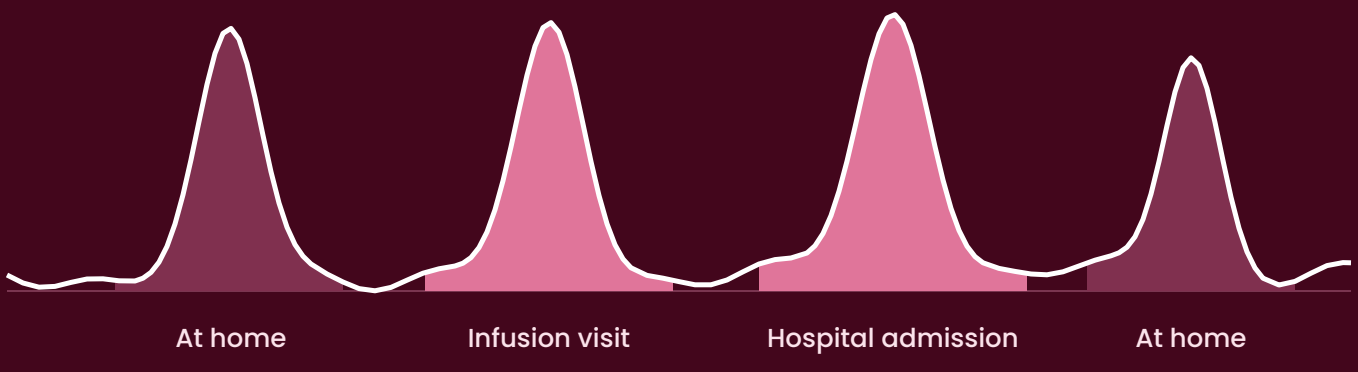
painimation

WHITE PAPER

SICKLE CELL DISEASE · CLINICAL TRIAL ENDPOINTS

Counting Every Pain Event

A cautionary tale from sickle cell disease. How poor pain endpoints have failed clinical trials, and what better measurement would do for trial power.



Expressive Painimation Co.

October 2026 · painimation.com

EXECUTIVE SUMMARY

Sickle cell disease shows how poor pain endpoints fail trials

Clinical trials that evaluate pain depend on defining and measuring it accurately. Sickle cell disease (SCD) shows how hard it is to do both. Pain events are a primary endpoint in many SCD trials, yet there is no consistent definition of a pain event and no reliable method for both capturing and characterizing every event.[1,2] Most phase 2 and 3 trials count only events that lead to an emergency department (ED) visit or hospitalization. Daily diary studies show that most SCD pain events are managed at home, where these endpoints miss them.[3–7] Several landmark SCD trials over the past decade failed to meet their pain-related endpoints (Table 1). These failures are costly, place substantial burden on patients and clinical teams, and can stop promising treatments from advancing. Clinical trials cannot fully evaluate treatment effects when they fail to measure much of the pain patients experience.

Better pain measurement could make clinical trials more efficient and more informative. Capturing events managed outside health care, distinguishing different pain types, and tracking changes in pain characteristics may give a more complete picture of treatment response. More complete and consistently defined event capture could increase statistical power and reduce the number of participants needed to evaluate a therapy. Characterizing which pain events respond to treatment could also help researchers understand how a drug works, identify the patients most likely to benefit, and design more targeted trials.

In our simulations of a drug that reduces every crisis by 30%, counting every reported event reduced the required sample size by 21% to 30% when all participants seek hospital care at the same rate, and by 42% to 77% when care-seeking varies between participants. More events do not automatically mean more power. The gain depends on event rates, the size of the treatment effect, measurement error, and how care-seeking varies, and Section 2 states each assumption. One in 7 closed SCD trials on ClinicalTrials.gov was terminated because it could not enroll enough participants (Section 2), so every participant a trial can save matters.

AT A GLANCE

62% to 90%
Share of pain events managed at home across daily diary studies[3–7]

7 of 9
Representative phase 2/3 SCD trials that showed no benefit on pain or pain events

1 in 7
Closed SCD trials on ClinicalTrials.gov that were terminated for failure to enroll

48%
Industry-led phase 2/3 SCD efficacy trials that used a pain, VOE, or utilization endpoint

21% to 77%
Fewer participants needed in our simulation when every reported event is counted

THREE TAKEAWAYS

01 **Pain events are inconsistently defined and inadequately characterized.** SCD trials use different definitions of a pain event, and conventional endpoints provide limited information about pain type, quality, and change over time.[1,2] Better measurement could help distinguish the pain experiences that treatments are meant to address.

02 **Most SCD pain events are missed by conventional trial endpoints.** Daily diary studies find that 62% to 90% or more of pain events are managed at home.[3–7] Because most trials rely on ED visits and hospitalizations, they miss much of the pain patients experience. Whether an event reaches the hospital also depends on factors beyond pain severity, such as transportation, cost, access, and social support.

03 **Better pain measurement could improve trial efficiency and reveal treatment effects.** In our simulations, capturing all reported pain events reduced the required sample size by 21% to 77%, depending on care-seeking assumptions. Measuring pain quality and other event characteristics could also show which symptoms respond to treatment and which patients benefit.

