

Optimizing CAR-T therapy delivery in the Italian healthcare system: economic and organizational insights in follicular lymphoma

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ABSTRACT

Introduction: Follicular Lymphoma (FL) is the second most common lymphoid malignancy, with 20% of patients progressing within 24 months of first-line therapy. Chimeric antigen receptor T-cell (CAR-T) therapies have improved outcomes in relapsed or refractory FL, yet their use requires significant resources and complex care pathways. Although outpatient CAR-T programs have shown promising safety and feasibility, limited evidence exists on their organizational, economic, and ethical implications in the Italian healthcare setting. This study compares the current CAR-T pathway for FL patients with a virtual optimized scenario incorporating outpatient management in selected phases.

Methods: A multidimensional framework was applied to assess differences between standard in-hospital care (Standard Pathway) across three Italian public hospitals (Genoa, Rome, Perugia) and a partially outpatient model (Efficient Pathway). Literature review and expert consultations validated existing practices and informed optimization criteria. Structured surveys provided quantitative and qualitative inputs. Economic modelling estimated three-year full costs using patient-level data, while organizational and ethical aspects were evaluated through Likert scales.

Results: Efficient Pathway shifted bridging therapy, post-infusion monitoring, and follow-up to outpatient settings, reducing total costs from € 611,070 (As-Is) to € 497,421 (To-Be). Organizational benefits included increased bed capacity (average score: 4.9/6) and consumable utilization (average score: 4.3/6), while ethical gains were observed in treatment accessibility (average score: 4.3/6).

Conclusions: Introducing outpatient management into CAR-T phases may provide economic, organizational, and ethical advantages when supported by clear eligibility criteria and structured monitoring. As CAR-T indications expand, pathway redesign will be essential to ensure equitable access and sustain healthcare system resources.

Keywords: CAR-T, Economic impact, Follicular Lymphoma, Organizational impact, Outpatient

Introduction

Follicular lymphoma (FL) is the second most common subtype of non-Hodgkin lymphoma (NHL) after diffuse large B-cell lymphoma (DLBCL), accounting for approximately 20% of all NHL diagnoses (1). It is an indolent B-cell lymphoproliferative disorder with an estimated incidence in Italy of

about 2.8 cases per 100,000 inhabitants per year. FL primarily affects older adults, with a median age at diagnosis between 60 and 65 years, and it shows an almost equal distribution between sexes (2).

Despite significant therapeutic advances over the past two decades—particularly with the introduction of anti-CD20 monoclonal antibodies and chemoimmunotherapy—FL remains a relapsing-remitting disease. Approximately 20% of patients experience disease progression within 24 months of first-line treatment (POD24) (3), and subsequent relapses are often characterized by shorter remission durations, reduced responsiveness to treatment, and increased clinical aggressiveness (4).

The advent of Chimeric Antigen Receptor T-cell (CAR-T) therapy has transformed the therapeutic landscape for several B-cell malignancies, including FL (5). Pivotal clinical trials (6,7) and real-world studies (8,9) have demonstrated

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high overall response rates and durable remissions in heavily pretreated FL patients. In Italy, CAR-T therapies for FL are reimbursed after two or more lines of prior treatment by the Italian Medicines Agency (AIFA) (10) and recommended by national scientific societies' guidelines (11).

However, the introduction of CAR-T therapy has also generated substantial organizational and economic challenges. Treatment delivery requires authorization by AIFA-accredited centers, multidisciplinary coordination, specialized staff, and intensive monitoring during and after infusion (10). The current standard of care involves inpatient administration, mainly due to the potential for acute complications such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) (7). While this approach ensures patient safety, it also results in prolonged hospitalizations, high bed occupancy, and high costs for healthcare providers within the Italian National Health Service.

Recent evidence and clinical experience suggest that outpatient management of CAR-T therapy could be a feasible alternative for selected low-risk patients. Some studies indicate comparable safety and efficacy outcomes between inpatient and outpatient administration, along with improved patients' quality of life and more efficient resource utilization (12,13). Nevertheless, evidence on the organizational, economic, and ethical implications of outpatient CAR-T treatment remains limited, especially in the Italian context. Most published studies have primarily focused on clinical efficacy and product-related cost-effectiveness, leaving a substantial gap in knowledge regarding healthcare delivery models and their sustainability (12). Notably, a recent national consensus work in FL by Marchetti et al. (2025) (14) identified several organizational inefficiencies and highlighted that patient journey redesign, including improved selection and monitoring processes, is essential to ensure safe and sustainable CAR-T delivery. However, despite these insights, the economic and organizational impact of such optimized models remains unexplored in Italy.

To address these gaps, the present study applies a Health Technology Assessment (HTA) framework (15) to compare two organizational models for CAR-T management in patients with FL:

1. The inpatient-based model or Standard Pathway (As-Is).
2. A partially outpatient model optimized for resource efficiency or Efficient Pathway (To-Be).

Assuming equivalent clinical efficacy and safety, the research evaluates the economic, organizational, and ethical dimensions of implementing an outpatient-based approach. The findings aim to provide preliminary evidence supporting more efficient, patient-centered, and value-based models for CAR-T therapy delivery in Italy and similar healthcare systems.

Methods

Study design

This study adopted a methodological approach based on the principles of HTA to conduct a comparative analysis

between two alternative organizational scenarios for the management of patients with FL eligible for CAR-T cell therapy (15).

In this analysis, the term “Efficient Pathway” refers to a structured care pathway in which selected low-risk patients undergo part of the CAR-T treatment process—such as lympho-depleting chemotherapy and early post-infusion monitoring—in outpatient (without overnight hospital admission) (16). This model is implemented under strict clinical selection criteria and with continuous medical supervision. The outpatient approach in the Efficient Pathway does not replace inpatient care in high-risk or clinically unstable patients, but it represents a complementary, efficiency-oriented pathway for eligible individuals (17).

Setting and participants

The study was conducted from the perspective of hospital providers and involved three public Italian centers authorized to administer CAR-T therapy for hematologic malignancies:

- Azienda Ospedaliera di Perugia—Ospedale Santa Maria della Misericordia
- Azienda Ospedaliera Universitaria Policlinico Umberto I di Roma
- IRCCS Policlinico San Martino di Genova

At each center, a multidisciplinary CAR-T team—including hematologists, hospital pharmacists, specialized nursing staff and biologists—participated in expert consensus meetings, validated clinical-organizational contents, and provided analytical input data.

