Feasibility Report

A stakeholder-informed assessment of the clinical, operational, technological, and economic requirements for cytokine release syndrome (CRS) monitoring in outpatient settings following CAR-T and T-cell engager therapies

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Executive summary

The technology to monitor CRS remotely already exists. What's missing is the care model built around it.

CAR-T and T-cell engager (TCE) therapies have expanded treatment options for people with blood cancers who had few remaining options. Yet access stays concentrated in a small number of specialized centers: patients often travel long distances and remain near the treating hospital for weeks, and most community settings (where roughly 85% of cancer patients receive their care) cannot yet deliver these therapies safely. A central reason is cytokine release syndrome (CRS), the most common serious side effect, which today relies on intensive in-person monitoring to mitigate the risk. Expanding who can receive these therapies depends on being able to monitor for CRS safely closer to home.

Digital health technologies (DHTs) may support this shift by providing more continuous and objective insights into patients during their treatment. This requires defining the evidence, care pathways, and operational models needed for scalable CRS monitoring closer to home, and evaluating how DHTs can contribute to this evolving model of care.

Through DECODE CRS, a pre-competitive collaboration focused on expanding access to CAR-T and TCEs through CRS monitoring, we brought together clinicians, digital health developers, regulators, payers, patient advocate groups, and drug sponsors through multidisciplinary workshops and in-depth interviews to explore the clinical, operational, and financial requirements necessary to move CRS monitoring out of the clinic, and to assess the role of DHTs in supporting this transition.

> **KEY FINDING**
>
> The barrier to expanding access is not detecting CRS. It's ensuring a care team can safely act when CRS is detected outside of a clinical setting. An early warning algorithm that spots a potential CRS event is only useful if there is clear clinical accountability and transparent escalation pathways for what happens next.

This assessment examined what it would take to make that possible across three dimensions of feasibility:

Clinical feasibility for outpatient CRS monitoring

What is required to safely extend CRS monitoring into outpatient settings, and how can DHTs support clinicians, workflows, and escalation pathways?

- CRS monitoring today is variable. Some patients get frequent in-person checks; others are asked to self-report a fever over the phone. This variability limits the consistency of both CRS detection and the care patients receive. It also limits access to the high-quality data needed to develop and validate CRS early warning algorithms and to advance CRS de-risking products.

- Most patients can be safely monitored outside the hospital when the right support and infrastructure are in place, consistent with a growing body of outpatient CAR-T experience (see Section 2). Patient selection continues to rest on established clinical judgment rather than on the monitoring technology. The factors that already guide outpatient eligibility (caregiver support, ability to engage with monitoring, cognitive and functional status, reliable access to care, and a clinical risk profile appropriate for outpatient management) remain the prerequisites for safe outpatient care.
- After-hours alert management remains highly variable across clinical settings. Successful implementation will require clearly defined 24/7 alert routing and escalation pathways that align with established clinical workflows.
- CRS monitoring requires a flexible approach that can be adapted across CAR-T and TCE therapies. While the clinical need for monitoring remains consistent and the same monitoring capabilities may be applicable across these therapies, implementation will need to account for differences in the timing and trajectory of CRS, regulatory requirements, outpatient pathways, site capabilities, and care model maturity.

Technical considerations for CRS monitoring

What data, algorithm capabilities, and system requirements are needed for a CRS monitoring product to generate clinically meaningful insights, support timely decision-making, and integrate into care workflows?

- Technology selection should prioritize fit-for-purpose sDHTs with demonstrated verification, usability validation, analytical validation, and clinical validation (the V3+ framework) for the physiologic measures relevant to CRS. Additional practical considerations include measurement frequency, wear duration, battery performance, connectivity, data quality and missingness, and integration with clinical workflows.
- A CRS early warning algorithm is not the only enabler for CAR-T and TCE access. It's one component of a larger care model that also needs standardized clinical protocols, trained staff, 24-hour escalation coverage, patient and caregiver education, and implementation models that are clinically feasible, operationally sustainable, and aligned with the needs of health systems and those responsible for funding care.
- A CRS early warning algorithm should support clinical decision-making and not replace clinical judgement. Algorithm-generated alerts should inform clinical assessment, while clinicians retain responsibility for interpreting the information and making all diagnostic and treatment decisions.

Value of outpatient CRS monitoring

Does the economic and regulatory environment support this shift, and who needs to see value for adoption to happen?

- The financial incentive for outpatient CRS monitoring extends beyond reimbursement for the technology. Stakeholders highlighted that the broader value proposition includes improving patient-centered outcomes, reducing the burden of hospital-based monitoring, enabling more efficient use of healthcare resources, and increasing capacity to deliver CAR-T and TCE therapies.
- Adoption will depend on demonstrating value to multiple stakeholders, whose priorities differ: health systems may prioritize operational capacity and care efficiency; community practices, feasibility and support for local management; payers, evidence of improved outcomes and reduced utilization; and sponsors, improved treatment delivery and real-world evidence generation. Because the party that bears the cost of implementation is often not the one that captures the benefit, adoption cannot rest on any single value case. It depends on aligning incentives across the care pathway (see **Section 5**).
- Evidence generation will be essential for adoption. Stakeholders will require evidence demonstrating technical performance as well as clinical utility, workflow impact, patient outcomes, healthcare resource utilization, and economic value. Notably, the CRS monitoring workflow can serve as part of this evidence infrastructure with continuous data collected during routine outpatient monitoring generating the technical-performance and clinical-utility evidence sponsors and payers require, making it a dual-purpose investment rather than a cost line alone.

The findings from this assessment provide a foundation for defining the clinical, operational, technical, and implementation requirements needed to support safe, scalable CRS monitoring in the outpatient setting. Continued collaboration across clinicians, technology developers, regulators, payers, and therapy sponsors will be essential to translate these requirements into sustainable care models that enable broader access to CAR-T and TCE therapies while maintaining safe, patient-centered care.

Methodology

This assessment is based on qualitative evidence from a precompetitive, pharmaceutical-based consortium, a multidisciplinary stakeholder workshop, and a series of in-depth interviews. The assessment started from the patient pathway, identifying what is required to safely enable outpatient CRS monitoring as part of a decentralized, patient-centered model of care. This approach considers the clinical, operational, and support systems needed to help patients remain safely outside of the hospital while maintaining timely access to care when required, and assessing how DHTs could address these requirements and the value they may add.

The consortium

The DECODE CRS consortium is a cross-sector collaboration convened by the Digital Medicine Society (DiMe) and Ametris to expand safe, patient-centered access to CAR-T and TCE therapies, including through outpatient CRS monitoring. The consortium participated in recurring subject matter expert (SME) discussions that provided ongoing input into key questions related to CRS monitoring, clinical workflows, DHT requirements, algorithm development, and implementation considerations. These discussions helped identify areas of consensus, highlight unresolved questions, and refine the requirements evaluated through the broader feasibility assessment.

The interviews

Twelve interviews were conducted with a diverse group of stakeholders. Participant responses were de-identified and grouped by role.

Table 1: We conducted 12 interviews with a diverse group of subject matter experts on CRS.

Stakeholder	Interviews
Oncology nurse specialist	1
Community oncologist	1
Oncologist	1
Sponsor / drug developer	1
Clinical / translational researcher	2
Digital health / remote-monitoring expert	3
Market-access expert	1
Regulatory expert	2
Total	12

Interviews were analyzed thematically, coding for recurring ideas about clinical feasibility, implementation, digital health design, and commercial viability. Where stakeholders agreed, we treated that as a strong signal. Where they disagreed (e.g., What performance must a CRS early warning algorithm demonstrate? Do CAR-T or TCEs represent the bigger near-term opportunity?), we preserved that disagreement as an important finding of the current environment and focused on these areas in the workshop (see Appendix B). Interviews were designed to capture breadth across stakeholder perspectives. Consistent with a qualitative, purposive approach, we treated cross-stakeholder agreement as signal, preserved disagreement as a finding, and carried unresolved questions into the workshop for broader input.

The workshop

Participants (n=24) spanned academic and community care settings and represented clinicians (3), clinical researchers (n=2), digital health developers (n=6), payors (n=2), patient advocates (n=2), regulatory experts (n=1), and sponsors (n=8). Discussion centered on current monitoring practices, differences between CAR-T and TCE monitoring needs, the operational requirements for safe outpatient care, DHT performance requirements, and the economics of adoption.