THE SOLUTION

Expressive Painimation is a full-service, end-to-end, secure electronic clinical outcome assessment (eCOA) platform built on more than 15 years of digital health research in pain trials. Participants enroll, consent, and report from their own phone or browser. They show where their pain is, what it feels like, and how strong it is using abstract pain animations (painimations), and they flag pain events as they happen, at home or in the hospital. Trial teams receive scored event data from one system and one vendor.

01 · THE PAIN ENDPOINT PROBLEM

SCD offers a cautionary tale for any trial that depends on a pain endpoint

Its trials have defined pain events inconsistently, counted only the events that reach a hospital, and recorded little about each event beyond whether it occurred. Most of the phase 3 trials reviewed here showed no benefit on pain. This section describes what went wrong, and Section 2 estimates what better measurement would do for trial power. In this paper, a pain event is any acute episode of SCD pain, whatever its cause, and VOE and pain crisis follow the definition each trial used.

Pain events define whether SCD therapies work in clinical trials.

SCD affects about 100,000 people in the United States and 7.74 million worldwide.[8,9] Pain is its most frequent symptom and the leading reason patients seek emergency and hospital care.[10] SCD therapies are approved or abandoned on their ability to reduce pain events. Crizanlizumab reduced pain crises by 45.3% in phase 2, then showed no difference from placebo in its confirmatory phase 3 trial, and the European Medicines Agency revoked its authorization.[11–13] Voxelotor met its hemoglobin endpoint without reducing VOEs and was withdrawn worldwide in 2024 after post-marketing studies showed more VOEs and deaths.[14,15]

Crizanlizumab	PHASE 2 · SUSTAIN Pain crises fell 45.3% (n=198)[11]	PHASE 3 · STAND No difference from placebo (n=252)[12]	2023 European authorization revoked[13]
Voxelotor	PHASE 3 · HOPE Hemoglobin endpoint met[14]	SAME TRIAL VOEs not reduced[14]	2024 Withdrawn worldwide after more VOEs and deaths in post-marketing studies[15]

SCD pain takes several forms that are difficult to characterize and distinguish.

The acute VOE results from microvascular occlusion and inflammation. Chronic pain affects 30% to 40% of adults with SCD and fluctuates from day to day.[16] The two overlap. The AAPT taxonomy for acute SCD pain, developed through the ACTTION public-private partnership with FDA, states that acute pain episodes were classically attributed to vaso-occlusion but that chronic pain may also contribute to their pathogenesis, which "adds complexity to their diagnosis and management." Its working group defined acute SCD pain with 4 diagnostic criteria plus 2 modifiers to account for the influence of chronic pain.[1] The companion chronic taxonomy derived a single condition, chronic SCD pain, with 3 more modifiers reflecting different clinical features.[2] The field needed 2 taxonomies and 5 modifiers to describe one patient's pain. In practice, 21.8% of 156 youth hospitalized at 4 children's hospitals for a VOE met criteria for widespread pain, a different clinical phenotype, and they reported higher chronic functional disability (30.4 vs 22.2; P = .02).[17] One in 5 admissions coded as acute vaso-occlusion carried a chronic widespread pain phenotype. The American Society of Hematology guidelines name limited understanding of the complex biological differences between acute and chronic pain as a barrier to targeted treatment.[18]

2 and 5
taxonomies and modifiers needed to describe acute and chronic SCD pain[1,2]

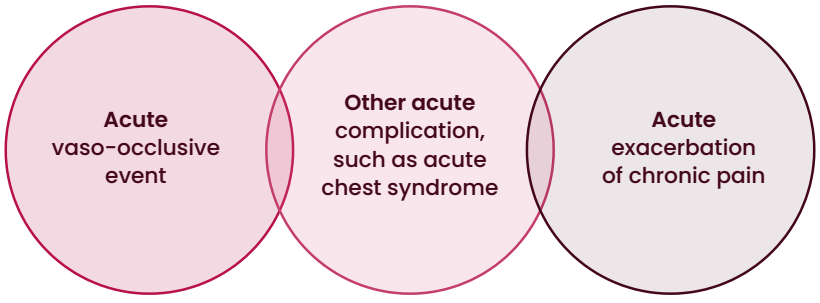
1 in 5
youth hospitalized for a VOE met criteria for widespread pain[17]

30% to 40%
of adults with SCD live with chronic pain[16]

Pain events drive SCD health care costs and mortality.

They account for 85% of ED and inpatient encounters, most of the $1.6 to $1.7 million lifetime cost of SCD care, and earlier death.[19–23]

What a single SCD pain event can be

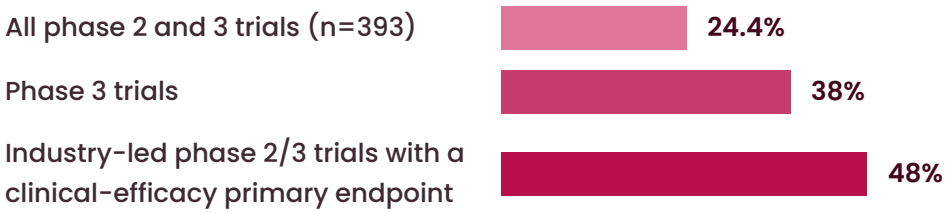


The kinds overlap, and trial definitions differ in which of them they count.[1,2,11,24]

Pain events are the most common trial endpoint, yet they lack a consistent definition.

