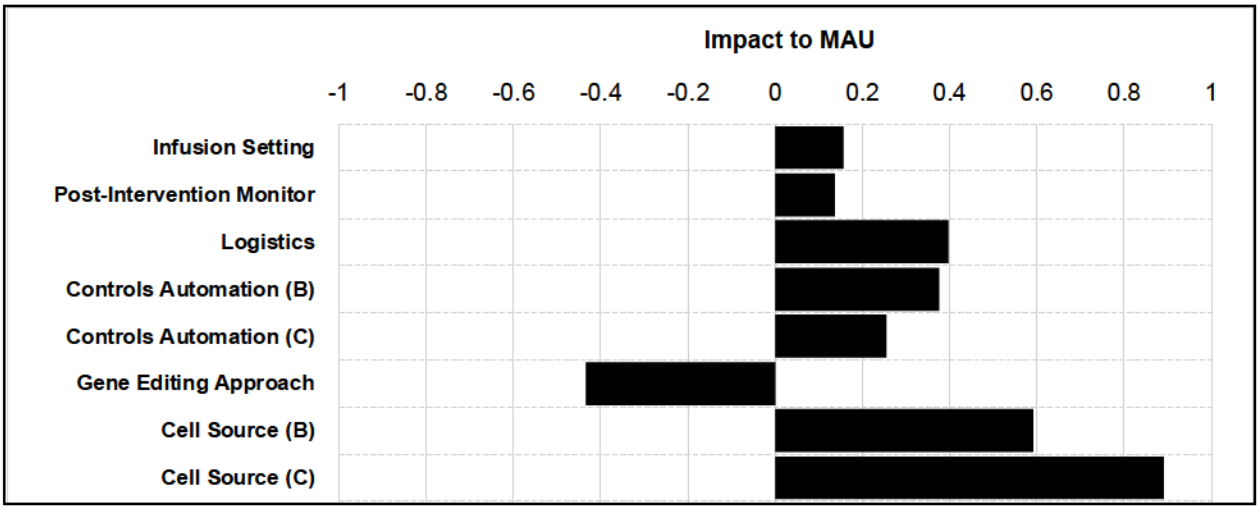

Figure 10. *Normalized sensitivity analysis on multi-attribute utility (MAU).*

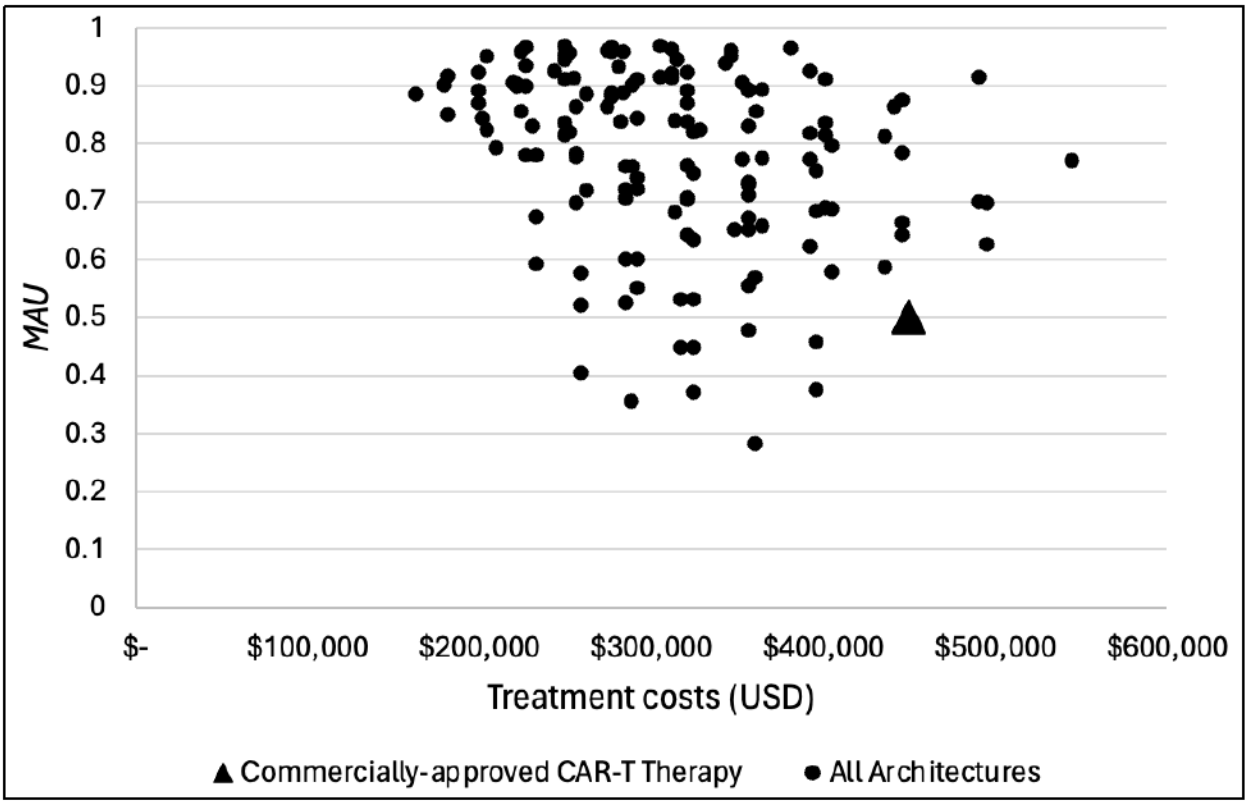

Figure 11. *Multi-attribute utility analysis showcasing standard architecture for CAR-T cell therapy fulfilment (black triangle).*

