



Paediatric Drug Optimization for Sickle Cell Disease: priorities for research and development in children

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Sickle cell disease remains a major cause of childhood morbidity and mortality, particularly in sub-Saharan Africa. In September, 2025, WHO convened the Paediatric Drug Optimization for Sickle Cell Disease process to review approved therapies, pipeline candidates, and potentially curative approaches, and define priorities for children and adolescents. Hydroxyurea (hydroxycarbamide) was confirmed as the leading near-term priority, with age-appropriate soluble or dispersible formulations identified as essential to improve equitable paediatric access; preferred and minimum characteristics were defined through a formal target product profile. Among investigational agents, pyruvate kinase activators and decitabine plus tetrahydrouridine (NDec) emerged as promising candidates for paediatric investigation on the basis of emerging efficacy data and programmatic potential. Intersecting research priorities included identifying appropriate clinical trial endpoints, strengthening early and inclusive paediatric investigation, and proactively ensuring that the promise of potential cure through gene therapy does not delay investment in scalable disease-modifying treatments.

Introduction

Sickle cell disease is an inherited haematological disorder associated with recurrent vaso-occlusion, haemolytic anaemia, progressive organ dysfunction, and premature death. Clinical manifestations typically begin in infancy as fetal haemoglobin levels decline and include acute and chronic pain, anaemia, increased susceptibility to infections, stroke, and acute chest syndrome.^{1–3}

Sickle cell disease affects an estimated 7.74 million people globally, with more than 500 000 affected births each year.⁴ Most people with sickle cell disease live in sub-Saharan Africa, South Asia, the Middle East, and the Americas—particularly the Caribbean and Brazil—among populations of African descent. Despite this growing burden, sickle cell disease remains a neglected condition, with substantial inequities in access to comprehensive care and low research investment in the development of effective pharmacotherapies that improve quality of life or offer cure.⁵

Sickle cell disease greatly affects quality of life and, if not adequately managed, can lead to premature mortality. Sickle cell disease also contributes substantially to mortality in older children (5–9 years) and early adolescents (10–14 years), making it a major driver of child mortality, particularly in sub-Saharan Africa.^{6,7} Effective interventions, including diagnosis in the newborn period, completion of childhood immunisation, early initiation of antibiotic prophylaxis, use of disease-modifying therapy, and regular blood transfusions, can substantially improve survival and wellbeing, particularly when diagnosis is made in infancy.^{8,9} However, most people living with sickle cell disease are still unable to access high-quality care.¹⁰

For individuals living with sickle cell disease, the most promising approach to improve outcomes is to expand access to disease-modifying therapy, such as hydroxyurea (hydroxycarbamide), delivered alongside other interventions as part of a comprehensive package of care.

Hydroxyurea has been approved in many countries for paediatric use, supported by evidence of safety^{11,12} and long-term studies showing sustained clinical benefits in most patients, including improved quality of life, better growth, and reduced mortality.^{13,14} Despite these benefits, substantial barriers to access and uptake persist in many high-burden settings, driven by low availability, high cost, misconceptions about the safety profile, and gaps in access to age-appropriate paediatric formulations.^{15,16} Optimal use of hydroxyurea requires sustained adherence and regular laboratory monitoring, which are often difficult to sustain in low-income and middle-income settings, contributing to underdosing, treatment

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Key messages

- Hydroxyurea (hydroxycarbamide) remains the leading near-term priority for children with sickle cell disease. However, the absence of age-appropriate, affordable, and widely available formulations continues to constrain equitable access.
- The Paediatric Drug Optimization for Sickle Cell Disease process identified age-appropriate hydroxyurea formulations as short-term priorities and developed a target product profile to guide formulation development, regulatory strategy, procurement, and implementation.
- Among investigational therapies, pyruvate kinase activators—mitapivat, etavopivat, and tebapivat—and decitabine plus tetrahydrouridine (NDec) emerged as promising candidates for paediatric investigation, based on biological rationale, emerging efficacy signals, oral administration, and feasibility potential.
- Gene therapies offer potentially curative options, but their development, pricing, infrastructure requirements, and restricted availability in high-burden countries raise major equity concerns that must be addressed from the outset.
- The promise of potentially curative therapies must not delay investment in scalable disease-modifying treatments that can benefit far greater numbers of children in the near term. Scientific innovation in sickle cell disease should be guided by equity, feasibility, and public health relevance.
- Paediatric inclusion should be embedded early in therapeutic development, with studies using validated, patient-relevant endpoints that capture long-term benefit for people, including children, in high-burden settings.

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interruption, and variable response. Although additional disease-modifying agents and potentially curative approaches, including gene therapies, are emerging, their availability remains restricted, particularly for children in high-burden countries.¹⁷

In this context, WHO recently published guidelines for the management of children and adolescents with sickle cell disease,¹⁸ providing recommendations on rapid diagnostic tests that can be used at the point of care, antibiotic prophylaxis, prevention of complications, and clinical management of common manifestations. The guidelines strongly recommend the use of hydroxyurea for infants from 9 months, as well as for older children and adolescents. The guidelines also emphasise health-care system enablers for scale-up in high-burden settings, including the use of point-of-care tests, strengthening of health-care workforce capacity, inclusion in national essential medicines lists, integration into Integrated Management of Childhood Illness tools, and improved continuity of care.