Our analysis of 393 interventional phase 2 and 3 SCD trials on ClinicalTrials.gov found that 24.4% used a pain, VOE, or utilization primary endpoint, rising to 38% of phase 3 trials and 48% of industry-led phase 2/3 trials with a clinical-efficacy primary endpoint. Protocols differ in the care setting, treatment, and visit duration that define a VOE, and applying different definitions to the same trial data changed which participants were event-free.[24] The multinational DOVE trial found regional differences in pain perception, analgesic use, and VOE hospitalization.[25] The ASH and FDA endpoint consensus panels identified the pain endpoints with supporting data and called for research to develop and validate new ones.[26]

Share of SCD trials with a pain, VOE, or utilization primary endpoint



Source: Expressive Painimation Co. analysis of ClinicalTrials.gov registrations, 2026.

Utilization endpoints undercount events and can mask treatment effects.

Most trials count health care visits as a proxy for pain events, so they miss events managed at home.[27] An endpoint that misses most events loses statistical power and can fail to show a real effect. Of 9 representative phase 2/3 trials, 7 showed no benefit on pain or pain events (Table 1). Six missed their pain, VOE, or utilization primary endpoint. Voxelotor met its hemoglobin endpoint but did not reduce VOEs.

Of 9 representative phase 2/3 trials, 7 showed no benefit on pain or pain events.

Table 1. Nine representative phase 2/3 SCD trials. Seven showed no benefit on pain or pain events.

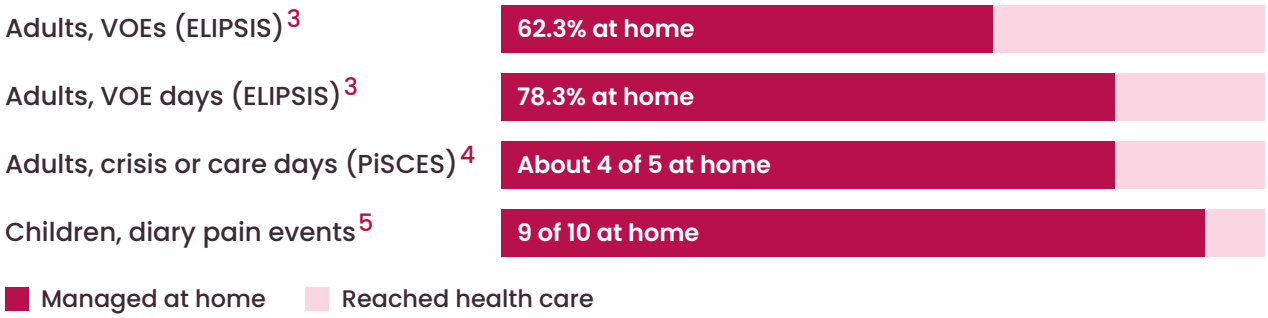
Agent and trial	Phase	N	Primary endpoint	Result
Hydroxyurea, MSH[28]	3	299	Annual rate of painful crises	Met, 2.5 vs 4.5 per year
Crizanlizumab, SUSTAIN[11]	2	198	Annual pain crisis rate	Met, 1.63 vs 2.98 per year (not replicated)
Voxelotor, HOPE[14]	3	274	Hemoglobin response >1.0 g/dL	Met on hemoglobin, VOEs not reduced
Crizanlizumab, STAND[12]	3	252	Annualized attended VOE rate	Not met
Prasugrel, DOVE[29]	3	341	VOE rate per person-year	Not met, RR 0.83
Ticagrelor, HESTIA3[30]	3	193	VOE rate	Not met, 2.74 vs 2.60 per year
Canakinumab[31]	2	49	Patient-reported pain (eDiary)	Not met
Rivipansel, RESET[32]	3	345	Time to discharge readiness	Not met, P = .79
Poloxamer 188, EPIC[33]	3	388	Time to last parenteral opioid	Not met, P = .09

Representative trials selected from our analysis of ClinicalTrials.gov registrations (see Methods notes).