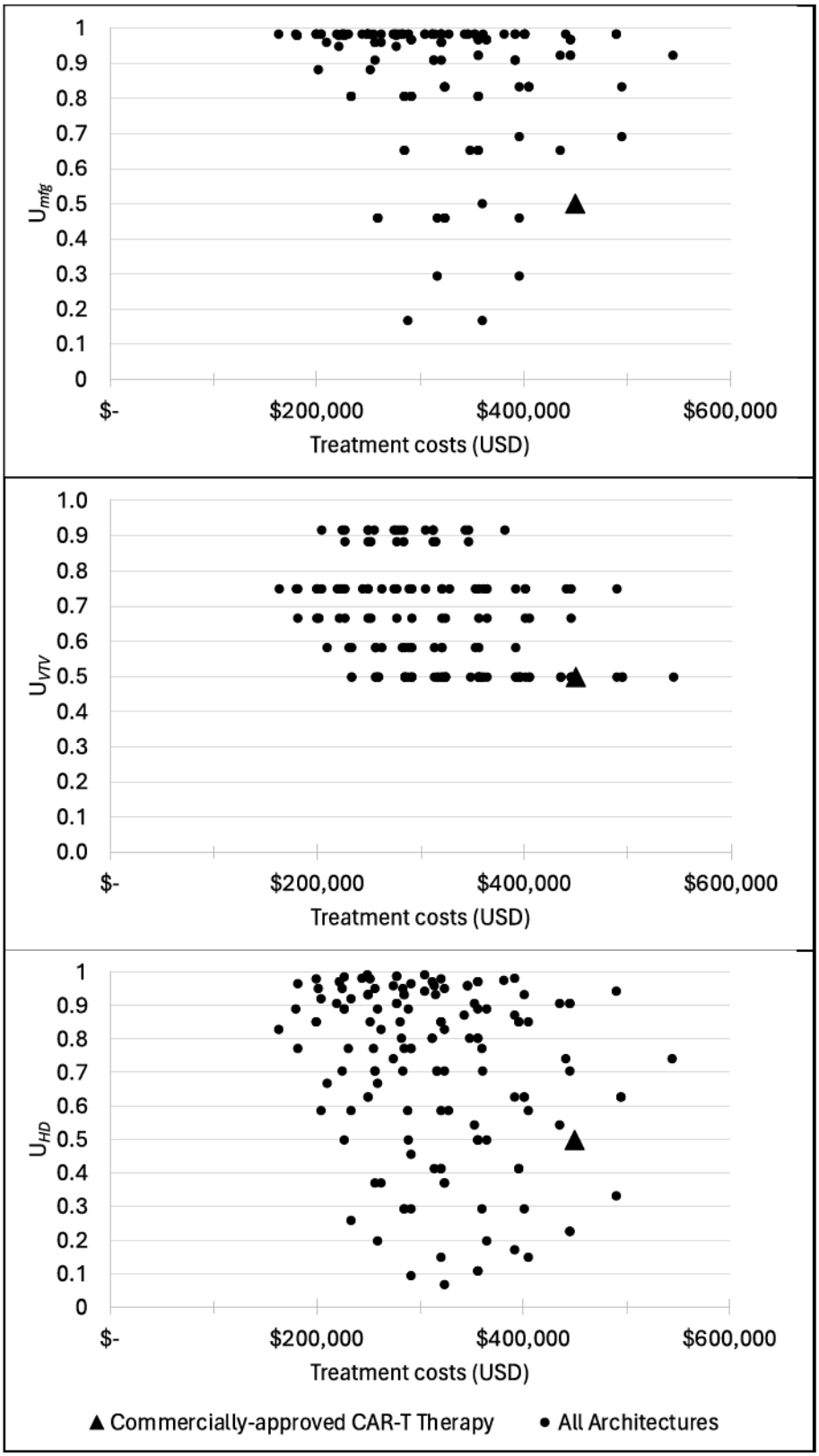

Figure 12. *Individual utility results. Top) Results of utility as a function of manufacturing success; Middle) Utility as a function of vein-to-vein timeline; Bottom) Utility as a function of hospital resource use as measured by days.*

As observed in **Table 7**, the range of costs across all architectures exceeds USD400,000. The total timeline ranges by almost 6 weeks while the vein-to-vein timeline can range by 3 weeks with 3 days as the shortest vein-to-vein timeline. Close to 40% of all architectures were expected to achieve near 100% manufacturing success with respect to drug product reaching the patient, which is largely a result of cell source (more abundant healthy cells) and improved process controls.

At the top of **Figure 12**, it can be observed that most architectures neighbor the saturation point (100%) for the utility in manufacturing success. Because not all decisions have an impact on vein-to-vein time, it can be observed in **Figure 12** (Center) that the results are coarser and in a horizontal pattern. Conversely, most decisions have an impact on hospital resource utilization. There is a wide distribution of results, which is an attractive space for exploration. This last insight which is clearly observed in the bottom graph of **Figure 12** is of critical importance because at present, there are not enough resources in the US healthcare system to support widespread adoption of cell therapies (Gatwood et al., 2024).

The impact of cell source based is such that three distinct parent fronts can be identified for each option with no overlap. This is typically indicative of a potentially new technological paradigm with changes in figures of merit for the field (de Weck, 2022). Of note, while all three curves presented in **Figure 13** are substantial improvements when compared to the standard approach, these are successively near one another.