Data sources and data collection

The reconstruction of the CAR-T Standard Pathway (As-Is) and the definition of the Efficient Pathway (To-Be) were based on a combination of literature and regulatory review, empirical information collected from participating centers, and expert elicitation. In particular, multidisciplinary meetings involving hematologists, hospital pharmacists, specialized nurses, and other CAR-T team members from the three centers were conducted to validate the Standard Pathway and to define the organizational assumptions underlying the Efficient Pathway.

Data were directly collected from the three participating centers through structured surveys and included: i) The annual number of eligible FL patients treated with CAR-T therapy; ii) The distribution of activities across inpatient and outpatient settings for each phase of the pathway; iii) The average number of resource units utilized per phase (e.g., inpatient days, day-hospital/day service accesses, monitoring visits); iv) Perceived information on resource utilization, organizational processes, and ethical perceptions.

Economic data were complemented by secondary sources, specifically Zallio and Bellini (18), which provided reference values for estimating direct healthcare and overhead costs in the Italian context. In particular, these data were used to derive standardized unit costs associated with each resource item (e.g. inpatient day, day-hospital access, diagnostic procedures).

Analytic framework

The methodological design followed a sequential three-phase structure (Supplementary 1):

1. Analysis of the current Standard Pathway (As-Is): mapping of the clinical and regulatory framework for FL patients eligible for CAR-T therapy.
2. Development of the optimized Efficient Pathway (To-Be): defining an alternative pathway introducing outpatient management for selected treatment phases and identifying organizational conditions required to ensure equivalent safety and efficacy.
3. Comparative analysis (To-Be vs. As-Is): assessing the economic, organizational, and ethical impact of the Efficient Pathway compared with the current Standard Pathway.

Economic analysis

The economic evaluation estimated direct healthcare and overhead costs for two scenarios:

- Standard Pathway (As-Is): all patients managed through standard inpatient care across all major phases.
- Efficient Pathway (To-Be): a proportion of patients managed in an optimized outpatient-enabled pathway for selected phases, maintaining equivalent safety and efficacy.

A patient-level costing (PLC) approach was used, calculating full costs per phase and projecting costs over a three-year horizon. Total costs were derived by combining unit costs with center-specific activity volumes, including inpatient days, day-hospital/day-service visits, procedures, and diagnostics.

Unit costs were obtained from a published Italian cost-accounting analysis (18), while activity volumes and organizational allocation of resources were derived from primary data collected in the participating centers. This hybrid approach allowed the model to maintain external consistency in cost estimation while preserving internal validity with respect to clinical practice.

Assumptions

The model was based on the following methodological assumptions:

- Hospital provider perspective, considering only direct healthcare and overhead costs.
- Clinical and safety equivalence across scenarios. This assumption was supported by the restrictive eligibility criteria applied to the selected patients included in the outpatient management model (To-Be). An accurate physician assessment was considered crucial to evaluate clinical predictive factors (e.g., baseline disease burden, comorbidities, number of prior therapy lines, pre-infusion biomarker levels) as well as biopsychosocial elements (e.g., patient readiness and availability of caregiver support). In addition, post-infusion monitoring safeguards—such as structured rapid re-admission pathways, targeted patient and caregiver education, and telemonitoring tools—were considered crucial to further reinforce safety standards.

- Clinical and organizational inputs provided by experts from participating centers were validated through multidisciplinary expert meetings.
- Economic values derived from Zallio and Bellini (18) are deemed transferable to the analyzed contexts.
- Unit cost estimates are assumed to be transferable across the participating centers due to similarity in organizational structures and cost-accounting practices within Italian public hospitals.
- FL is considered a lower-complexity indication compared with diffuse large B-cell lymphoma, with expected lower incidence of severe complications and reduced need for intensive care (19).

Model inputs

The economic model integrated two complementary categories of inputs: economic inputs and clinical inputs, which jointly determined the comparative cost estimation between the As-Is and To-Be scenarios.

Economic inputs

To compare the two organizational scenarios, all phases of the CAR-T care pathway were evaluated under two alternative management models:

1. Standard Pathway, reflecting the current standard of care in Italy, where most clinical phases are delivered under ordinary inpatient hospitalization.
2. Efficient Pathway, representing the optimized organizational model proposed in the To-Be scenario, where selected phases are shifted to outpatient or day-hospital settings for clinically eligible patients, while hospitalization is reserved for phases requiring intensive monitoring or for patients not meeting outpatient criteria.

Due to the lack of uniformly available center-specific cost-accounting data, unit costs were derived from Zallio and Bellini (18) to quantify the economic implications of these two approaches. This study provides data on full production costs for CAR-T processes within Italian hospital settings. These values include direct costs (medical and nursing personnel, pharmacological therapies, diagnostics, inpatient stay or outpatient activities, and specialist services) and indirect costs, incorporated through a standardized overhead mark-up of 25-27%, in line with Italian cost-accounting practices.

More specifically, Zallio and Bellini (18) applied an activity-based costing (ABC) (20,21) approach to identify, for each phase of the CAR-T pathway, the set of clinical activities performed and the corresponding resources consumed (e.g., human resources, pharmacological therapies, medical devices, diagnostics, and other operating costs).

In the present study, these phase-level costs were used as the economic starting point. Subsequently, phase-specific cost drivers (e.g., number of inpatient days or number of day-hospital/day-service accesses) were identified and used to redistribute the costs across the different organizational settings considered in the model. This allowed the recalculation of the full cost associated with each phase under the Standard and Efficient pathways.

Unit costs were associated with phase-specific cost drivers such as the number of inpatient days or day-hospital/day-service accesses, allowing for consistent comparison between organizational settings. For each center, full costs were recalculated by multiplying these unit values by observed or reported activity volumes for each phase, ensuring that the model remained sensitive to real organizational practices and differences in local resource utilization. Data are shown in Table 1.