Most SCD pain events occur outside health care settings

Daily diary studies in adults and children find that 62% to 90% or more of pain events are managed at home.[3–7] The most detailed recent estimate comes from ELIPSIS, a 6-month, noninterventional study in which 37 adults with SCD reported pain, medication use, and VOE days each day on an electronic diary. The 35 who completed the study reported 114 VOEs over 346 VOE days, and 62.3% of those events and 78.3% of VOE days were treated at home.[3] Earlier diary studies agree. In the PiSCES study of 232 adults and 31,017 diary days, participants reported crises managed without care on 12.7% of days and sought care on only 3.5%, so about 4 of every 5 days with a crisis or a care visit were managed at home.[4] In children, 9 of 10 diary-reported pain events were managed at home, a 4-week diary study of 25 children found that nearly all sickle cell pain was managed at home, and a caregiver diary study in infants and toddlers notes that more than 80% of VOEs are managed at home.[5–7]

Share of patient-reported pain managed at home



A crisis managed at home is not necessarily a milder one

Many home-managed episodes are mild to moderate, and half last a day or less, but a crisis managed at home is not necessarily a milder one. Home-managed and hospital-treated pain share clinical features and hematologic predictors, which suggests one continuum of pain rather than two kinds of event.[34] Whether a patient goes to the hospital depends on factors that trials do not measure, including transportation, cost, access to care, psychosocial stress, social support, stigma, and past experiences with emergency care.[35–38]

What decides whether a crisis reaches the hospital, beyond pain[35–38]

- Transportation
- Cost
- Access to care
- Psychosocial stress
- Social support
- Stigma
- Past experiences with emergency care

None of these factors is measured by a utilization endpoint, and none is changed by the drug under study.

A hospital visit reflects a patient's circumstances, not only the severity of the pain.

Existing measures do not adequately capture or characterize SCD pain events.

An SCD pain event can be an acute VOE, another acute complication such as acute chest syndrome or priapism, or an acute exacerbation of chronic pain, and trial definitions differ in which of these they count.[1,2,11,24] The field has struggled to define these event types and to tell them apart. The measures trials typically use record only whether an event occurred and how intense it was on a 0-10 scale. Patients report the first of these reliably. In ELIPSIS interviews, nearly all participants confirmed that the diary's description matched their crises and said they could tell crisis pain from everyday pain, and their symptoms and functioning were worse on the days they marked as crisis days.[39] The diary method, however, cannot show what type of pain a patient is having. It leaves out the patient's experience of pain and the specific characteristics that would show trialists whether a treatment is working, how it works, and which pain condition it helps.

The diary method, however, cannot show what type of pain a patient is having.

Pain intensity alone may not detect meaningful change.

IMMPACT recommends assessing physical and emotional functioning alongside pain intensity.[40] Across 75 randomized trials of psychological therapy for chronic pain, treatment improved disability (SMD, −0.32) more than pain intensity (SMD, −0.22).[41] On a 0-10 scale in SCD samples, that intensity effect is about 0.6 points, below the 1-point change patients rate as slightly better.[42] The field's consensus body attributes many failed chronic pain trials to their inability to detect benefit rather than to a lack of drug effect.[43]

On a 0-10 scale in SCD samples, the typical intensity effect is smaller than patients notice[42]



A multidimensional approach can improve pain measurement

Patients describe pain through quality, location, and spread, not intensity alone. In a 12-month analysis of 300 adults with chronic SCD pain, 0-10 intensity did not change despite improvement in other pain outcomes, while changes in the painimations participants selected and the body area they painted tracked improvement in PROMIS Pain Interference and ASCQ-Me episode severity.[44] Changes in pain quality carried clinical meaning. Participants whose pain newly took on a shooting quality reported worse pain interference than those whose shooting pain resolved.[44] A measure that records quality, location, extent, and intensity can show an event's start, peak, and recovery, whether or not it reaches care.

A YES-OR-NO PAIN DIARY RECORDS

- Whether an event occurred
- Intensity, 0–10

A MULTIDIMENSIONAL MEASURE RECORDS

- Whether an event occurred
- Intensity
- Pain quality, such as throbbing or shooting
- Location
- Body area affected
- Start, peak, and recovery

Participants whose pain newly took on a shooting quality reported worse pain interference than those whose shooting pain resolved.[44]

02 · WHAT BETTER MEASUREMENT WOULD DO FOR A TRIAL

SCD trials cannot afford to waste participants

Of 174 closed interventional SCD trials registered on ClinicalTrials.gov, 25 (14%) were terminated because they could not enroll enough participants, compared with 4 of 80 thalassemia trials.[45] A multicenter SCD pain trial closed early after enrolling 38 of a projected 278 participants.[46] Our own analysis found a median of 3.5 participants per site in SCD trials. Eligibility rules that require 2 or more medically attended crises in the past year also exclude patients whose crises are managed at home.[11] An endpoint that draws more information from each participant is one of the most direct ways to make an SCD trial feasible.

14%
of closed SCD trials were terminated for failure to enroll, vs 5% of thalassemia trials[45]

38 of 278
planned participants enrolled before a multicenter SCD pain trial closed[46]

3.5
median participants per site in SCD trials, from our ClinicalTrials.gov analysis

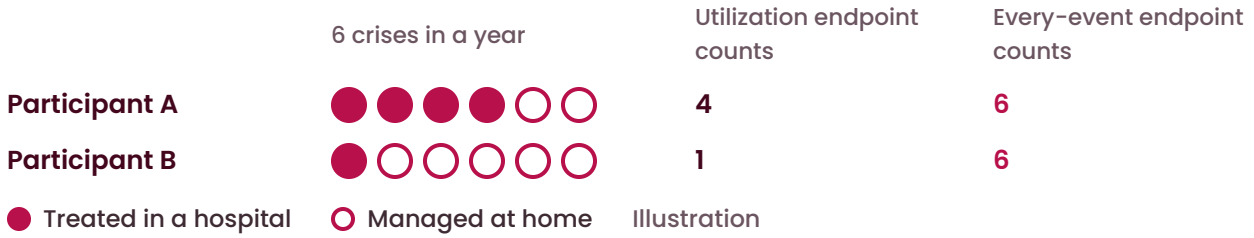
Counting every event adds statistical power.