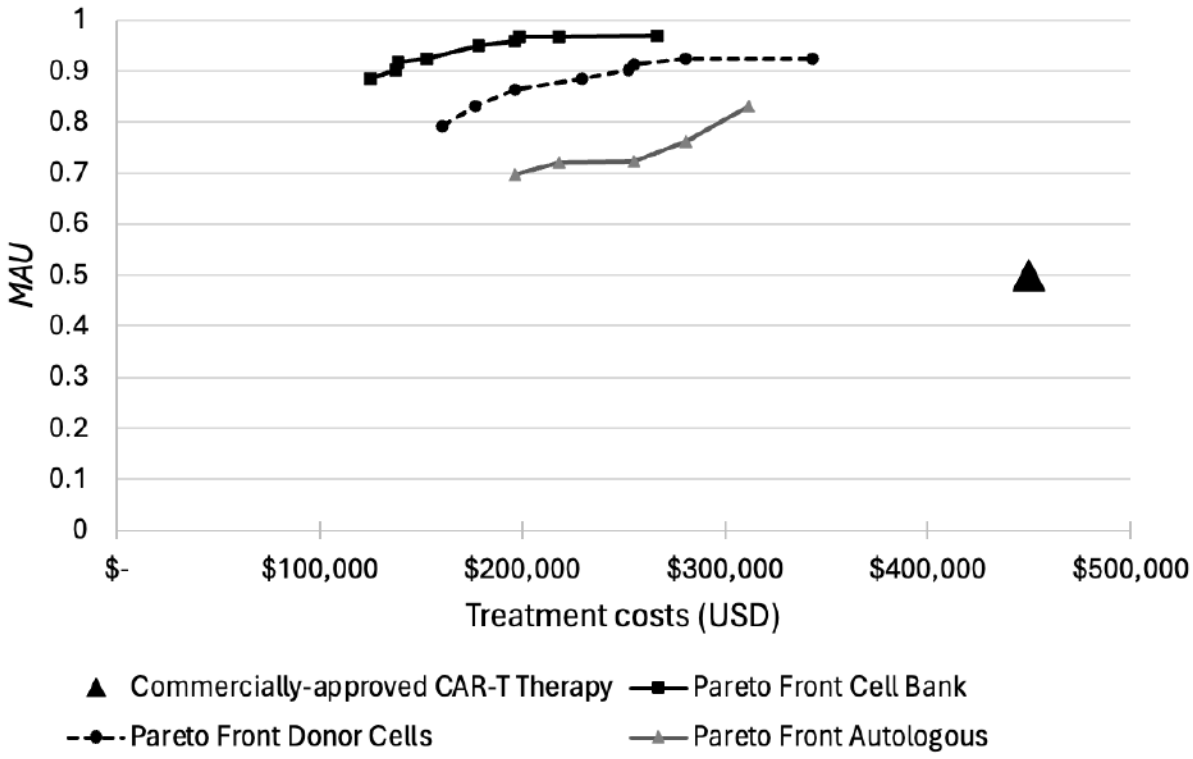

Figure 13. *Pareto fronts for architecture groups divided by cell source decision: Autologous (current standard), allogeneic donor cells, and allogeneic cells from a cell bank.*

4. Discussion

While one could assess that the use of a cell bank would radically transform the way CAR-T cell therapies are made and delivered to patients, there may be substantial opportunities to increase patient access to these therapies without changing cell sources. As observed in **Figure 13**, even within autologous cell therapies there are substantial opportunities to lower costs to the patient and increase access. Taking two architectures from **Figure 13** based on autologous cell sources we can see how automating some of the processes related to process controls as well as reductions in the time patients spend in a hospital setting could have a significant impact on costs to patients (**Table 8**).

Table 8. *Examples CAR-T cell therapies therapy architectures based on autologous cell sources offering potential patient access improvements.*

ID	Cell Source	Gene Editing	Controls Automation	Logistics	Post Monitor	Infusion Setting	Costs (USD)	MAU
40	Auto	Non-viral	Semi-auto	Predictive	Off-site	Decen.	196,466	0.698
39	Auto	Non-viral	Semi-auto	Predictive	Off-site	Central.	218,295	0.721

Of note, the model presented in this chapter could be transferred to different disease stages. An interesting use case would be the recent FDA approval of CARVIYTI® as a second line of therapy for the treatment of relapsed or refractory Multiple Myeloma. If the model presented here were to be used to evaluate such a decision, additional benefits/risks could be assessed. While this is likely to change the clinical impact simply by enabling access for patients at a much earlier disease state, the value of the therapy non-linearly increases as less patient dropout is likely to take place (i.e., a different Kaplan-Meier curve would be used to estimate value). It is also possible that this results in a lower manufacturing failure rate by having a higher number of relatively healthy patient immune cells for manufacturing. This may also reduce the burden on bridging chemotherapy.