Overhead costs were incorporated into the costing model as a percentage mark-up applied to direct healthcare costs (25-27%).

A detailed breakdown of the cost-drivers, unit costs, and corresponding source is reported in Table 1 and further detailed in Supplementary data 2 and 3.

Clinical Inputs

Clinical inputs defined patient progression through the care pathway and the distribution of activities between inpatient and outpatient settings.

First, centers provided the number of eligible patients per year, which constituted the population entering the model.

Data were collected for 2024 and 2025, while projections for the third year were derived from observed growth trends, resulting in an average of 3 patients in 2024 and 5 patients in 2025 (Table 2). This distribution allowed the model to incorporate dynamic expansion in patient volumes with an estimated average of 7 patients in year 3. These volumes are consistent with the highly specialized nature of CAR-T therapy, which is delivered in a limited number of accredited centers and typically involves relatively small but increasing patient cohorts.

Second, for each phase of the CAR-T pathway, clinical experts quantified the percentage of patients managed in the inpatient versus the outpatient-enabled setting under both scenarios. These proportions varied by center and were particularly relevant for phases susceptible to outpatient transition, namely bridging chemotherapy, early post-infusion monitoring, and follow-up visits. For instance, while the As-Is scenario entailed 100% inpatient management across all phases, the To-Be scenario included outpatient transition for up to 52% of patients during bridging, 83% during early monitoring, and 83% during follow-up (Table 3).

These distributions were based on clinical eligibility criteria validated during multidisciplinary expert meetings

TABLE 1 - Summary of the cost drivers considered

Phases	Activities	Zallio & Bellini (2021)				Standard Pathway		Efficient Pathway	
		Full cost	Cost driver	Hospital Admissions/ Inpatient stay (days)	Unit cost	Hospital Admissions/ Inpatient stay (days)	Unit cost	Hospital Admissions/ Inpatient stay (days)	Unit cost
Phase I	Eligibility assessment, T-cell collection, and genetic engineering	4,660.1 €	Number of DH/DS admissions	4.0	1,165.03 €	4.0 DH/DS admissions	4,660.1 €	4.0 DH/DS admissions	4,660.1 €
Phase II	Bridging or disease-control chemotherapy (for progressing patients) – A	12,820.0 €	Days of inpatient stay	7.2	1,780.56 €	6.8 days of inpatient stay	12,167.1 €	3.0 DH/DS admissions	7,006.2 €
	Bridging or disease-control chemotherapy (for progressing patients) – B	4,670.8 €	Number of DH/DS admissions	2.0	2,335.40 €				
Phase III	CAR-T infusion/early post-infusion monitoring	55,536.1 €	Days of inpatient stay	29.1	1,908.46 €	13.5 days of inpatient stay	23,219.6 €	8.3 days of inpatient stay	15,903.8 €
Phase IV	Post-infusion follow-up	4,961.8 €	Number of DH/DS admissions	7.0	708.83 €	4.0 DH/DS admissions	2,835.3 €	5.3 DH/DS admissions	3,780.4 €

Legend. DH/DS: Day Hospital/Day Service



and ensured that variations across scenarios arose from organizational reallocation rather than differences in clinical outcomes.

TABLE 2 - Center-level patient numbers

	Center 1	Center 2	Center 3	Average
Year 1	2	2	5	3
Year 2	4	3	7	5
Year 3	6	5	10	7

Note: Values represent the number of patients with FL eligible for CAR-T therapy treated annually within the participating centers.

Model Structure and Analysis

The model followed a population-based structure, assigning all eligible patients to the Standard Pathway (As-Is) and then reassigning them to the To-Be scenario, which combined the inpatient setting with the efficient outpatient-enabled setting for eligible patients. For both scenarios, annual and cumulative costs were calculated over a three year analytic horizon. The economic impact was quantified as the cost difference between the two scenarios and expressed as the potential cost reductions from the introduction of the Efficient Pathway, both in absolute terms (€) and as a percentage (%) of the baseline cost (Fig. 1).

Sensitivity analysis

A deterministic sensitivity analysis assessed the robustness of the economic results by varying key model parameters. The analysis focused on variables with the greatest potential impact on total costs, including:

- Patient allocation to outpatient versus inpatient pathways: ±20% variation in the proportion of eligible patients managed in the To-Be scenario (22,23).
- Unit costs of key activities: ±20% changes in the cost per inpatient day, day-hospital visit, CAR-T infusion, and laboratory tests (22,23).
- Overhead cost mark-up: ±5% variation in the allocation of indirect costs (24,25).
- Patient population growth: ±10% changes in the projected number of eligible patients per year (24,25).

Each parameter was varied individually to determine its effect on total and per-patient costs. Results were presented as tornado diagrams and scenario comparisons, highlighting the parameters with the greatest influence on the economic impact of the outpatient-enabled pathway.

Organizational and ethical analyses

A preliminary assessment of organizational feasibility was first conducted to identify the enabling conditions required to safely implement the outpatient-enabled CAR-T pathway. Subsequently, the organizational and ethical dimensions of the transition to the outpatient-enabled CAR-T model were assessed as HTA domains, using a mixed-methods approach combining qualitative and quantitative tools (26). CAR-T team members from the three centers completed structured questionnaires based on two validated HTA frameworks [Mini-HTA (27) and EUnetHTA Core Model (15)]. Overall, the assessment was analytically structured into three components: (i) organizational feasibility conditions (ex-ante assessment), (ii) organizational impact (ex-post assessment), and (iii) ethical impact (ex-post assessment).