A pain-event trial estimates a treatment effect by comparing event rates between arms, and the sample size it needs rises as the number of events each participant contributes falls.[47] A patient with 2.5 hospital-treated crises a year may have 6.5 or more in total.[3] When an endpoint misses events at the same rate in both arms, the rate ratio stays the same, but the trial loses events and the statistical information they carry.[48] Confidence intervals widen, power falls, and the absolute difference between arms shrinks. Other diseases show the same pattern. In chronic obstructive pulmonary disease (COPD), daily diaries recorded 2.7 exacerbations per person-year, but only 0.8 were reported to clinicians, and unreported exacerbations still worsened health status.[49] In an earlier diary cohort, only 51% of exacerbations were reported, with no difference in symptoms between reported and unreported events.[50] Those findings led to diary-based exacerbation measures such as EXACT, the first patient-reported outcome to undergo FDA qualification review.[51]

Utilization endpoints add noise that has nothing to do with the drug.

The factors that decide whether a patient goes to the hospital, such as transportation, cost, access, stress, and social support, differ from one participant to the next.[35–38] Two participants with the same number of crises can therefore contribute very different hospital counts. That variation inflates the variance of a utilization endpoint and the sample size needed to see past it. An endpoint that counts every event the participant reports removes that source of noise.

Same pain, different hospital counts



Illustration

How we modeled it.

We simulated 1-year, 2-arm trials with event counts drawn from a negative binomial distribution, the standard model for overdispersed event counts.[47]

- Placebo participants have 2.45 hospital-treated events a year, similar to recent placebo arms.[11,30]
- The share of all events managed at home is 62%, 78%, or 90%, spanning the diary estimates above.[3–5] Total events are therefore 6.5, 11.1, or 24.5 a year.
- The drug reduces every event by 30%, whether it is managed at home or in the hospital.
- Individual event rates vary between participants (negative binomial dispersion, 1.0), and each trial is tested at 2-sided $\alpha = .05$.
- **Same care-seeking.** Every participant takes the same share of crises to the hospital. This is the conservative case.
- **Varied care-seeking.** The share of crises each participant takes to the hospital varies between participants (SD, 0.12 to 0.20), reflecting the barriers above.
- The utilization endpoint counts only hospital-treated events. The half-capture endpoint adds half of home-managed events, a deliberately loose estimate. The full-capture endpoint counts every event participants report.

Table 2. Participants per arm needed for 80% power, by share of events managed at home.

Care-seeking	Endpoint	62% at home	78% at home	90% at home
Same for everyone	Utilization	185	185	185
	Half of home events counted	157	146	135
	All reported events counted	**147**	**137**	**130**
Varies between participants	Utilization	253	331	555
	Half of home events counted	162	151	138
	All reported events counted	**147**	**137**	**130**

Counting every reported event reaches 80% power with 130 to 147 participants per arm

Power to detect a 30% reduction in every event (2-sided α = .05) in a 1-year trial