A note on scope

This is a qualitative, stakeholder-informed feasibility assessment. It identifies requirements, barriers, and opportunities. It does not establish the clinical effectiveness of any specific CRS monitoring product, and it does not resolve exactly what sensitivity, specificity, or alert thresholds a future CRS algorithm should achieve. Those remain open questions for prospective validation.

1. CRS monitoring in the evolving immunotherapy landscape

TCE and CAR-T cell therapies have transformed the treatment landscape for several blood cancers over the last decade, offering new therapeutic options for patients with previously limited treatment choices. As their use grows, improving patient access will depend on developing care models that support safe, consistent delivery across a wider range of healthcare settings. CRS is a common, well-characterized, and increasingly manageable adverse event associated with these therapies. However, the need for timely recognition, monitoring, and intervention historically contributed to care models concentrated in specialized centers or academic hospitals with the expertise and infrastructure required to support these patients.

While this model has supported safe delivery of these therapies, it also creates challenges for broader access, requiring some patients to travel significant distances for treatment and placing capacity constraints on specialized centers. As approximately 85% of cancer patients receive care from community oncology providers (Tucker et al, 2022), there is growing interest in approaches that enable appropriate CRS monitoring and management closer to where patients live, while maintaining robust safety and escalation pathways.

A growing body of experience now supports the feasibility of outpatient delivery for these therapies. A patient monitoring program at Mayo Clinic managed 123 patients receiving CAR-T in the outpatient setting, with CRS occurring in 75% of patients at a median of 3 days post-infusion (Paludo et al, 2023). Across four Sarah Cannon Transplant and Cellular Therapy Network sites, outpatient CAR-T was implemented using remote patient monitoring and 24/7 nurse oversight as a scalable multi-site care model (Ash et al, 2024) and focused reviews have begun to translate this experience into practical recommendations for community-based centers (Perez et al, 2024). To date, this evidence base is concentrated in CAR-T; comparable outpatient monitoring data for TCE therapies remain limited, an important gap given differences in the timing and trajectory of CRS across treatment modalities. The opportunity is to build on these learnings to define the evidence, requirements, and care models needed to support safe, scalable CRS monitoring across a broader range of settings.

The growing clinical experience with outpatient CAR-T and TCE therapies has demonstrated that decentralized CRS monitoring is feasible in appropriately selected patients when supported by structured care pathways and established escalation processes. However, considerable variation remains in how outpatient CRS monitoring is implemented, and there is limited consensus on the clinical, operational, technical, and evidence requirements needed to support broader adoption across healthcare settings.

DHTs including wearable sensors for remote vital-sign monitoring, electronic patient-reported outcomes (ePROs), and clinical decision-support algorithms may provide an important enabling layer within these evolving care models. However, technology alone will not enable broader adoption. Successful implementation will depend on standardized monitoring approaches, appropriate patient selection, trained care teams, reliable escalation pathways, clear clinical workflows, and integration into healthcare systems.

2. Clinical considerations for outpatient CRS monitoring

Implementation and clinical infrastructure

Today's monitoring is patchwork

In the inpatient setting, CRS monitoring is structured and well-resourced with established protocols, dedicated clinical care teams, and EHR-integrated pathways. Outside of those settings, practice varies enormously, from scheduled in-person visits and telemedicine check-ins to patients or their caregiver reporting temperature over the phone every 4-6 hours while awake or only if a fever arises. A community oncologist interviewed for this project described current practice bluntly, noting patients are typically asked to report a fever, sometimes an oxygen level, and rarely much else.

With no shared baseline for what good CRS monitoring looks like, each site is effectively improvising or left to devise their own processes. Standardizing this monitoring is necessary, but as stakeholders emphasized, is not the only piece where difficulties lie.

The real barrier is what happens after CRS detection

The ability to detect the CRS onset, a temperature above 38° C, is required for outpatient delivery of these therapies; however, the ability to detect a fever alone is not sufficient. A critical challenge is ensuring patients can be assessed, managed, and rapidly returned to appropriate care when concerns arise.

Inpatient monitoring provides access to multidisciplinary teams capable of timely assessing symptoms, initiating treatment, and escalating care when required. As monitoring moves beyond the inpatient setting, these capabilities must be reproduced through clearly defined clinical pathways rather than proximity to the treatment center.

Stakeholders consistently identified several requirements for safe outpatient CRS monitoring, including the ability to:

- ✔ **Recognize patients at risk of clinical deterioration** and understand the likely trajectory of CRS progression.
- ✔ **Define clear escalation thresholds** that trigger timely clinical assessment and intervention.
- ✔ **Ensure rapid access to appropriate care**, supported by established communication pathways and escalation processes.

The value of including DHTs for CRS monitoring depends on their ability to support clinical teams by providing timely, actionable information within established workflows. Successful implementation therefore requires alignment across technology, clinical processes, operational infrastructure, and patient support systems.

Outpatient CRS monitoring workflow

The purpose of CRS monitoring is not only to identify potential deterioration, but also ensure that clinically meaningful information leads to timely and appropriate clinical action.

Stage	Purpose	Key requirements
1. Patient assessment	Recognize meaningful changes in a patient's condition during treatment.	✔ Patients/caregivers able to communicate symptoms and concerns. ✔ Care team able to access and interpret physiologic measurements and patient-reported symptoms. ✔ Timely information exchange via remote monitoring, scheduled assessments, or in-person evaluation as needed.
2. Clinical review and interpretation	Determine whether a change is expected variation, warrants closer follow-up, or is a potential CRS concern requiring intervention.	✔ Standardized approaches for reviewing patient information. ✔ Information collected through monitoring must be interpreted within the context of the individual patient, including treatment timing, symptoms, clinical history, and overall condition. ✔ Clear ownership for clinical assessment and decision-making. ✔ Defined thresholds for escalation and intervention. ✔ Documented pathways for responding to changes in patient status.
3. Clinical response and escalation	Ensure timely access to clinical assessment and intervention when a patient's condition changes.	✔ Predefined response processes spanning continued monitoring, additional assessment, treatment initiation, or escalation to a higher level of care.
4. Documentation and continuity of care	Maintain a coordinated care pathway so monitoring supports ongoing decision-making rather than isolated assessments.	✔ Changes in condition, clinical decisions, and the timing of interventions documented over time and communicated across care teams. ✔ Continuous physiologic monitoring paired with real-time reporting of clinical interventions.

Documentation must also capture the timing of interventions that can alter the physiologic signals being monitored. Treatments given before escalation to higher-level care (including antipyretics and immunosuppressive therapies such as corticosteroids or tocilizumab) can change the parameters used to assess whether a patient is deteriorating, and in some cases slow that deterioration. Interpreting monitoring data therefore depends on knowing precisely what was administered and when, so that physiologic trends can be understood in the context of treatment. Because these interventions are typically administered in clinic or

emergency settings while physiologic monitoring may continue at home, the same patient generates data across multiple settings and care teams. Interpreting monitoring data therefore depends on knowing precisely what was administered and when, regardless of where it was given. Safe outpatient monitoring thus requires both continuous physiologic monitoring and precise, real-time reporting of clinical interventions.

Foundational requirements for outpatient CRS monitoring

The workflow above describes how outpatient monitoring operates in practice. Delivering it safely depends on a set of underlying conditions being in place. Outpatient CAR-T and TCE experiences demonstrate that successful programs depend on a well-coordinated care model. Findings from stakeholder engagements, supported by published clinical experience, identified a minimum set of requirements across different treatment settings including appropriate patient selection, standardized CRS management protocols, trained clinical teams, defined monitoring workflows, caregiver support, and reliable escalation pathways (Oluwole et al., 2024, Garfall et al., 2025, Yanovsky et al., 2023).

While the requirements themselves are consistent across settings, how each is operationalized will vary according to treatment modality, product labels, institutional resources, and local care models. Academic and specialty centers with established immunotherapy programs may already have many of these capabilities through outpatient pathways, while community oncology practices and newer treatment centers may need to strengthen these capabilities before implementing an outpatient CRS monitoring model ([Appendix C] details how the care model adapts across academic and community settings).

Based on these findings, an Outpatient CRS Monitoring Readiness Checklist (Appendix A) was developed to support planning across care settings. It provides a practical review for assessing preparedness across six domains: clinical care model readiness, monitoring and workflow readiness, workforce and operational readiness, patient and caregiver readiness, financial sustainability, and technology enablement where outpatient CRS monitoring forms part of the care model. Modality-, product-, and site-specific requirements should then be incorporated to reflect individual treatment pathways and local practice while maintaining consistent principles for safe outpatient care. Together, these domains help ensure that monitoring is supported by appropriate clinical ownership, standardized workflows, patient support, and reliable escalation pathways.