TABLE 3 - Distribution of patients managed in inpatient versus outpatient settings across the As-Is and To-Be scenarios

	As-Is		To-Be (Center 1)		To-Be (Center 2)		To-Be (Center 3)		To-Be (Average)	
	Inpatient setting	Outpatient setting	Inpatient setting	Outpatient setting	Inpatient setting	Outpatient setting	Inpatient setting	Outpatient setting	Inpatient setting	Outpatient setting
Eligibility assessment, T-cell collection, and genetic engineering	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%
Bridging or disease-control chemotherapy (for progressing patients)	100%	0%	50%	50%	30%	70%	65%	35%	48%	52%
CAR-T infusion	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%
CAR-T early post- infusion monitoring	100%	0%	0%	100%	0%	100%	50%	50%	17%	83%
Post-infusion follow-up	100%	0%	0%	100%	0%	100%	50%	50%	17%	83%



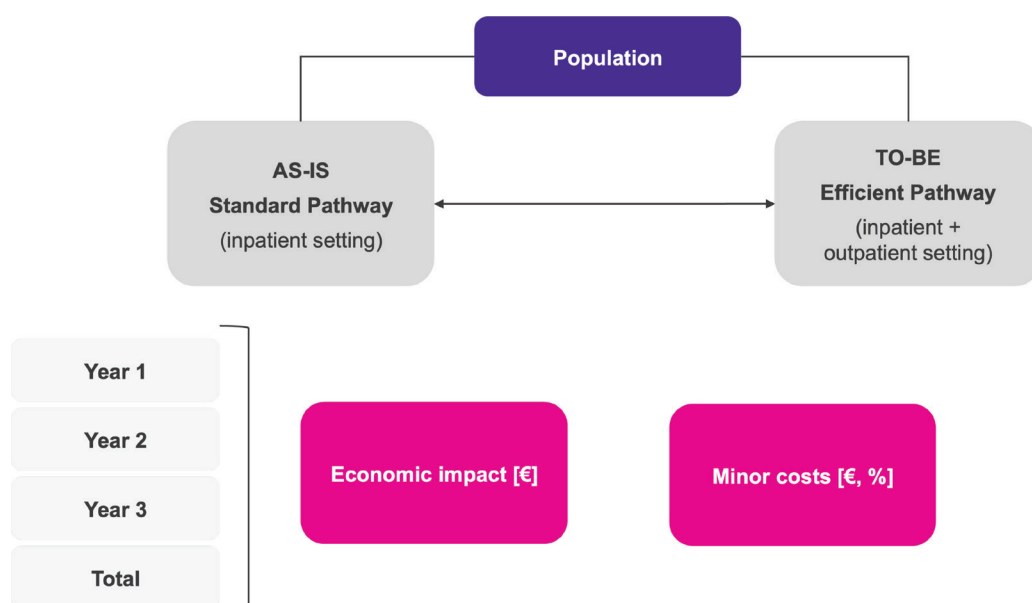


FIGURE 1 - Graphic representation of the model.

(i) Organizational feasibility conditions

Organizational feasibility conditions were evaluated ex-ante to identify the criteria required to safely enable the transition from inpatient to outpatient management for selected CAR-T patients. The assessment focused on ensuring timely access to care in case of complications, continuity of clinical monitoring, effective coordination of outpatient activities and resources, and adequate support for patients and caregivers throughout the outpatient phase, as essential safeguards to mitigate clinical and ethical risks.

Participants rated the relevance and applicability of criteria required to ensure a safe transition from inpatient to outpatient management using a 4-point forced-choice ordinal scale (from 1 to 4). This approach was chosen because the assessment focused on assessing feasibility in a directional way rather than on measuring the magnitude of change, encouraging respondents to express a clear judgement from low to high feasibility or relevance and limiting the use of neutral responses. Results were measured and presented as relevance and implementation feasibility mean scores. The full questionnaire, including all organizational feasibility conditions, is provided in Supplementary 4.

(ii) Organizational impact

Organizational impact captured the perceived ex-post effects of the Efficient Pathway compared with the Standard Pathway on hospital resources, care processes, and internal organization. The assessment explored how the outpatient model influenced resource utilization, coordination across units, internal workflows, and operational processes related to patient management and pathway implementation. The assessment was based on a structured questionnaire including specific organizational impact items covering these domains, which is reported in Supplementary Material 5.

(iii) Ethical impact

Ethical impact captured the perceived ex-post ethical implications of the Efficient Pathway compared with the Standard Pathway, with a focus on accessibility of care, patient and caregiver experience, professional–patient relationships, and perceived safety in relation to adverse event management. The assessment was conducted using a structured questionnaire including specific ethical impact items covering these domains, which is reported in Supplementary Material 6.

For both organizational impact and ethical impact, participants provided ratings using a 7-point Likert scale ranging from –3 (strong negative impact) to +3 (strong positive impact), with 0 indicating no change compared with the Standard Pathway. Raw scores were normalized to a 0-6 scale (with 3 representing a neutral impact) and visualized using target plots to facilitate interpretation and comparison across domains.

Results

Phase I—Baseline framework (As-Is scenario)

The reconstruction of the clinical–organizational As-Is pathway for FL patients eligible for CAR-T therapy was developed through a combined review of scientific and regulatory sources (28-31) and subsequently validated by multidisciplinary CAR-T teams across the three participating centers. This process confirmed that the Standard Pathway is primarily shaped by requirements specified in the applicable Summaries of Product Characteristics (SmPCs), by local standards of operation and by national regulations governing CAR-T administration. Specifically, these guidelines mandate:

- (i) lymphodepleting chemotherapy in the week preceding infusion when clinically indicated, and anesthesiologic, neurological and cardiologic assessments;

- (ii) daily post-infusion monitoring to detect early manifestations of CRS, ICANS, or other toxicities;
- (iii) physician-driven decisions regarding hospitalization during the immediate post-infusion phase;
- (iv) the requirement for patients to remain in proximity to the qualified center for at least four weeks following infusion.

Consensus meetings with CAR-T teams confirmed that Italian centers have established relatively homogeneous clinical–organizational pathways within these constraints. Through this joint reconstruction, four fundamental phases of the CAR-T workflow were identified, each characterized by distinct resource requirements and monitoring needs:

1. Eligibility assessment, T-cell collection, and genetic engineering: typically delivered through coordinated outpatient services and specialized apheresis procedures.
2. Bridging or disease-control chemotherapy: administered to patients with disease progression while awaiting CAR-T manufacturing.
3. CAR-T infusion and early post-infusion monitoring: the phase with the highest risk of acute AEs and the strongest rationale for standard inpatient management.
4. Post-infusion follow-up and outpatient surveillance: routine clinical evaluations, laboratory tests, and toxicity monitoring over the weeks after discharge.