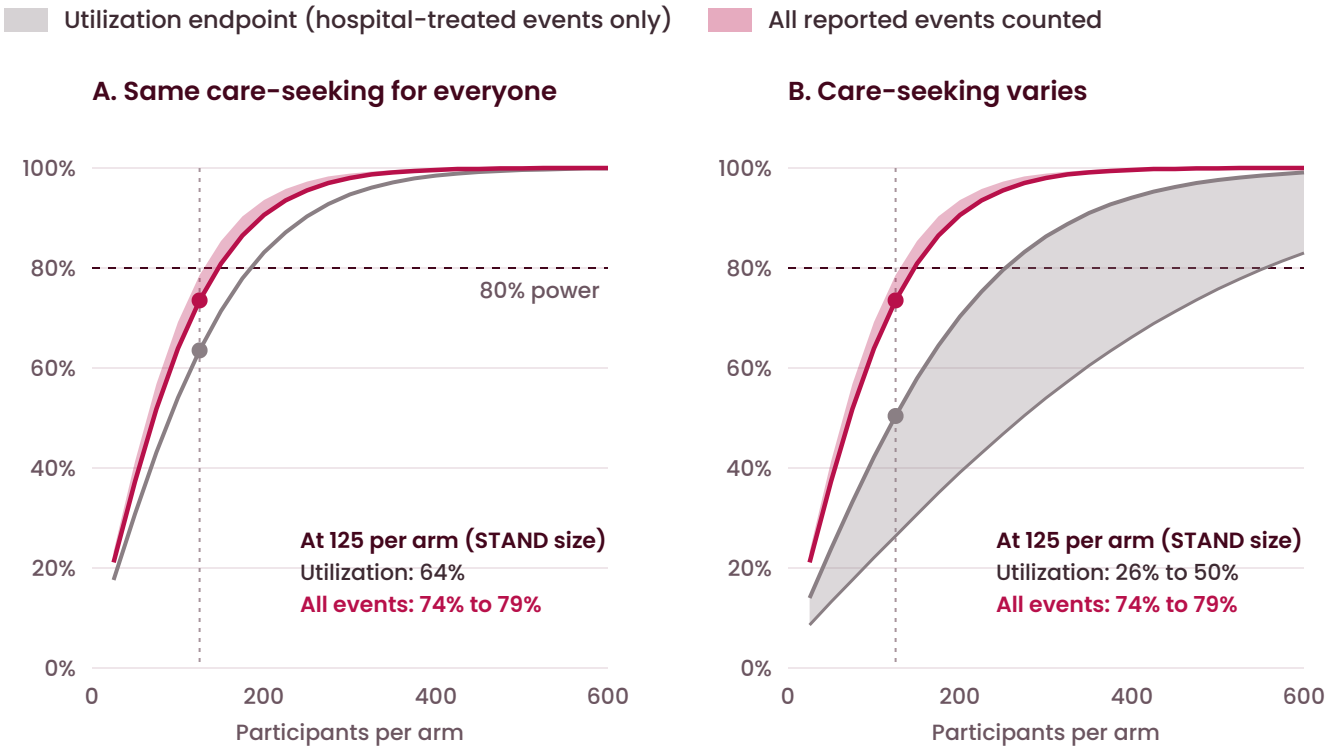


Figure 1. Expressive Painimation Co. simulation. Negative binomial model, dispersion 1.0, drug reduces every event by 30%. Shaded bands span 62% to 90% of events managed at home.

WHAT THE SIMULATION SHOWS

- **Counting every event shrinks the trial even in the most conservative case.** When every participant seeks hospital care at the same rate, counting all reported events cuts the trial from 370 participants to 260 to 294 (21% to 30% fewer), because each participant contributes more events.
- **When care-seeking varies, as it does in practice, the gain is larger.** The utilization endpoint needs 506 to 1,110 participants, or 145 to 318 sites at the median of 3.5 participants per site. Counting every reported event needs 260 to 294 participants and 75 to 84 sites, 42% to 77% fewer. Counting only half of home-managed events still needs 36% to 75% fewer.
- **A trial the size of STAND would be underpowered on utilization alone.** STAND, the phase 3 trial of the P-selectin inhibitor crizanlizumab, enrolled 252 participants.[12] With 125 participants per arm, power is 26% to 64% on the utilization endpoint and 74% to 79% when all reported events are counted.
- **Trials reach a clear answer with fewer participants, even when the drug does not work.** A trial sized to detect a 30% reduction with 80% power also has about an 80% chance of ruling out that reduction when the drug does nothing. Counting every event reaches that answer with 260 to 294 participants instead of 370 to 1,110, so fewer patients are exposed to an ineffective drug and fewer scarce participants are used up.
- **The absolute difference between arms grows.** The utilization endpoint sees 0.74 fewer events per participant-year on drug. Counting every event shows 1.95 to 7.35 fewer, a difference trialists, regulators, and patients can feel.

The pattern held across levels of overdispersion.

At the most conservative home share of 62%, counting every event needed 85 participants per arm against 123 (same care-seeking) or 174 (varied care-seeking) on the utilization endpoint when dispersion was 0.5, and 209 against 247 or 332 when it was 1.5. Independent modeling has also shown that technology-based endpoints can raise trial power and the probability of phase 3 success.[52]

These are illustrative simulations, not results of a Painimation trial. More events do not automatically mean more power. The gain depends on event rates, the size and consistency of the treatment effect, measurement error, and how care-seeking varies. The simulations assume that captured home events are true events, that capture does not differ by arm, and that the drug works equally on home-managed and hospital-treated events. If reported events include false positives, or capture differs by arm, the gain shrinks. Additional validation studies are ongoing.

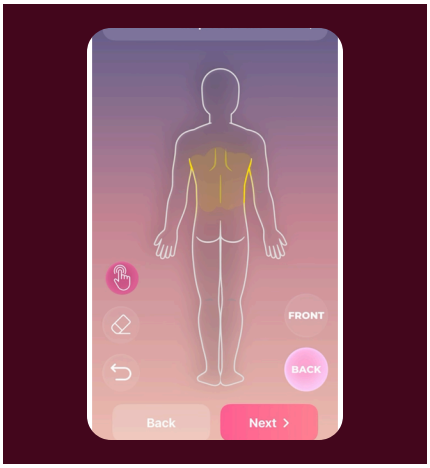
03 · THE SOLUTION

An end-to-end eCOA built for pain

Expressive Painimation is a full-service eCOA platform that can replace a trial's existing eCOA vendor. It runs the whole participant data path in one secure system, from enrollment to data transfer. The platform is built on more than 15 years of digital health research in pain trials, and our team has tested mobile health apps in clinical studies since 2009. Painimation has been tested against established pain measures in adults with chronic pain and validated in adults with SCD, and the platform is running in clinical studies today.[44,53,54]

What participants do.