Most patients can be supported through outpatient monitoring with the right infrastructure

Outpatient CRS monitoring requires a patient-centered approach that identifies the support and resources a patient needs for safe care outside the inpatient setting. Patient selection should be integrated into the overall care model, ensuring that individuals have the clinical, logistical, and support requirements needed to participate in outpatient monitoring while maintaining clear pathways for escalation when needed.

A patient-centered outpatient model assesses patient and caregiver readiness across key areas, including caregiver support, ability to participate in monitoring, access to care, and

clinical risk profile, with processes in place to address identified barriers and provide additional support when needed.

- **Caregiver support:** Ensure every patient has a dedicated support person to assist with symptom recognition and timely reporting.
- **Cognitive capacity:** Assess the patient's ability to understand monitoring instructions, communicate changes in symptoms or condition, and engage with the care team as required.
- **Technology comfort:** Verify the patient's ability to use the provided monitoring tools comfortably and consistently.
- **Geographic feasibility:** Confirm the patient lives or can obtain housing throughout the greatest CRS risk window within a reasonable distance of care and has reliable transportation for urgent clinical needs. The appropriate distance will depend on the therapy, treatment protocol, patient-specific needs and circumstances, site capabilities, and established escalation pathways.
- **Clinical risk profile:** Select candidates whose overall health and disease status are appropriate for outpatient management, keeping defined escalation pathways ready for those who require them.

These considerations should guide implementation of the outpatient model rather than function as standalone exclusion criteria.

The "who answers at 2 a.m.?" problem

> "As you move into smaller practices, it becomes more about who's going to respond at 2 o'clock in the morning, and having an answer for that."
>
> *— Digital health / Remote-monitoring expert*
>
> "That's the trouble with outpatient, too: our providers change all the time, whoever's covering night shifts, so it's just ensuring that it's available to everyone if there's an alert."
> *— Oncology Nurse Specialist*

Every monitoring program must establish an explicit ownership model for overnight and off-hours alert responses. It should define who is responsible for reviewing patient information, assessing concerns, and coordinating escalation to ensure that potential safety concerns lead to timely clinical action. Coverage approaches may vary by site and available resources, including:

- **Local nursing coverage (direct ownership):** Site commit dedicated 24/7 staffing resources to maintain full local control over every alert.

- **Centralized monitoring hub (external coverage):** External clinical support provides CRS monitoring coverage, ranging from after-hours and gap coverage to full 24/7 monitoring. Cost and complexity vary with scope and the degree of technical and clinical integration with local systems.
- **Hybrid triage model (digitally supported):** Triage is supported by technologies, which may include sDHTs and digital platforms, to prioritize and route change in clinical status to the local on-call clinical team. This approach maintains local clinical ownership and judgment while ensuring a reliable, automated escalation path for urgent alerts.

The appropriate model will depend on site capabilities, patient volume, available resources, and integration with care pathways.

Integrate Emergency Departments into the clinical safety pathway

The Emergency Department (ED) is a critical, high-risk node in the care network for outpatient CAR-T and TCE administration. During time-sensitive acute events, patients often present to the nearest local ED. If the ED clinical team is unfamiliar with CAR-T and TCE toxicities, they risk mismanaging the patient (e.g., performing an immediate, invasive intubation or unnecessary sepsis workup instead of administering steroids or tocilizumab, as appropriate.)

To aid in appropriate and timely care, sites must implement a two-pronged preparation strategy to ensure patient safety. First, proactively map patient residential locations relative to capable emergency facilities and provide those local EDs with specific CRS recognition guidelines, management protocols, and direct 24/7 contact lines for the treating oncology team. Consider enhancing relationships through encouraging those sites to establish "stroke alert"-style pager systems or direct triage bypass agreements to admit the patient immediately to an appropriate unit, avoiding delays in the ER. Second, mandate a structured patient education protocol that emphasizes the importance of immediate disclosure of therapy history upon ED arrival. Ensure the patient always carries a hard-copy clinical wallet card detailing the therapy, date of infusion, and emergency contact numbers. This dual-readiness approach ensures that patient disclosure triggers an immediate, EHR-connected response, preventing life-threatening delays in care and ensuring that ED staff do not have to reconstruct a patient's care status during a time-sensitive event which may lead to incorrect or unnecessary workups and treatments.

Adapting to therapy-specific requirements

CRS monitoring models should be adjustable to the therapy’s dosing and risk pattern. For CAR-T therapies, this may involve a front-loaded monitoring period following infusion. For TCEs, monitoring may need to restart or intensify around each step-up dose rather than follow a single continuous protocol. The table below illustrates the kind of product-level variation a CRS monitoring model needs to accommodate; it is not exhaustive and should be validated against current labeling at the time of deployment.

CAR-T vs. TCE: CRS and monitoring profile at a glance

Table 2: How CAR-T and TCE CRS profiles translate into different monitoring requirements

Characteristic	CAR-T	TCEs
CRS event profile	Single defined post-infusion observation period	Observation re-triggered at each step-up dose and the first full dose; recurrence possible with re-treatment
Typical onset window	Most CRS begins within the first several days and resolves within about two weeks of infusion in real-world experience	CRS clusters in the 12-48 hours after each step-up dose during a 1–2 week escalation schedule
Current monitoring norm	Daily in-person or facility-based monitoring for roughly two week, tapering through a shortened post-infusion window	Inpatient or closely supervised observation for up to 72 hours after each escalation dose, then clinic-based follow-up
Regulatory backdrop	Federal risk-mitigation requirements for driving distance and monitoring duration have recently been eased for approved products (FDA, 2025)	Regulatory requirements and product labeling remain more variable across agents. Some TCE products have had REMS requirements, and many labels include recommendations for monitoring during step-up dosing and early treatment periods when CRS risk is highest.
Best-fit role for digital CRS monitoring	Continuous, baseline-referenced monitoring through a single, well-defined post-infusion window	Configurable, dose-dependent monitoring that activates around each step-up dose and is reduced or not implemented between doses

CAR-T | For CAR-T, a defined post-infusion monitoring protocol should cover the initial 14-day post-infusion window where the vast majority of CRS events occur. Real-world experience across approved CD19- and BCMA-directed products demonstrates that CRS onset is generally concentrated within the first two weeks after infusion, and recent regulatory changes have reflected this evolving evidence by shortening required proximity-to-center and driving restrictions for selected products (FDA, 2025). The timing of CRS onset, however, varies substantially across individual CAR-T products, with some demonstrating earlier onset (1-3 days) and others a later (4-7 days) median time to CRS. The timing of CRS onset varies not only across CAR-T products but also between patients receiving the same product, influenced by patient-level factors such as disease burden and immune status. While most events cluster in the early post-infusion window, some patients may experience later onset well outside the typical period. These differences have important implications for outpatient care models, influencing the timing and intensity of monitoring, the duration of proximity to the treating center, and technology considerations such as duration of wear, battery life, and patient adherence. A low-burden monitoring approach may be particularly valuable in this context, extending coverage to capture atypical, later-onset events without imposing significant additional burden on patients.

TCEs | For TCEs, the monitoring platform should be designed around dose-triggered risk windows rather than a single post-treatment period. The system should capture baseline data before the first step-up dose, activate enhanced monitoring following each step-up dose and the first full dose, and support configurable monitoring intensity throughout the step-up period (Song et al., 2026). Because patients are often returning to the clinic daily or every few days during step-up dosing, monitoring should complement scheduled assessments by providing continuous oversight between visits and enabling earlier recognition of changes in clinical status. After successful step-up completion and demonstrated treatment tolerance, monitoring intensity should be adjustable based on patient risk and clinical confidence.

ILLUSTRATIVE CASE SCENARIOS

The scenarios below are composite, hypothetical illustrations built from the workflow patterns and failure modes stakeholders described. They are not records of actual patients and are intended to make the adaptation strategies above concrete, not to represent verified outcomes.