This phased analysis of the CAR-T pathway provided the foundation for Phase II, enabling the identification of steps suitable for reorganization in the To-Be scenario and

supporting the assessment of the potential clinical, economic, and organizational impacts of these changes.

Phase II—Development of the Efficient Pathway (To-Be)

Phase II focused on defining the Efficient Pathway (To-Be) based on an outpatient-enabled model developed through iterative multidisciplinary expert discussions. This phase identified which steps of the CAR-T pathway could be reorganized for low-risk patients. The resulting model preserves the clinical core of the As-Is scenario while introducing targeted modifications in the phases of lymphodepleting chemotherapy and early post-infusion monitoring (Fig. 2).

In the Standard Pathway, these steps are routinely performed during inpatient stays. However, the Efficient Pathway allows lymphodepletion to occur in a day-hospital or day-service setting for eligible patients, followed by extended observation periods and next-day clinical reviews. The early post-infusion phase, traditionally characterized by continuous inpatient monitoring, is reconfigured into structured outpatient follow-up, supported by daily assessments, 24/7 on-call availability, and the requirement for patients and caregivers to remain within one hour of the treating center. Other phases of the pathway remain unchanged, as they do not benefit from outpatient reorganization or already occur outside inpatient settings.

The feasibility of this model was explored and depends on conditions such as nearby accommodation (within one hour’s reach), operational readiness of outpatient units, and comprehensive patient and caregiver education to support early recognition of AEs (Fig. 3).

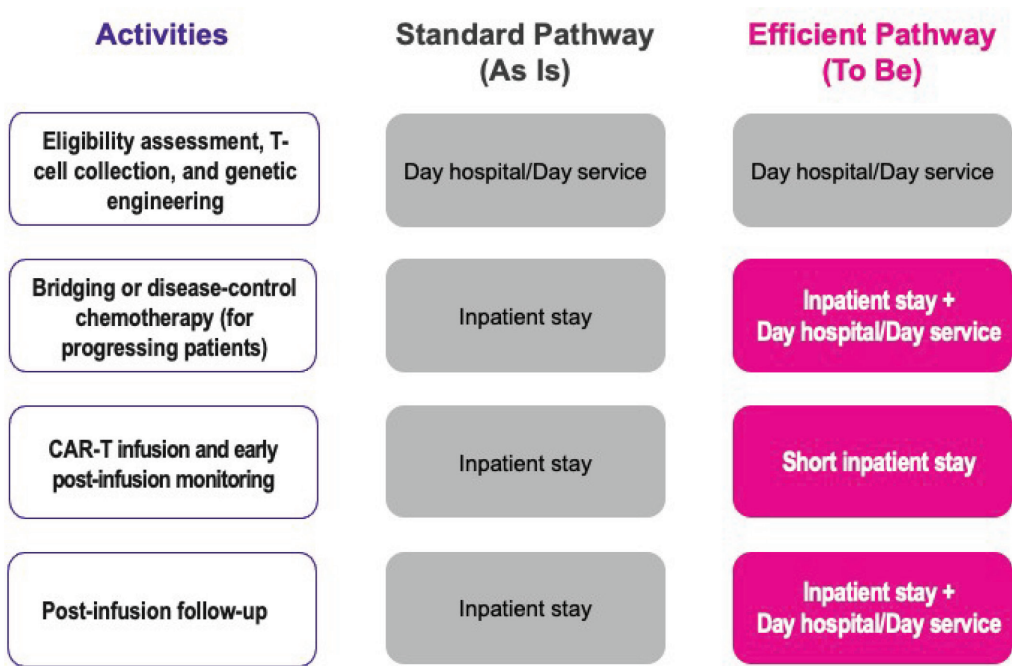


FIGURE 2 - Development of the Efficient Pathway. Short inpatient stay: compared to the Standard Pathway, the Efficient Pathway reduces post-infusion inpatient stay through early discharge and outpatient monitoring for selected patients



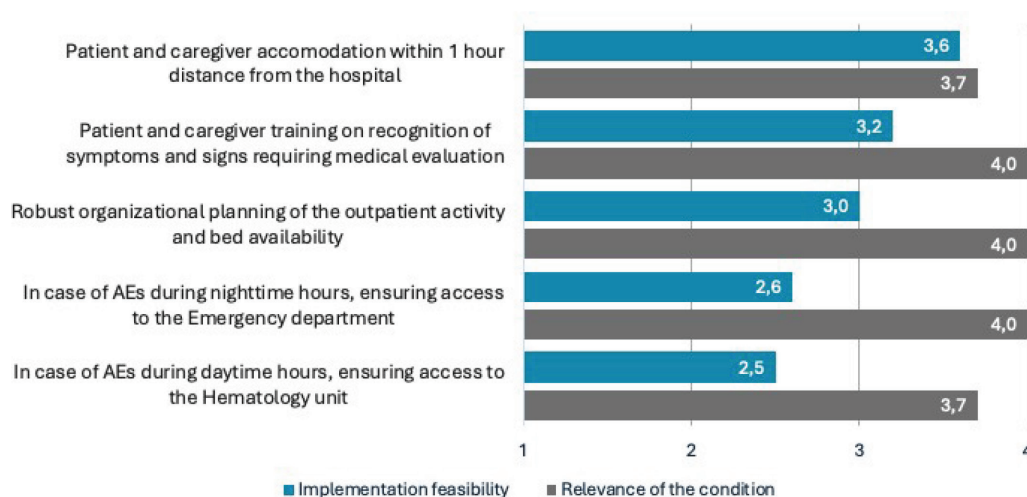


FIGURE 3 - Organizational and safety conditions to ensure transition from the Standard to the Efficient Pathway. Likert scale ranging from 1 (lowest) to 4 (highest).

Phase III—Comparative analysis (As-Is vs To-Be)

Economic impact

Table 4 illustrates the total economic impact of transitioning from the Standard Pathway (As-Is) to the optimized Efficient Pathway (To-Be) over a three-year time horizon. Comparative analysis demonstrated a reduction in mean overall cost from € 611,070 (As-Is scenario) to € 497,421 (To-Be scenario), yielding aggregate savings of € 113,649. At the individual level, the mean cost per patient declined from € 42,882 (As-Is) to € 34,907 (To-Be), corresponding to unit cost reductions of € 7,975 (–19%).