But the purpose of this model is to highlight the challenges related to patient access to cell therapies as a layer above QALYs and cost-effectiveness. The above-mentioned approval as a second line of treatment is likely to worsen challenges related to hospital resource availability; For that, a deeper investment on ambulatory centers and post-therapy monitoring technologies are needed.

In the use case presented above, one can evaluate over a hundred architectures to provide valuable insights for decision-makers by helping them understand the downstream and upstream impacts of a particular decision across multiple metrics or utilities of interest. This multi-attribute utility framework can aid in building R&D pipelines, commercialization strategies, and capacity planning for healthcare networks. This holistic approach allows decision-makers to evaluate the ripple effects of their choices on

different aspects of the system, such as manufacturing processes, logistics, patient outcomes, and resource allocation. For instance, businesses committed to the development of donor-based allogeneic cell therapies could look at the impact of their strategy by focusing on other system-level nodes or decisions. As can be observed in **Figure 14**, the synthetic data used in this model would suggest that for donor-based therapies the approach taken by hospitals towards post-infusion monitoring would define dominant architectures.

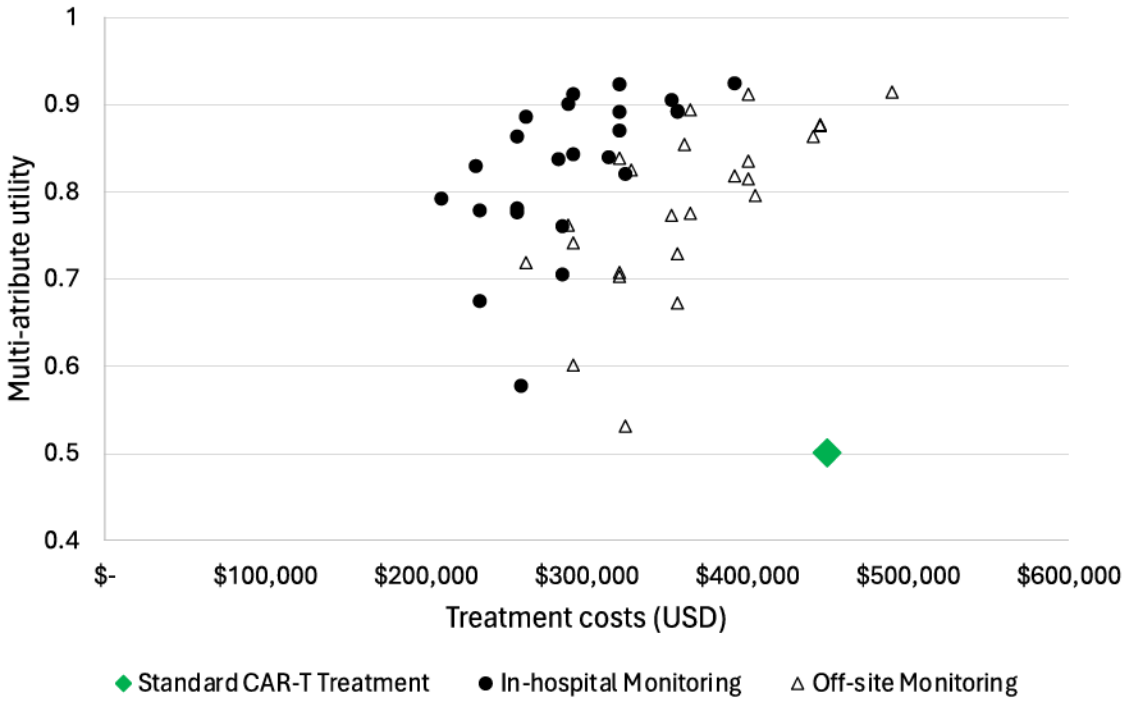

Figure 14. *Trade space for donor-based allogeneic CAR-T cell therapies.*

For instance, the multi-attribute utility framework could help pharmaceutical companies assess the impact of different gene editing approaches or cell sources on factors like costs, reimbursement strategy, manufacturing fulfillment timelines, and ultimately, patient access, which is the focus of the use case. Similarly, healthcare networks could leverage this framework to understand how different post-infusion monitoring strategies might influence resource utilization and overall treatment costs. This approach seamlessly scales by adding further decision points and other utilities of interest.

There are some necessary considerations in identifying opportunities for implementing this framework. As complexity decreases, the value of the framework also decreases thus stakeholders must consider the complexity and validity of the data available prior to implementing this framework for decision-making. The objectives under consideration should be conflicting or in tension so that a real trade space can be developed. Lastly, and not fully explored in this study, one benefit of this framework is that quantitative and qualitative data can be used to develop a trades pace.

5. Conclusions and Future Works

Multiple studies have individually looked at different decisions evaluated in this thesis and their corresponding impact. Elements related to infusion setting and gene editing approach have been studied to understand impact on patient access (Snyder et al., 2021; D. K. Y. Zhang et al., 2023). However, this could be the first implementation of a multi-attribute utility framework evaluating the downstream and upstream effects of architectural decisions across various stages of the CAR-T cell therapy lifecycle.