Case example 1: TCEs – RPM as "dose-anchored" step-up support
Modality: BCMA-directed TCE | Site type: Community oncology infusion center

A community site administers step-up dosing to a patient with relapsed/refractory multiple myeloma. Because CRS risk is dependent on each TCE administration during this treatment scheduling, the monitoring platform is configured for dose-dependent activation. CRS monitoring is initiated during the "high-vigilance" window for 48 hours following each step-up dose, and frequency reduced or paused between doses. When the patient reports a temperature spike within the monitoring window following the second step-up dose, the CRS monitoring system automatically correlates the event with the recent dose and escalates the alert to the appropriate clinical lead.

Why this works: This differentiates TCE monitoring from CAR-T. By anchoring monitoring to the greatest CRS risk window of the step-up dose, the site avoids the resource drain of continuous 2-week monitoring, making the workflow sustainable for a community team managing multiple patients on different treatment schedules.

Case example 2: The "ED bypass" protocol
Modality: CD20-directed TCE | Site type: Community practice unaffiliated with the treating center

A patient receiving a TCE through a community oncology program develops fever and confusion outside of clinic hours and presents to a local emergency department. Because the site has established a CRS emergency pathway, the ED team can rapidly identify the patient's therapy history, recognize the potential for CRS or ICANS, and consult the designated oncology clinical team. The pathway includes proactive engagement with local emergency departments, including education on approved CAR-T and TCE therapies, CRS recognition and management considerations, and direct communication pathways with the treating oncology care team. Patient education reinforces the importance of immediately disclosing their treatment history including providing the wallet card when seeking urgent care.

Why this works: Outpatient CRS monitoring requires ED integration, particularly for after-hours events. Rapid access to therapy history and oncology support enables timely recognition, appropriate management, and coordinated escalation.

Translating clinical requirements into technology capabilities

The clinical feasibility for outpatient CRS monitoring define the workflow, decision points, and response pathways needed to support safe patient care. DHTs may provide an enabling layer by improving access to timely patient information, supporting structured clinical review, and helping integrate monitoring into established care workflows The technology assessment that follows evaluates whether available digital health capabilities can meet these clinical requirements, including the data needed to support assessment and the role of CRS early warning algorithms.

3. Technical considerations for CRS monitoring

The role of digital health technologies (DHTs)

Even in established programs where outpatient delivery has been shown to work, experienced providers described continued reservations about monitoring and managing CRS outside the inpatient setting, a caution that grows as care models extend to patients farther from the treating center or in more rural settings. Realizing safe expansion into these settings will depend on better data about how CRS onsets, progresses, and is managed, so that new care pathways are built on observed evidence rather than extrapolation. This is where DHTs may contribute most directly.

Outpatient CRS monitoring shifts responsibility for recognizing changes in patient condition outside the treatment center. While education, scheduled assessments, and patient-reported symptoms remain essential components of care, there are limitations to relying only on intermittent clinical encounters or patient or caregiver symptom reporting. Digital health technologies may provide an additional layer of support by enabling more continuous visibility into a patient's physiological state between clinical assessments. For patients and caregivers, this may provide reassurance that changes in condition can be communicated and reviewed earlier. For care teams, DHTs may provide additional context to support clinical decision-making, identify patients who require assessment earlier, and reduce unnecessary inpatient care. DHTs should be viewed as an enabling component of a broader CRS care pathway, rather than a replacement for patient engagement, clinical assessment, or established escalation processes.

Selection of DHTs for outpatient CRS monitoring

Selection of sDHTs for outpatient CRS monitoring should prioritize DHTs that are fit for purpose (evaluated against the V3+ framework of verification, usability validation, analytical validation, and clinical validation), including the ability to capture physiologic measures relevant to early identification of CRS. A wide range of sensor-based DHTs (sDHTs) are commercially available to support remote physiologic monitoring in various form factors (e.g., wrist-worn, adhesive patches, rings, chest straps). Sensor modality also determines which physiologic signals can be reliably derived and where measurement may be limited in specific populations — for example, ECG-based measures can be affected by cardiac technologies such as pacemakers, and PPG-based measures can be degraded by poor peripheral perfusion. These limitations are particularly relevant in CRS monitoring, where perfusion and hemodynamic changes are themselves signals of interest. sDHT selection should be guided by analytical validity of individual algorithms, sampling frequency, duration of wear, battery life, connectivity requirements, and the ability to reliably collect and transmit data during periods of acute illness.

Patient usability should also be considered. Stakeholders across interviews and the workshop emphasized sDHTs should add minimum burden to the patient and clinical staff by enabling passive data collection when possible, providing straightforward onboarding, supporting long-term wear, and requiring minimal maintenance. The sDHT selection should consider the needs of the intended patient population, including physical limitations, digital

literacy, caregiver involvement, charging requirements, skin sensitivity, and the ability to maintain adherence during periods of fatigue, fever, reduced functional status, or altered mental status.

Outpatient monitoring also requires reliable connectivity and integration with clinical infrastructure. sDHTs should support appropriate data transmission approaches for the home and community setting, including WiFi, Bluetooth connectivity, cellular transmission, or other mechanisms that enable timely transfer of physiologic data. Sensor-generated data should integrate with clinical infrastructure using standardized data models and interoperable interfaces. Stakeholders cautioned against creating isolated data silos or being restrictive to specific DHTs as those could create additional operational barriers (e.g., extend internal approval times for acquiring a new technology when alternative fit-for-purpose sDHTs are available).

Human-in-the-loop clinical decision support

The clinical value of sensor-generated physiologic data depends on transforming measurements into interpretable information that supports clinical decision-making. Continuous or high-frequency data collection may provide greater temporal resolution than episodic measurements, enabling characterization of physiologic patterns and changes over time that may not be apparent with intermittent assessments. Realizing this potential requires reliable measurement, appropriate data processing, and presentation of explainable, actionable insights that integrate into clinical workflows. These capabilities are central to the development of trustworthy CRS de-risking products that support earlier recognition and management of CRS (DiMe, 2025).

Within these products, CRS early warning algorithms may provide an additional layer of decision support by integrating sensor-derived data to identify patterns that may indicate changing risk and support timely clinical review. CRS early warning algorithms should be designed to provide actionable insights, identify meaningful physiologic changes, and support timely clinical review within established care pathways.

> **HUMAN-IN-THE-LOOP**
>
> Every clinically meaningful alert requires interpretation by a trained healthcare professional. The algorithm's job is to answer “who needs attention and why?” The clinician's job is to decide what happens next.
>
> Capabilities in this field are expected to expand, and future intended uses may support different models of clinical oversight. Any such change would carry its own validation and regulatory requirements, and would need to be established before altering the role of human interpretation described here.

Design considerations for a trustworthy CRS early warning algorithm

- **Consistent clinical inputs**
  An algorithm's ability to distinguish concerning changes from normal variation depends on being developed against consistent clinical determinations of when CRS occurred and how it progressed. These determinations always involve a degree of clinical judgment, but the more consistently CRS is identified, graded, and documented, the stronger the basis for developing and validating the algorithm.
- **Personalized baselines**
  Population-wide thresholds can generate both false alarms and missed early warning signs because normal heart rate, oxygen saturation, temperature, and activity can vary between patients based on several non-treatment dependent causes such as chronic health conditions or medication the patient might be on. Effective monitoring relies on an individualized pre-treatment baseline and evaluates subsequent changes relative to that patient's own reference state instead of relying on fixed population-based thresholds.
- **Trends over snapshots**
  Rather than triggering on a single reading crossing a fixed line, stakeholders want algorithms that recognize patterns (e.g., a temperature that's been climbing for six hours, or a heart rate that's crept 25% above baseline). An individualized baseline captures not only a patient's typical values but their normal range of fluctuation (including expected daily rhythms, such as lower heart rate overnight) so that monitoring can distinguish meaningful change from ordinary variation.
- **Explainable alerts**
  Clinicians need to understand why an alert was generated. Alerts should identify the specific physiologic changes contributing to concern (e.g., "Heart rate increased 25% above baseline with persistent fever following step-up dosing") rather than presenting an unexplained risk score.
- **Workflow integration**
  Even a high-performing algorithm will fail if it generates excessive false alerts or disrupts clinical workflows. Alert delivery should integrate with established communication pathways and electronic health records, minimize false-positive burden and manual data review, and support timely clinical response. Across stakeholder interviews, workflow integration consistently emerged as a primary determinant of successful adoption. While core monitoring components including symptom collection, clinician review, and escalation pathways can be standardized, CRS early warning algorithms should remain configurable to accommodate differences in immune effector therapies. Monitoring triggers, observation windows, alert timing, and tapering criteria should adapt to specific products without requiring entirely new technology.