The one-way sensitivity analysis confirmed the robustness of the economic model across all tested parameters. Variations in patient allocation to the outpatient pathway, unit costs of major clinical activities, overhead mark-ups, and patient population growth produced differences in the magnitude of cost reductions attributable to the Efficient Pathway but did not alter the direction of the results: the To-Be model remained cost-saving compared with the As-Is configuration across all scenarios (Table 5).

The model showed the highest sensitivity to changes in outpatient uptake and fluctuations in the unit costs of key clinical activities, while variations in overhead rates and

TABLE 4 - Economic impact (overall and per-patient) of Standard Pathway (As-Is) vs Efficient Pathway (To-Be)

Year	Economic impact (overall)			Economic impact (per-patient)		
	As-Is	To-Be	Δ (To-Be-As-Is)	As-Is	To-Be	Δ (To-Be-As-Is)
Year 1	128,646 €	104,720 €	-23,926 €	9,028 €	7,349 €	-1,679 €
Year 2	192,969 €	157,080 €	-35,889 €	13,542 €	11,023 €	-2,519 €
Year 3	289,454 €	235,621 €	-53,834 €	20,313 €	16,535 €	-3,778 €
Total	611,070 €	497,421 €	-113,649 €	42,882 €	34,907 €	-7,975 €

TABLE 5 - One-way deterministic sensitivity analysis

Parameter	As-Is	Base	Lower Bound	Upper Bound
		To-Be	To-Be	To-Be
Patient allocation to the outpatient pathway	611,070 €	497,421 €	520,151 €	474,691 €
Unit costs of key activities (inpatient day, DH visit, CAR-T infusion, labs)	611,070 €	497,421 €	397,937 €	596,905 €
Overhead cost mark-up	611,070 €	497,421 €	405,848 €	517,160 €
Patient population growth	611,070 €	497,421 €	481,713 €	513,129 €

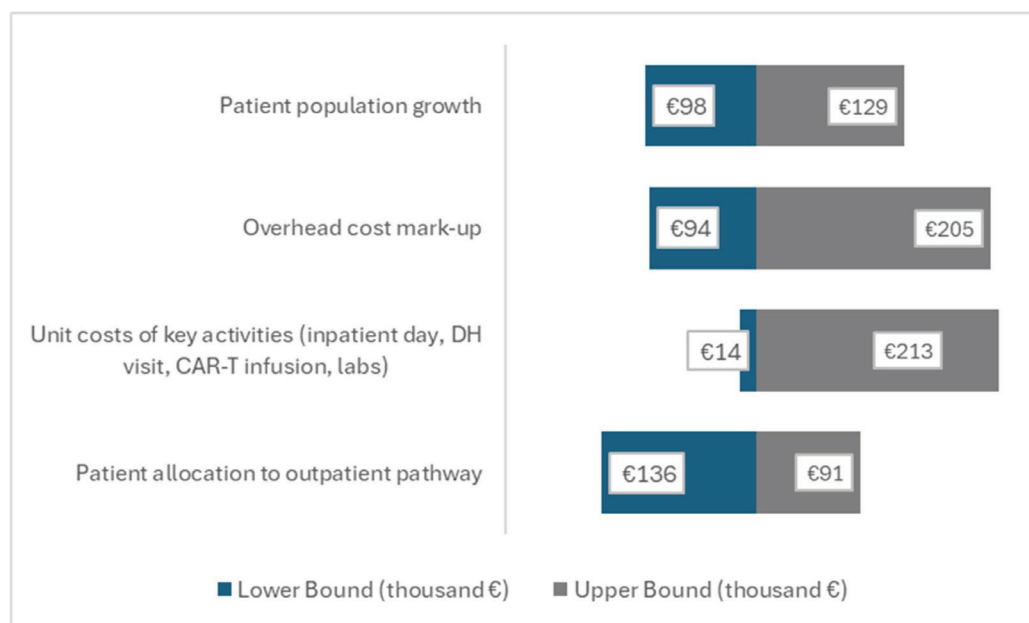


FIGURE 4 - One-way deterministic sensitivity analysis (cost reductions' variations *1000). DH: Day Hospital.

patient numbers had comparatively smaller effects. Overall, the range of observed outcomes consistently supported the economic advantage of the redesigned outpatient-enabled pathway (Fig. 4).

Organizational and ethical impact

The survey achieved a response rate of 56.5% (13 of 23 participants). Results, reported as average score, (Figure 5) revealed positive evaluations from the transition across the

following domains: bed capacity (4.9), consumables (4.3), professionals (4.3), facility space (4), medical equipment (3.8), clinical care pathways (3.8), pharmaceuticals (3.6), internal processes within the reference unit (3.5) and procurement processes (3.4).

Neutral or slightly negative impacts were observed for: inter-unit coordination processes (3.1), staff training on patient management procedures (3), meetings required for transition to the optimized scenario (2.9) and information and staff time to patient/caregiver (2.9).