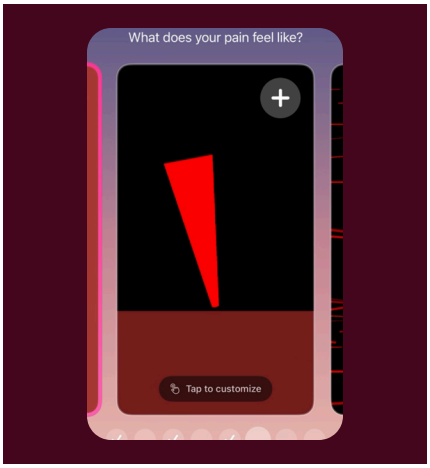
Participants download the app or open it in a browser, complete eligibility screening and electronic consent, and report from home. Each day, or as often as once a week depending on the protocol, they paint where it hurts on a body map, choose from 8 painimations that show how the pain feels, and adjust each one until it matches. When a pain event starts, they flag it in the moment. A full Painimation entry takes under 2 minutes, uses images rather than words, and returns pain quality, intensity, location, and body area, plus a 0-100 Painimation Score.[54]



STEP 1

Paint where it hurts

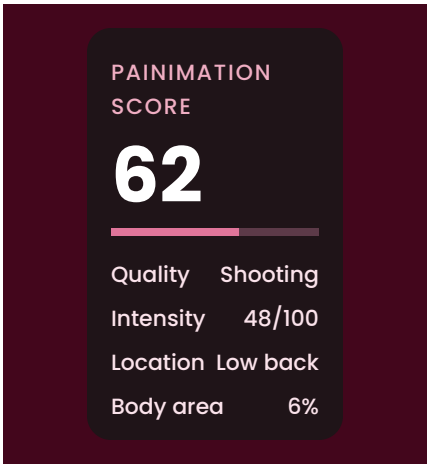
A front and back body map records location and body area.



STEP 2

Choose and adjust painimations

Eight painimations show how the pain feels. Each is adjusted until it matches.



STEP 3

Scored on entry

Quality, intensity, location, and body area, plus the Painimation Score. Example values.

What trial teams receive

One eCOA diary that also records 0-10 intensity, mood, energy, medication use, and care-seeking, with standardized questionnaires such as PROMIS, ASCQ-Me, PainDETECT, and EQ-5D-5L at protocol milestones.

Remote enrollment and electronic consent, so participants do not need to live near a sickle cell center.

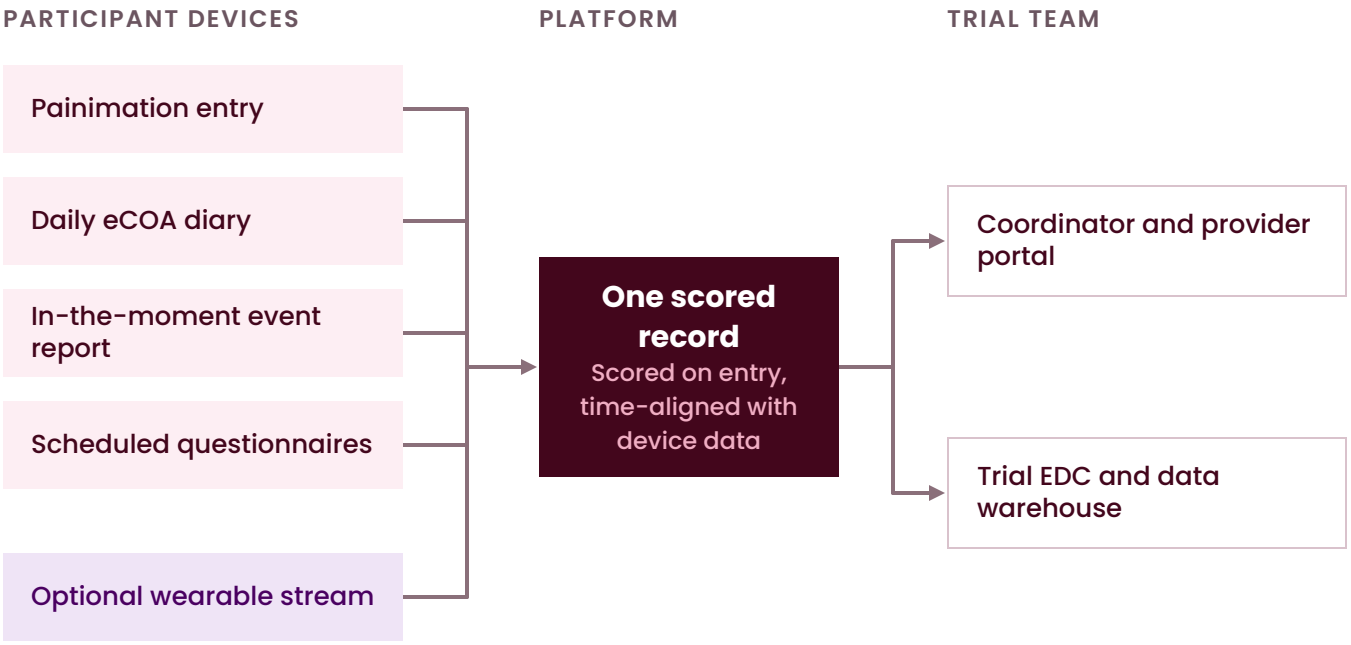
A coordinator and provider portal for tracking participants, monitoring adherence, and exporting data.