Establishing an individualized baseline

A key advantage of incorporating DHT-enabled monitoring over episodic vital sign assessment is the ability to establish an individualized baseline before the period of highest CRS risk. Rather than relying solely on population-based thresholds or a single

pre-treatment measurement, continuous measurement enables subsequent physiologic changes to be interpreted relative to each patient's own reference state. This approach may improve early detection of clinically meaningful deterioration while reducing unnecessary alerts resulting from normal inter-patient physiologic variation (Rajeeve et al, 2026).

A comprehensive individualized baseline incorporates clinical characteristics, physiologic measures, and patient-reported symptoms and function. sDHTs are available to continuously capture physiological measures through wearables and remote platforms, and patient-reported outcomes may be assessed through ePRO and other digital reporting mechanisms.

- Clinical baseline: patient characteristics, immune effector therapy, comorbidities, medications (particularly steroids, antipyretics, and antihypertensives), baseline symptoms, neurologic assessment, laboratory values, and oxygen requirements
- Physiologic baseline: continuous or frequent measurements of heart rate, temperature, respiratory rate, oxygen saturation, activity, and other available sensor-based clinical measures
- Patient-reported baseline: patient-reported symptoms and functional impact, including fatigue, cognitive function, and ability to perform usual daily activities

These components serve distinct roles. Continuous physiologic measures provide the primary inputs for algorithmic monitoring and alerting. Patient-reported symptoms and functional status can support clinical interpretation and ongoing assessment by the care team. Patient characteristics, including comorbidities and concurrent medications, primarily inform patient selection and provide context for interpreting physiologic change.

Unlike a single clinic vital sign assessment, continuous monitoring establishes both the patient's typical physiologic range and expected variability. Baseline generation should incorporate sufficient longitudinal data to account for normal circadian and day-to-day fluctuations while ensuring adequate signal quality and wear time before monitoring begins (Avery et al, 2024).

The appropriate duration of baseline collection remains context-dependent and may vary based on the therapy, monitoring objective, and available evidence. Reported baseline approaches remain preliminary and come from small studies whose performance estimates are not yet robust. They are best understood as early illustrations that even simple individualized baselines can outperform fixed population thresholds, rather than as validated targets. With that in mind, reported approaches have ranged from several hours of monitoring before treatment to multiple days of wearable data collection. For example, wearable data available for at least 5 hours during the day or 2 hours overnight across at least 2 days or nights have been proposed as one approach for establishing an individualized reference state (Paludo et al, 2026). In CAR-T, available studies have demonstrated feasibility using continuous physiologic data collected during the 2-5 hours before infusion, providing sufficient data to establish an individualized reference state immediately preceding treatment (Rajeeve et al, 2026). For TCE, where CRS risk recurs with each step-up dose, establishing the baseline before the first step-up dose allows monitoring to be referenced

against the patient's pre-treatment state, with recalibration considered during low-risk intervals if clinically meaningful physiologic changes occur.

Continuous physiologic data should not be interpreted as isolated measurements but summarized into patient-specific reference ranges and trends. Published digital biomarker work has proposed using rolling observation windows (e.g., 60-minute median smoothing with 10-minute step intervals) to reduce the impact of motion artefacts and transient physiologic fluctuations before generating alerts, although these approaches require prospective validation in CRS monitoring populations (Rajeeve et al, 2026, Avery et al, 2024).

Algorithm performance requires a context-specific balance between sensitivity and specificity

The optimal balance between sensitivity and specificity for CRS early warning algorithms remains context-dependent. Higher sensitivity may catch more true CRS events earlier but risks alert fatigue and unnecessary escalations; higher specificity preserves clinician trust but risks missing early CRS progression. Rather than defining a single universal performance threshold, CRS early warning algorithm evaluation should consider the intended clinical use case, patient population, monitoring environment, and available response infrastructure. Retrospective characterization (precisely establishing what an algorithm identifies, and with what accuracy and bias across relevant subgroups) can provide substantial evidence of clinical value and should inform the design of subsequent prospective evaluation.

Monitoring should support appropriate intervention

Improved detection capabilities must be balanced with the risk of unnecessary intervention. Increased monitoring may identify more physiologic changes and lead to more alerts, which could lead to over treatment of CRS, including increased use of medications like tocilizumab or steroids, even when that additional intervention isn't beneficial, and could affect the efficacy of the immunotherapy. CRS early warning algorithm design should prioritize clinically meaningful trends that warrant review rather than simply identifying any deviation from baseline. Several design choices reduce this risk: individualized baselines and trend-based logic limit alerts driven by normal variation; explainable alerts that name the specific physiologic change let clinicians judge whether intervention is warranted rather than reacting to a risk score; and human interpretation of every clinically meaningful alert keeps the decision to treat with the care team. Together these help ensure monitoring supports timely, appropriate intervention while minimizing unnecessary use of supportive medications.

Algorithm development roadmap

Robust validation of a CRS early warning algorithm cannot rest on analytical validation alone. Establishing clinical and usability validation requires real-world evidence gathered in the intended patient populations and with the specific technologies involved, which is why development follows a structured, sequential path (Figure 1) rather than moving from analytical validation directly to scaled deployment. A critical mistake highlighted by

implementation experts is attempting to launch clinical pilots without rigorous validation. This staged approach maintains safety, optimizes thresholds, and ensures operational readiness before broader deployment.

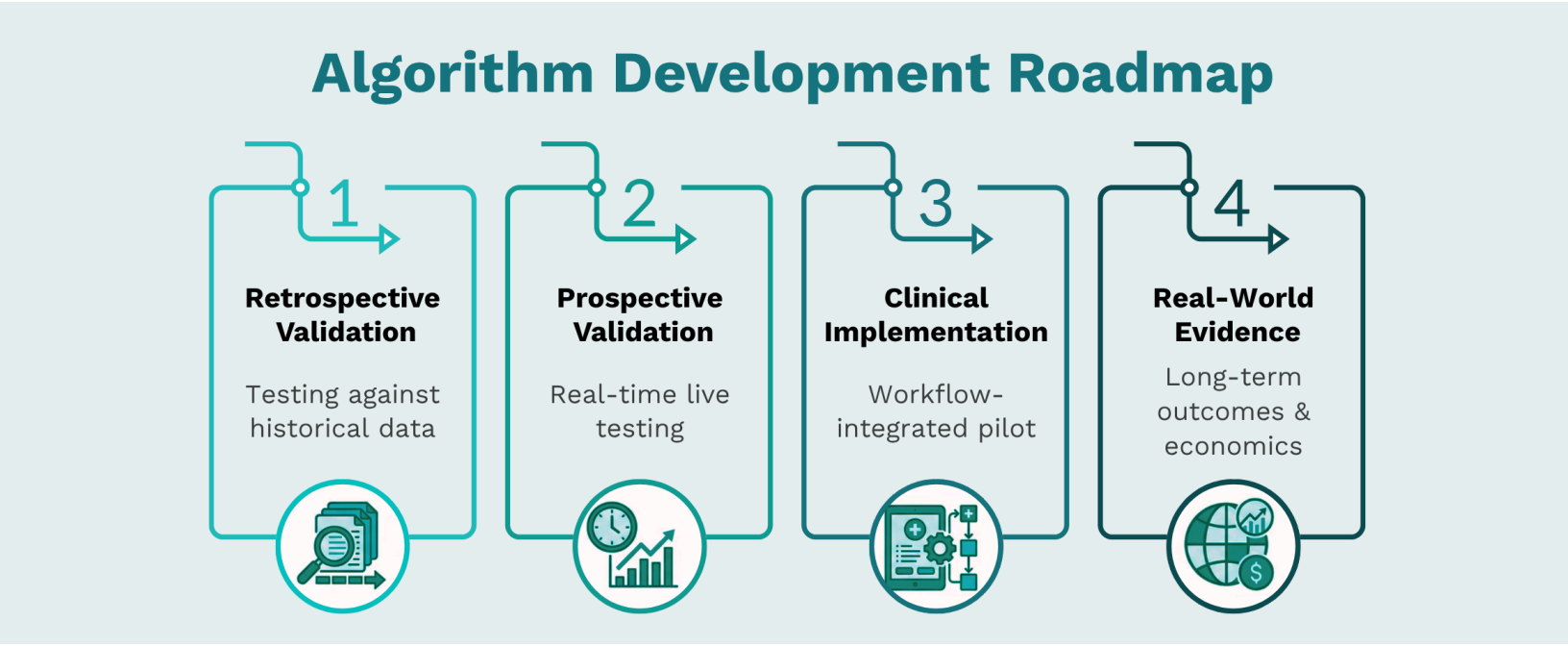

Figure 1. The path from historical data to real-world evidence. Skipping ahead to clinical implementation without prospective validation was a repeated stakeholder concern.