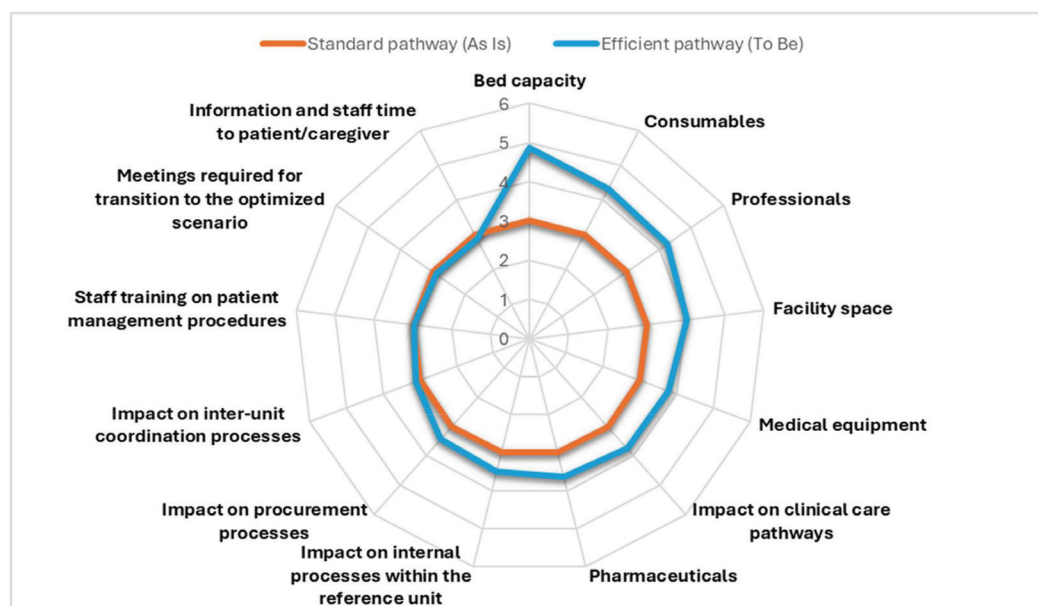


FIGURE 5 - Organizational impact: Standard Pathway (As-Is) vs Efficient Pathway (To-Be). Likert scale ranging from 0 (lowest) to 6 (highest).

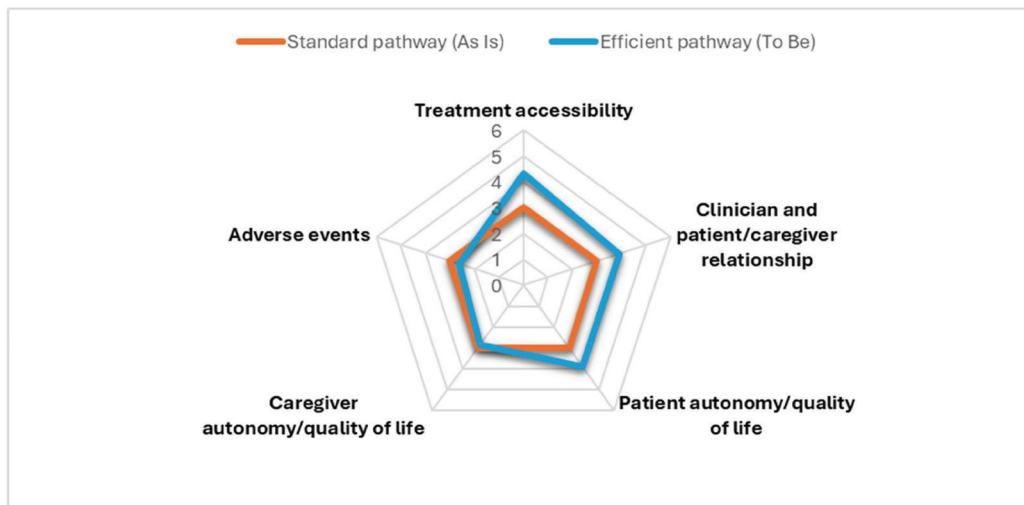


FIGURE 6 - Ethical impact: Standard Pathway (As-Is) vs Efficient Pathway (To-Be). Likert scale ranging from 0 (lowest) to 6 (highest).

The ethical impact assessment (figure 6) yielded positive scores for treatment accessibility (4.3), clinician-patient/caregiver relationship (3.9) and patient autonomy/quality of life (3.9), while caregiver autonomy/quality of life (2.9) and AEs (2.6) recorded slightly negative scores.

Discussion

This analysis represents one of the first Italian studies assessing the organizational and economic impact of virtually introducing an outpatient CAR-T management model for FL patients. Evidence on outpatient CAR-T care remains limited and heterogeneous, with most available data originating from U.S. and Canadian centers, where outpatient infusion and structured home-monitoring programs have been successfully implemented for selected patients (12,13). Despite differences in regulatory frameworks and reimbursement systems, these experiences consistently demonstrate that outpatient pathways can reduce inpatient resource consumption and improve patient experience, provided that robust eligibility criteria and rapid-access toxicity management are in place. Our findings align with this emerging evidence, while specifically addressing the Italian regulatory context, which mandates inpatient monitoring for several CAR-T indications and requires patient proximity for at least 30 days post-infusion.

Within this context, our results demonstrate that real-locating selected phases—particularly bridging chemotherapy in progressing patients, early post-infusion monitoring, and follow-up—to an outpatient setting (DH/DS) can generate meaningful efficiencies without compromising clinical outcomes.

The economic evaluation, based on a PLC methodology aligned with European costing frameworks for CAR-T therapy (30), shows that the Efficient Pathway achieves cost reductions as early as year 1, with cumulative three-year cost reductions of € 113,649. These findings parallel those of Fowler et al. (13), who reported substantial cost reductions in outpatient CAR-T models. However, our approach is more

conservative, maintaining inpatient infusion while optimizing pre- and post-infusion phases, an adaptation better suited to current Italian regulatory requirements and to support progressive implementation. The robustness of the economic conclusions was further confirmed by the one-way sensitivity analysis: even when applying parameter variations aligned with commonly accepted ranges in European health economic evaluations (typically ± 10 -20%) (24,25), the Efficient pathway remained consistently cost-saving. Although the magnitude of cost reductions varied—most notably with changes in outpatient uptake and unit costs—the direction of impact never reversed, reinforcing the stability of the model. Similar patterns have been observed in other economic evaluations of CAR-T and high-cost oncologic therapies, where inpatient length-of-stay remains the dominant cost driver and outpatient regimens maintain their economic advantage under parameter uncertainty (12,13).

Several conditions identified in this analysis—including the availability of structured rapid re-admission pathways, proximity of patient and caregiver accommodation to the treating center, structured education of patients and caregivers, and organizational flexibility in outpatient activity planning—should be interpreted as key prerequisites for the implementation of outpatient CAR-T pathways. In the Italian setting, authorization standards, accreditation requirements for CAR-T centers and internal hospital's standards of operations, define a set of minimum structural and organizational criteria that ensure a baseline level of preparedness for CAR-T delivery (10). These standards provide a common foundation across centers; however, the prerequisites identified in the present analysis extend beyond minimum accreditation requirements and reflect an additional level of organizational structuring needed to support an outpatient-based management model.