A multi-attribute utility analysis framework, while useful for evaluating and comparing different options based on multiple criteria, has certain limitations. One key shortcoming is the deterministic nature of the analysis, which fails to account for the inherent uncertainties and risks associated with complex systems like cell therapy manufacturing and delivery. A stochastic analysis that incorporates the probability of success for each architectural option would provide a more comprehensive assessment, particularly when considering the technological complexities involved in approaches such as gene editing or logistics management.

More presently, the model would benefit from the use of inputs extracted from real-world evidence along with assessing the probability of success for each architectural decision. This could be achieved, as an example, through Monte-Carlo analysis in which a probability distribution function is allocated for options within each decision. On the surface, options for cell source would have a high degree of certainty for autologous sources, a lesser probability of success for allogeneic donor-based cell sources (these

have already shown success in clinical trials), and a low probability of success for the lesser proven option of a cell bank.

The multi-attribute utility framework assumes a centralized decision-making process, which may not accurately reflect the reality of cell therapy ecosystems. Different stakeholders, such as hospitals, regulatory bodies, and pharmaceutical companies, often have varying degrees of influence over specific aspects of the system. For instance, while hospital staff may have little control over the gene editing approach used in CAR-T cell manufacturing, they play a crucial role in determining the post-infusion monitoring protocols. Conversely, pharmaceutical companies may have limited influence on how hospitals choose to monitor patients after CAR-T infusion, despite having a significant stake in the overall success of the therapy. This fragmentation of decision-making authority across multiple stakeholders poses challenges in terms of aligning incentives and priorities, which may not be adequately captured in a traditional multi-attribute utility analysis.

Lastly, the framework presented in this study could be expanded for shared decision-making. The framework sheds light on preferences from each stakeholder, typically through techniques like rating scales, pairwise comparisons, or direct utility assessments. This ensures that the relative importance assigned to each attribute reflects the stakeholders' values and priorities. A model in which utilities have evolved from individual stakeholder perspectives (i.e., payers vs. healthcare providers) can provide a structured pathway for negotiations and prioritization. Of personal importance, and when considering the perspective of different stakeholders, this framework can be easily adapted by innovators considering the challenges with providing access to groundbreaking therapeutic modalities in developing nations.

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