Regulatory considerations

Intended use is the foundational regulatory decision for a CRS monitoring solution: it determines the applicable regulatory pathway, the reimbursement mechanism, and the required model of clinical oversight. DiMe's Digital Health Regulatory Pathways resources offer a structured approach for determining a product's intended use, and FDA's guidance on Clinical Decision Support Software (FDA, 2026) and on AI-enabled device software functions (FDA, 2025) describe how the agency approaches these functions.

It is useful to distinguish what is evaluated at the product level from what is established at the institutional level. The CRS monitoring technology is a regulated product: its intended use, validation, and safety case (including human factors, how alerts are delivered and acted upon, and mitigation of failure modes such as missed or delayed alerts) fall within regulatory oversight. Institutions, in turn, are responsible for the governance arrangements around deployment: which clinical entity owns each alert, how accountability is allocated across the clinician, practice, health system, and technology provider, and the staffing and contractual structures that support the service. The two are complementary but they are established through different mechanisms.

On the product side, a regulatory strategy should establish that the technology is fit for purpose using an evidence-based validation framework such as DiMe's V3+ (verification, analytical validation, clinical validation, and usability validation), and should address best

practices for digital health software including evidence, privacy & security, and usability. Continuous physiologic monitoring also generates large volumes of patient-generated health data, requiring thoughtful governance around data ownership, privacy, retention, and integration into the clinical record.

On the institutional side, unresolved liability questions can remain a barrier to commercial scaling. Specifically, if an algorithm correctly generates an alert, but no clinical action is taken and the patient deteriorates, responsibility boundaries can become highly complex and contested. Mitigating this requires explicit governance documentation defining clear boundaries among the bedside clinician, the medical practice, the broader health system, and the technology company. This documentation must incorporate:

- **Clear alert ownership:** Defining exactly which clinical entity is legally responsible for receiving, evaluating, and acknowledging each incoming notification.
- **Standardized response protocols:** Establishing mandatory clinical pathways and standardized timeframes for clinical triage once an alert is confirmed.
- **Bidirectional documentation standards:** Automating the capture of alert delivery times, viewing times, and subsequent clinical actions to ensure a comprehensive audit trail.

Current DHTs for CRS monitoring keep a clinician in the loop: every clinically meaningful alert requires interpretation by a trained healthcare professional. Capabilities in this field are expected to expand, and future intended uses may support different models of clinical oversight, but any such change would carry its own validation and regulatory requirements and would need to be established before the role of human interpretation described here is altered. Whether a given product is reimbursed (through remote monitoring or an emerging software-service pathway), or paid for from operational budgets will depend on how its intended use is defined (see **Section 4**).

These considerations highlight that a CRS monitoring product must integrate reliable sensing, clinically meaningful analytics, explainable decision support, and appropriate governance to translate physiologic data into actionable clinical insights. The next question is whether these capabilities create sufficient value to support sustainable adoption.

4. Economic considerations for outpatient CRS monitoring

The business case

The economic case for CRS monitoring rests on care delivery, not billing codes: potential improvements in care, reduction of avoidable healthcare utilization, preservation of clinical capacity, and the ability to safely expand access to complex immunotherapies. Remote-monitoring reimbursement may offset some cost, but it does not fully capture where the value actually lies.

As one stakeholder noted:

> "The reimbursement is not the issue here. It's freeing up the beds. That's the thing that's important. Anything that you get as a reimbursement from, like, $28 per month remote-patient-monitoring CPT code billing is just never going to be worth it compared to actually getting this person to be able to go back home, and then I have my hospital bed."
> *— Sponsor*

Different stakeholders may capture different sources of value

- Health systems and hospitals value freed-up beds (avoiding a hospital bed-day costs approximately $3,000 per day (Ferreri et al., 2025)) and expanded treatment capacity though how much this matters depends heavily on how constrained their current capacity already is.
- Academic centers see an opportunity to extend their expertise to satellite sites and discharge patients with more confidence, while needing to maintain oversight and standardization across locations.
- Community oncology practices may rely on the technology to support detection of CRS. They're also asking whether it will let them safely keep and manage these patients locally, given real constraints on staffing and overnight coverage.
- Payers want to see the performance evidence for a CRS early warning algorithm backed by measurable impact such as hospitalization, ICU use, patient quality of life, and total care cost.
- Sponsors benefit from expanded patient access, but were cautioned against letting any outpatient CRS monitoring requirement become a barrier (e.g., tying it too closely to drug labeling which may further restrict patient access if the technology is not accessible).

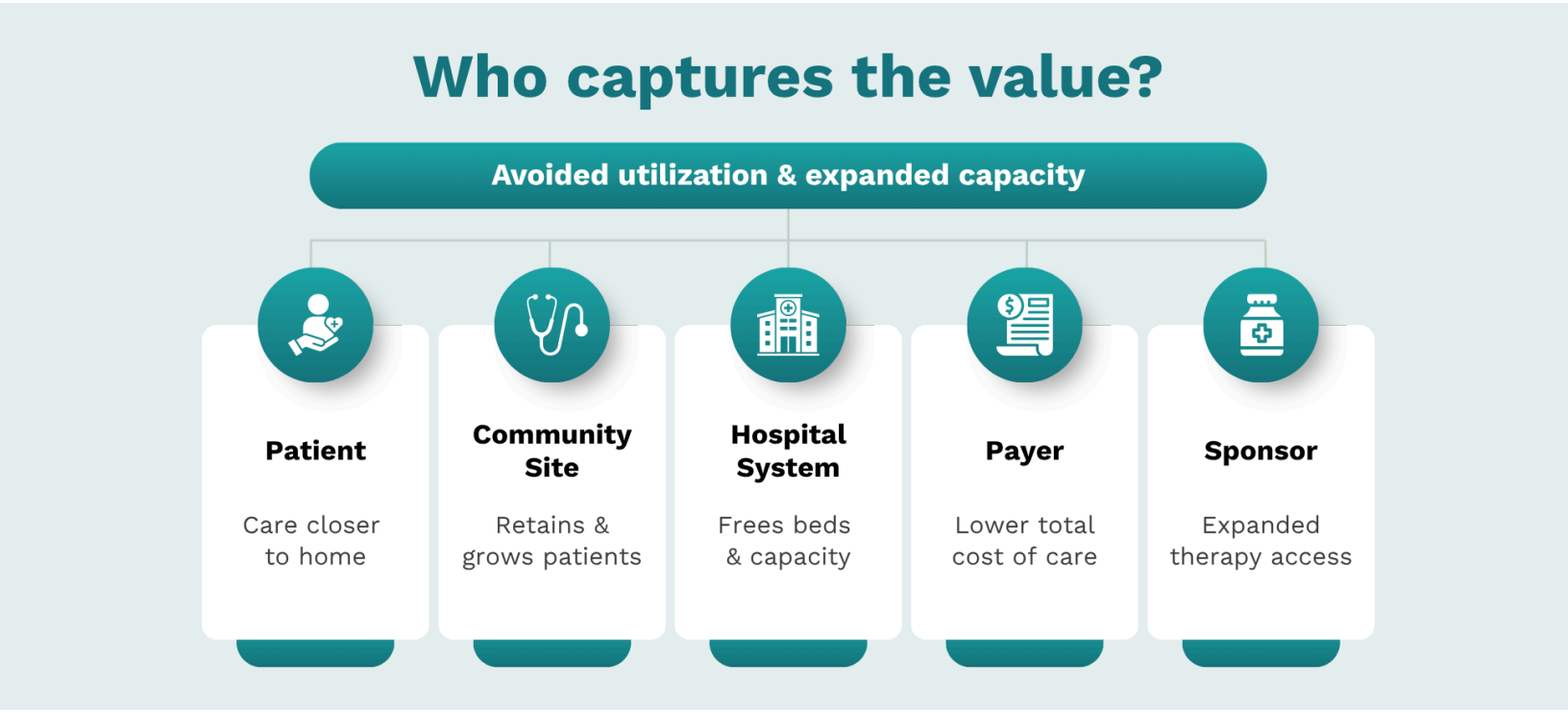

Figure 2. The value of DHTs for outpatient administration of CAR-T and TCEs is stakeholder-dependent. The strongest commercial model for a CRS early warning algorithm explicitly accounts for every node on this map.