Accordingly, the Efficient Pathway evaluated in this study should be interpreted as applicable to contexts that are able to undertake this further organizational step, rather than as a universally transferable model. From a scalability perspective, this consideration helps explain why adoption of outpatient

CAR-T pathways may vary across centers. Highly mature hub centers may be better positioned to move beyond baseline accreditation requirements and implement new organizational arrangements, whereas centers with lower organizational maturity may require phased implementation strategies, targeted investments, or integration within regional hub and spoke networks to achieve comparable readiness.

The organizational assessment aligns with international literature on CAR-T service redesign, which emphasizes that outpatient care may alleviate pressure on hematology wards, increase bed availability, and optimize facility space (12). In our study, bed capacity showed the greatest improvement, followed by consumables, professional resources, facility space, and medical equipment. These improvements are largely attributed to early discharge and DH/DS management, which free up beds for reallocation, optimize space utilization, reduce consumables, and improve medical equipment use compared with standard hospitalization. Conversely, as expected, the transition requires increased investment in patient/caregiver education and coordination meetings during implementation (32).

Beyond economic and organizational considerations, the ethical assessment provides important insights into stakeholder perspectives. When appropriate clinical and organizational criteria are met, the outpatient regimen may enhance CAR-T treatment accessibility for patients with FL, support patient autonomy and quality of life, and strengthen the clinician-patient/caregiver relationship. However, caregiver burden emerged as a concern, likely reflecting their central role in supporting patients throughout the pathway, including monitoring, assisting with daily activities, and transporting patients to the center for scheduled visits. The lower score for AEs suggests that clinicians may perceive toxicities monitoring and management as more challenging in outpatient settings. Nonetheless, emerging evidence on outpatient CAR-T management (33) suggests that tools such as telemedicine visits and dedicated re-admissions pathways may mitigate these concerns, as also explored in our study. Despite these advances, significant gaps remain in predicting AEs risk in CAR-T-infused patients and selecting candidates for outpatient care (34). Concerns about the timely detection and management of AEs remain crucial in both the literature and our findings (12). Although prospective studies and institutional experiences show that outpatient CAR-T can be safe when supported by structured monitoring tools—such as telemedicine, standardized checklists, and immediate re-admission pathways—clinicians in our study expressed reservations regarding AE management outside the inpatient setting in contexts where these organizational processes are not yet fully consolidated. The relatively modest feasibility scores observed for the establishment of dedicated daytime and nighttime pathways further indicate that current infrastructural and monitoring arrangements may not yet be sufficient to fully support timely detection and management of AEs, highlighting the need to strengthen these systems prior to large-scale implementation of outpatient CAR-T models.

Despite these strengths, several limitations warrant consideration. Methodologically, the analysis does not encompass

all HTA domains in full detail, with safety and efficacy that were assumed equivalent based on expert consensus rather than directly measured. As detailed in the Methods section, this assumption rests on restrictive eligibility criteria and structured post-infusion monitoring; however, real-world rates and AEs severity (e.g., CRS, ICANS) may still differ, potentially affecting the comparative outcomes of inpatient versus outpatient management (35).

In addition, the economic evaluation relies on cost estimates adapted from Zallio and Bellini (18) rather than center-specific micro costing. While this approach aligns with other early economic evaluations of CAR-T in Europe, it may limit the precision and external validity of the findings. Regarding generalizability, only three experienced Italian CAR-T centers participated, which may restrict applicability to centers with different levels of maturity, staffing, infrastructure, and caseload. Since the To-Be scenario represents an exploratory exercise not yet implemented in Italian real-world practice, several prerequisites for transferability to active CAR-T centers were nonetheless identified. These include relevant organizational conditions such as a dedicated structured pathway to ensure safety through rapid re-admission and AEs management, availability of nearby accommodation for patients and caregivers, appropriate education for both, and internal unit flexibility in scheduling and coordinating admissions and discharges.

The organizational and ethical analyses were generated through qualitative Likert-scale assessments, which reflect clinicians' perceptions rather than objective metrics, and may therefore be subject to response bias.

Data collection, based primarily on expert meetings, structured surveys, and a final consensus exercise, may introduce subjectivity and anchoring effects. While expert elicitation is a recognized approach in early HTA and pathway redesign, it cannot fully substitute for empirical observations or large-scale operational data. Future research should incorporate prospective observational data and real-world cost measurements to validate the assumptions and quantify actual resource utilization under outpatient management.

Finally, this analysis evaluates a virtual outpatient scenario rather than an implemented clinical program. Real-world implementation may require additional organizational investments—such as dedicated rapid-admission pathways, telemonitoring tools, and caregiver support systems—that were not fully captured in the model and may influence both economic and organizational outcomes.

Conclusions

The lack of evidence on the organizational, economic, and ethical implications of outpatient CAR-T treatment for FL in the Italian setting—combined with the expected increase in eligible patients and the growing need for innovative management models—highlights the relevance of the research question. Our findings provide preliminary but valuable evidence supporting the feasibility and potential benefits of outpatient CAR-T management of FL patients within Italian high-complexity hematology centers. The implementation of a mixed model that maintains inpatient care for the most critical patients while shifting selected phases to an outpatient

setting could substantially reduce hospital costs, both in aggregate terms and per patient, while proving to be more sustainable and scalable. Although the economic impact of professional resource optimization was not directly measured, it is reasonable to expect that personnel time could be reallocated to other activities, further enhancing internal unit efficiency.

The convergence of positive economic, organizational, and ethical indicators—together with sensitivity analyses confirming model robustness—suggests that selective pathway optimization may represent a viable strategy to improve efficiency and patient experience. Notably, recent SmPC updates of CAR-T therapies in FL (36–38) introduce more flexible management in the post-infusion period, expanding physician discretion and enabling a gradual transition toward more streamlined monitoring models. These regulatory developments reinforce the relevance and timeliness of our study, providing an enabling framework for the outpatient approaches assessed. However, successful implementation will require careful patient selection, robust monitoring infrastructure, and adequate caregiver support. Prospective observational studies are needed to validate these projections and inform evidence-based pathway redesign across the Italian CAR-T network.

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