Scored data in real time and delivery to the trial's EDC or data warehouse by API or scheduled transfer.

Support for 21 CFR Part 11 audit trails and electronic signatures, system validation, secure hosting, HIPAA, and GDPR.

iOS and web apps, and integration into partner systems. In the multisite PRESENCE trial, Painimation runs inside a partner's Android app.[55]

Measurement science support from our scientists on event definitions, scoring rules, and analysis plans.



Every participant report and device stream lands in one scored, time-aligned record that the trial team monitors and receives.

An optional wearable module.

Trial teams that want physiologic corroboration can add a smartwatch module that records activity, sleep, heart rate, and related signals on the same days. The module is optional. The core pain-event endpoint does not depend on it, and participants do not need a smartwatch to take part. In SCD, Apple Watch heart rate and activity data detected high pain with an area under the curve of 0.90 during hospital care and 84.5% accuracy in the day hospital.[56,57] In our wearable study within the multinational phase 3 SCD-CARRE trial, 85.2% of participants with baseline device data met wear criteria, and daily steps and active time tracked 6-minute walk distance and functional class.[58]

The evidence behind painimations.

Painimation was built through human-centered design with patients, clinicians, and designers.[59] In the interviews that started that work, patients called the 0-10 scale vague and ambiguous. In the first clinical study, adults at a chronic pain clinic completed Painimation alongside the McGill Pain Questionnaire and PainDETECT. The painimations they chose corresponded with the McGill words they endorsed, and the electrifying painimation correlated with PainDETECT scores (r = .35) and identified self-reported nerve damage as well as the 9-item PainDETECT did, from a single selection. Most participants found Painimation useful for describing their pain (87.0%), and 80.2% said they would use it to communicate with providers.[54] In 359 adults with SCD, painimation choices were associated with pain intensity, interference, frequency, severity, and opioid misuse,[53] and over 12 months they tracked improvement that 0-10 intensity did not.[44] In Ghana, children and adults completed Painimation quickly (average, 102 seconds), and the study found it feasible for reporting pain.[60] Painimation serves as a patient-reported outcome in the multinational SCD-CARRE trial and in PRESENCE,[55,61] and it has been used at more than 25 clinical sites in 5 countries.

80.2%
of 162 adults would use it with providers[54]

r = .35
electrifying painimation vs PainDETECT[54]

102 s
average completion time in Ghana[60]

25+
clinical sites in 5 countries

04 · FOR TRIAL TEAMS

How trialists can use the platform now

Trial teams do not need to wait for a qualified endpoint to benefit from better pain data.

01 **Run the trial's full eCOA.** Painimation, the eCOA diary, scheduled questionnaires, eConsent, and the coordinator portal run in one system, in place of a separate eCOA vendor.

02 **Add Painimation as a secondary endpoint.** Painimation outcomes run alongside standardized measures such as PROMIS Pain Interference and ASCQ-Me and alongside the trial's VOE endpoint.

03 **Count home-managed events as an exploratory endpoint.** Painimation event data build evidence for a future primary or key secondary endpoint while the trial reports the endpoint regulators already accept.

04 **Characterize pain phenotypes.** Painimation and body-area data show change in pain quality and extent, not only intensity.

05 **Enroll beyond the sickle cell center.** In-app screening, consent, and remote onboarding reach patients who live far from trial sites.

Ongoing validation

Additional validation studies are ongoing, including tests of a prespecified pain-event rule against blinded clinician adjudication.

Request a 20-minute demonstration

The participant experience, the data the platform returns, and how it fits your protocol.

team@painimation.com

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Methods notes. The trial counts, endpoint shares, and median of 3.5 participants per site come from Expressive Painimation Co.'s own analysis of ClinicalTrials.gov registrations, conducted in 2026. We identified interventional phase 2 and phase 3 trials enrolling people with SCD and classified each trial's primary endpoint as pain, VOE, health care utilization, or other. Table 1 lists 9 representative trials from this set. The Section 2 simulations held the hospital-treated event rate at 2.45 per participant-year, applied a 30% reduction to every event, and varied the share of events managed at home (62%, 78%, and 90%). Event counts were drawn from a negative binomial distribution (gamma-Poisson, shared individual frailty, dispersion 1.0) for 1-year, 2-arm trials. In the varied care-seeking case, each participant's probability of taking a crisis to the hospital was drawn from a beta distribution with the same mean and a concentration of 5 (SD, 0.12 to 0.20). Sample sizes and power were computed analytically and confirmed by 3000 Monte Carlo replicates per scenario, including the probability of ruling out a 30% reduction when the drug has no effect. Search terms, coding rules, and simulation code are available on request.

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