Value extends beyond cost to patient access

Beyond direct cost, an outpatient model lets patients remain near home, family, and caregivers during a demanding treatment window rather than relocating for weeks near a tertiary center, a burden that falls disproportionately on lower-income and geographically distant patients. In a SEER-Medicare analysis of third-line-or-later DLBCL, CAR-T recipients were more likely to live in higher-income areas, and patient distance to the nearest treatment center predicted the likelihood of being treated; the same analysis modeled that equalizing travel distance between poorer- and better-access states could increase CAR-T utilization by roughly 38% (Chung et al., 2025).

For CAR-T, this shift is already underway. In June 2025, the FDA removed REMS requirements for all approved CD19- and BCMA-directed autologous CAR-T therapies, eliminating site-certification and on-site tocilizumab requirements, shortening the recommended post-infusion proximity period from four weeks to two, and reducing driving restrictions from eight weeks to two (FDA, 2025). In easing these requirements, the FDA pointed to accumulated evidence that CRS and ICANS risks are manageable, providing an early sign that regulatory barriers to community-site delivery are beginning to lift. For TCEs, the evidence is earlier-stage: step-up dosing still carries product-specific hospitalization considerations, but real-world outpatient programs are beginning to show feasibility. In a Mayo Clinic series, teclistamab step-up dosing was delivered outpatient with a remote-monitoring kit and command-center support; about a third of patients developed CRS, nearly all low-grade, and all cases resolved with supportive care (Sandahl et al., 2025).

Adoption requires alignment of economic incentives across the care pathway

Outpatient CRS monitoring creates potential value across the healthcare system, but the costs of implementation and the benefits realized may occur in different parts of the care pathway. The primary economic value proposition is reduced healthcare resource utilization, particularly avoided inpatient monitoring days, hospitalizations, and ICU escalation. For health systems with capacity constraints, reducing unnecessary inpatient utilization can create meaningful operational value by improving bed availability and enabling more efficient use of specialized resources.

At the same time, community practices may need to invest in staff training, technology infrastructure, and workflow redesign to support outpatient monitoring. The value to community sites extends beyond utilization savings, including the ability to retain patients within their practice, maintain continuity of oncology care, and avoid unnecessary transfers to distant academic centers.

A scalable adoption model will require alignment across these stakeholders. Potential approaches include health-system-supported investment where avoided utilization benefits are captured, shared-care models between academic and community sites, early implementation support during market development, and value-based arrangements tied to measurable outcomes and healthcare resource utilization.

A hybrid care model may provide a practical pathway for expansion therapy access, with specialized centers supporting therapy administration and early high-risk monitoring periods while community practices assume a greater role in ongoing monitoring and management connecting teams through a digital monitoring workflow. This approach may preserve specialized expertise while extending care closer to where patients live and improving system capacity.

What evidence will actually change practice

The accuracy of a CRS early warning algorithm alone will not drive adoption. Evidence that outpatient delivery of CAR-T can achieve comparable outcomes at lower cost is already emerging (Hansen et al., 2023). The question is therefore what evidence would give a CRS early warning algorithm enough credibility for clinicians, health systems, and payers to adopt it. Stakeholders described a three-phase evidence path: first, a feasibility study showing the alert workflow and technology work reliably in practice; second, prospective clinical validation showing real impact on time-to-intervention, hospitalization, and safety; and third, a real-world comparative evaluation of the current care versus use of the CRS early warning algorithm that can speak directly to cost, capacity, and utilization, since that's the evidence health systems and payers say they actually need.

The evidence required for adoption will vary by stakeholder. Health systems may prioritize reductions in clinician workload, emergency department visits, hospital admissions, and treatment interruptions. Payers increasingly expect evidence of improved outcomes and cost-effectiveness. Pharmaceutical sponsors often emphasize adherence, persistence, safety monitoring, and real-world evidence generation. Consequently, commercialization and evidence-generation strategies should be developed in parallel rather than sequentially.

Potential payment and adoption pathways

Clinical value does not automatically translate into sustainable revenue. For CRS monitoring technologies, commercialization depends on aligning with reimbursement mechanisms, demonstrating measurable clinical and operational value, and identifying stakeholders willing to pay. At least four potential payment pathways exist, each involving different customers, evidence requirements, implementation challenges, and sales cycles. In practice, a durable business model will likely combine multiple pathways rather than rely on a single reimbursement source. The pathways below are established commercialization mechanisms in general use; they are presented as potential routes whose feasibility will depend on the value evidence and intended-use positioning discussed above.

1. Provider billing through RTM/RPM reimbursement

The most established reimbursement pathway is through healthcare providers using existing Remote Therapeutic Monitoring (RTM) and Remote Physiologic Monitoring (RPM) CPT codes, depending on the technology, intended use, and clinical workflow. RTM may be relevant for symptom-based monitoring and clinician-guided management, whereas RPM may apply when DHT-generated physiologic measurements are incorporated into care. Recent CMS updates have increased flexibility for shorter monitoring durations: the CY2026 Physician Fee Schedule finalized new codes covering remote physiologic monitoring over a 2–15 day period rather than requiring a full 16 days, making reimbursement more feasible for episodic treatments such as CAR-T and TCEs (CMS, CY2026 Physician Fee Schedule Final Rule). These code families are well established for remote monitoring in other clinical areas; RTM's defined scope currently centers on musculoskeletal, respiratory, and behavioral health monitoring, so billing for CRS monitoring would extend an existing reimbursement mechanism into a new clinical area rather than rely on established precedent. Remote CRS monitoring itself is an active area of clinical investigation in CAR-T and TCE care, but a dedicated reimbursement pathway has not yet been established. Importantly, CMS reimburses eligible providers directly. In this model, technology vendors license their platform to hospitals or physician practices, which bill payers and retain reimbursement. Medicare has not historically offered a dedicated reimbursement category for standalone clinical software, requiring developers to work within existing payment mechanisms. This is beginning to change: in its CY2027 outpatient payment proposed rule (July 2026), CMS proposed a new 'Software as a Medical Service' (SaMS) category for software that supports clinical decision-making through algorithmic analysis, distinct from remote physiologic and therapeutic monitoring. Whether a CRS monitoring product would fall under RPM/RTM or an emerging SaMS pathway depends on how its intended use is defined; the SaMS proposal remains in a transitional, not-yet-finalized state.

2. Value-based oncology payment models

Value-based oncology models may provide an important pathway for realizing the economic benefits of outpatient CRS monitoring. Programs such as the CMS Enhancing Oncology Model (EOM) provide participating practices with monthly care management payments and performance-based incentives tied to quality and total cost of care rather than individual services (EOM, 2025). Within these arrangements, technologies that reduce emergency

department visits, avoidable hospitalizations, treatment interruptions, or unnecessary toxicity-related utilization may generate meaningful return on investment. These environments may support subscription or per-member-per-month pricing models based on demonstrated reductions in healthcare utilization and improvements in care quality. The EOM itself is an active CMS model, but its use to reimburse CRS monitoring specifically is illustrative; we are not aware of published rollout or performance data for monitoring tools within these arrangements.

3. Pharmaceutical sponsor and manufacturer partnerships

Pharmaceutical manufacturers have strong incentives to support CRS early warning algorithms that improve treatment delivery, generate real-world evidence, and facilitate broader access to complex immunotherapies. Potential partnership models include therapy-specific monitoring platforms, manufacturer-supported patient services, clinical trial monitoring, and post-marketing evidence generation. Early-stage collaborations with pharmaceutical sponsors may provide funding for product development while simultaneously generating the clinical evidence needed for broader market adoption. Such partnerships must be carefully structured to comply with anti-kickback, fraud and abuse, and patient inducement regulations, which often favor provider-mediated deployment or appropriately designed patient support programs.

4. Enterprise health-system adoption

Health systems and cancer centers may adopt a CRS early warning algorithm as part of their infrastructure required to deliver complex immunotherapies. Enterprise purchasers increasingly evaluate such technologies as clinical infrastructure, weighing clinical validation, workflow integration, quality improvement, workforce efficiency, patient safety, and accreditation goals (Marwaha, 2022). Health systems operating under capitated or integrated payment models may realize financial benefit directly through avoided admissions and improved resource utilization (e.g., the bed-day and utilization economics quantified earlier in this section) making demonstrated operational and clinical value the driver of purchasing decisions.

Building a sustainable economic model

Rather than relying on a single reimbursement mechanism, the most resilient commercialization strategy is likely to evolve over time. Early-stage platforms may first establish value through clinical research collaborations or pharmaceutical-sponsored programs that generate both funding and evidence. As clinical and economic outcomes become established, health systems can adopt the technology using reimbursement mechanisms such as RPM/RTM where appropriate, while enterprise purchasing, value-based care contracts, and pharmaceutical partnerships provide complementary revenue streams. In the near term, sustainable growth is likely to depend more on demonstrating measurable clinical and operational value to health systems and industry partners than on the emergence of a dedicated reimbursement code specifically for this category of DHT.

5. The path forward

What's next for the field

This assessment indicates that outpatient CRS monitoring is a feasible approach to support broader delivery of CAR-T and TCE therapies, provided it is implemented within an established clinical care model. Most patients can be monitored safely outside the hospital when the necessary supports are in place, including sound patient selection based on clinical judgment, clearly defined 24/7 alert routing and escalation, reliable return-to-care, and integration with emergency services. Within that model, a CRS early warning algorithm can extend clinical visibility beyond the clinic and support earlier identification of patients who may require escalation, but it remains one component of the care model and adds value only when its outputs reach an accountable clinician within an established workflow.

Developers and pilot sites have begun to demonstrate that sensor-based and ePRO monitoring can support earlier detection of events, more timely intervention, and management in community settings. This early work provides an important foundation. What the field now requires is evidence at greater scale and rigor, including larger, multi-site prospective studies and real-world comparisons against current care, particularly outside specialized centers, to establish where and for whom this approach meaningfully changes outcomes. Progress also depends on capturing and reporting CRS events consistently across sponsors and sites, so that events can be compared within and between modalities and can serve as a reliable basis for developing and validating CRS algorithms. The **CRS Adjudication Framework** is a practical step toward that consistency.

Stakeholders described a staged evidence path, best pursued through pilots conducted in partnership with treating centers, including the community and non-academic sites where access is most constrained. Each pilot addresses a distinct question from clinical and technical perspectives, but both inform the test that most determines site and clinician confidence: whether these therapies can be managed as safely outside specialized centers as within them, with comparable rates of serious adverse outcomes:

- **Clinical:** whether the care model fits clinical workflows and meets a real clinical need across different site types and settings, not only pilot institutions. Practice varies even within a single health system, and alert routing, escalation, and coverage may sit with the site, the platform, or a shared arrangement; as more sites across these settings adopt a common care model, the field can build the evidence needed to support delivery at scale.

- **Technical:** whether algorithm performance holds under real outpatient conditions, including sensitivity, specificity, lead time, and false-positive burden, while the monitoring workflow itself generates the technical performance and clinical utility evidence, making each pilot a dual-purpose investment rather than a cost.

Pursued together, these pilots advance the field from feasibility toward the clinical validation and real-world comparative evidence that health systems and payers have identified as necessary for adoption. Getting there is a shared undertaking that requires clinicians, technology developers, regulators, payers, and therapy sponsors aligning on

evidence requirements; adopting consistent approaches to capturing and reporting CRS events; and extending care models to the community and non-academic settings where access is most constrained. This feasibility assessment and the accompanying **CRS Adjudication Framework** are offered as a foundation for that work.

CLOSING PERSPECTIVE

Outpatient CRS monitoring has the potential to enable safer, more scalable delivery of CAR-T and TCE therapies. Realizing this potential will require integration of reliable technology, clinically meaningful insights, and sustainable care pathways, developed together through coordinated pilots that validate both the clinical pathway and the monitoring approach in the settings where access is most constrained. Most evidence to date comes from CAR-T; the field will benefit as more programs pilot these approaches and share experience with TCEs, where outpatient evidence is still emerging.

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Appendix A. Site Readiness Checklist for Outpatient CAR-T and TCE Administration Supported by CRS Monitoring

Many sites will design their outpatient model with CRS monitoring workflows built in from the start, rather than adding them on afterward. The six domains below should be considered: the first five apply to every outpatient program regardless of monitoring approach, and the sixth applies only when RPM or DHT is part of the plan.

Clinical Capability

☐	CRS monitoring, detection, triage, and re-entry protocol documented
☐	Providers trained in CRS recognition, escalation, and treatment pathways
☐	Nursing competency in CRS management and escalation established
☐	Access to specialty consultation when needed
☐	Modality-specific workflow defined for CAR-T vs TCE products

Staffing & Ownership

☐	Named clinical owner for post-treatment patient monitoring
☐	Clinical workflow for alert review and response established
☐	Overnight and weekend coverage identified
☐	Backup coverage model in place

Patient & Caregiver Readiness

☐	Outpatient suitability assessed using site-defined clinical judgment/process
☐	Reliable caregiver identified
☐	Patient and caregiver education completed prior to therapy administration
☐	Return-to-care instructions documented and understood
☐	Transportation and proximity-to-care plan confirmed

Emergency Preparedness & Re-entry

☐	Re-entry pathway defined for daytime escalation
☐	Re-entry pathway defined for overnight/weekend escalation
☐	Hospital transfer or admitting relationship established (if applicable)
☐	Local emergency department briefed on CRS including education resources, management, and escalation pathways with contact information.
☐	Escalation communication plan documented
☐	Receiving site treatment capability/resources confirmed (if applicable)
☐	Bed/admission capacity or contracted access confirmed (if applicable)

Financial Sustainability

☐	Site-specific business case developed
☐	Staffing model and operational workflow impact assessed
☐	Resource and training burden assessed
☐	Value proposition defined for the site

Technology Infrastructure (If applicable)

☐	Human-in-the-loop clinical review process defined for alerts
☐	Technology access and support needs confirmed prior to therapy administration when appropriate
☐	Monitoring platform deployed and staff educated
☐	EHR integration completed or alternate alert visibility plan documented
☐	Alert routing defined and tested
☐	Data review workflow established
☐	Patient-specific physiologic baselines documented
☐	Threshold logic for escalation reviewed to reduce over-alerting and over-treatment
☐	Reimbursement and/or funding pathway identified

Workflows will vary by product and site; adapt this assessment to your local setting and to the specific CAR-T or TCE product.

Appendix B. Where stakeholders agreed and disagreed

Topic	Agreement	Divergence
Role of DHTs	Should support, not replace, clinicians	How much prediction vs. detection they should attempt
Human oversight	Always required	Exact degree of automation acceptable
Economic value	Driven by reduced utilization	Which stakeholder captures the financial benefit
Monitoring data	Continuous trend data is valuable	Optimal alert thresholds
Modality focus	Both need better monitoring	Whether CAR-T or TCEs are the bigger near-term priority
Performance goals	High accuracy needed	Exact sensitivity / specificity targets

Appendix C. Adapting the care model by site type: academic vs. community

The implementation of outpatient CRS monitoring will vary across care settings based on infrastructure, clinical expertise, and care pathways. Academic and community sites may benefit from remote CRS monitoring in different ways depending on their current workflows and operational requirements.

Readiness layer	Academic / specialized center	Community site
Protocol standardization	Typically already has an institutional protocol; the opportunity is digitizing and EHR-integrating an existing pathway	Often starting from informal, staff-dependent habits; needs a standardized protocol introduced alongside the technology, not after it
Clinical ownership	Dedicated cellular-therapy attending and nursing coverage frequently already exists	Requires an explicit, named physician and nursing lead, including backup and overnight coverage, that may not currently exist
Overnight / off-hours coverage	Often has in-house on-call clinician with CAR-T and TCEs expertise	Best served by the hybrid triage model that leverages DHT to prioritizes and routes alerts to the community care team
Staff training	Deep bench of staff already experienced with CRS grading and management	Training with supporting educational resources is a prerequisite to deployment for clinical care team
Return-to-care pathway	Hospital transfer and ED communication typically already integrated on one campus	Needs an explicit, tested pathway to the nearest capable facility, modeled on rapid-response frameworks like stroke or maternity triage
Technology fit	Priority is EHR integration and reducing duplicate documentation for already-trained staff	Priority is simplicity, low false-alarm burden, and clear escalation routing for staff who may see CRS infrequently