Paediatric Drug Optimization for Sickle Cell Disease

In parallel with normative work on the clinical management of children and adolescents with sickle cell disease, WHO is also advancing efforts to accelerate investigation and access to disease-modifying therapies. In September, 2025, WHO convened a Paediatric Drug Optimization for Sickle Cell Disease (PADO-SCD) process¹⁹ to identify short-term and long-term paediatric priorities by reviewing currently approved and emerging products in the research and development pipeline, including gene therapies. This meeting brought together academics, researchers, clinical experts, paediatricians, regulators, funders, and other key stakeholders involved in the research and development of therapeutics for sickle cell disease to discuss how to focus resources and research efforts on the most urgent unmet needs for children with sickle cell disease. PADO meetings have previously been convened by WHO for several disease categories, including HIV, tuberculosis, neglected tropical diseases, malaria, and epilepsy, showing the value of this consensus-building process in shaping and focusing research efforts and resources.^{20,21}

As part of the PADO-SCD meeting, priority-setting exercises were conducted through structured discussions informed by a comprehensive review of the literature and relevant WHO resources. These exercises covered both therapeutics already licensed to inform discussions on therapeutics to prioritise for short-term development (PADO priority list), and therapeutics in clinical development for a sickle cell disease indication. Before the meeting, investigational therapeutics were identified from a collated database drawing on two complementary sources available through the WHO Global Observatory on Health Research and Development: the WHO International Clinical Trials Registry Platform and

AdisInsight. Following additional screening and filtering, ten therapeutics were selected for discussion. A dedicated priority-setting framework, covering multiple relevant criteria, was developed and populated using published literature and direct engagement with product developers, with each attribute scored on a scale of 1 to 5 by a dedicated expert group. The resulting composite scores informed discussions on the therapeutics to prioritise for research and development in children in the medium and long term (PADO watch list), which was further refined through a post-meeting survey (via email) in which participants ranked their top three candidates with supporting rationale, and finalised during a follow-up meeting.

The PADO-SCD process also provided a platform for convening the hydroxyurea target product profile development group, in line with WHO's standard procedures.²²

The outcome of this process, described in this manuscript, will inform and support the alignment of funders, procurers, market coordination entities, researchers, innovators, generics manufacturers, product development partnerships, and regulators on priority products and strategies to improve access to sickle cell disease therapeutics.¹⁹

From product availability to paediatric priority setting in sickle cell disease

The current disease-modifying treatment landscape for sickle cell disease remains strikingly narrow, particularly for younger children. As of April, 2026, only a few therapeutics are approved and commercially available, including hydroxyurea, L-glutamine, crizanlizumab, and two gene therapies (exagamglogene autotemcel and lovotibeglogene autotemcel), although their regulatory status and commercial availability vary across jurisdictions. Only hydroxyurea (in children aged ≥9 months) and L-glutamine (in children aged ≥5 years) are options for most paediatric age groups; crizanlizumab is only approved for people aged 16 years and older. Gene therapies have been approved only for people aged 12 years and older. Approval and availability of these agents remain extremely restricted in many high-burden countries.

Hydroxyurea was identified as a priority product for children with sickle cell disease and was therefore included in the PADO-SCD priority list (panel 1),¹⁹ recognising that despite recent progress on affordability, formulation gaps continue to limit equitable paediatric access. In June, 2025, a major price reduction initiative targeting low-income and middle-income countries was announced for one quality-assured 500-mg capsule formulation.²³ However, this dosage form is poorly suited to younger children, who require flexible weight-based dosing (NCT06578507), careful dose titration, good acceptability, and safe administration when swallowing capsules is not feasible. Alternative formulations, including lower-strength capsules, dispersible tablets,

For the WHO International
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and oral suspensions, are available in some settings, but these options are either not widely accessible or remain suboptimal for routine paediatric use. To better define the formulation profile that should be advanced through generic development, a target product profile was developed to specify both preferred and minimum characteristics of hydroxyurea formulations for the management of sickle cell disease in children (panel 2; appendix pp 5–7).²⁴

Other approved therapies for sickle cell disease, including L-glutamine and crizanlizumab, were also reviewed to assess whether they should be prioritised for paediatric development. Although both products have regulatory approval in at least some settings, the available evidence was considered insufficient to support their prioritisation for children with sickle cell disease, and major research gaps remain.

L-glutamine was approved by the US Food and Drug Administration (FDA) in 2017 for use in children aged 5 years and older to reduce vaso-occlusive crises.^{25,26} However, the same dataset submitted to the FDA was not considered sufficient by the European Medicines Agency (EMA), whose Committee for Medicinal Products for Human Use issued a negative opinion citing insufficient efficacy evidence, high dropout rates, and no demonstrated benefit for hospitalisation; the company that developed the drug subsequently withdrew its application.²⁷ Preliminary real-world evidence has suggested potential benefit, with one small single-centre study reporting reductions in vaso-occlusive crises, hospitalisation days, and blood transfusions after 72 weeks of L-glutamine therapy; however, the small sample size limits the generalisability of these findings.²⁸ Acceptability remains a concern because the product is poorly soluble and crystalline, resulting in a gritty preparation that might be difficult for young children to take. Cost is also a major limitation, with prices in the USA far exceeding those of hydroxyurea. Broader prioritisation of L-glutamine would require stronger efficacy data, including head-to-head comparison with hydroxyurea, longer-term safety and efficacy data, paediatric dose-finding studies, and formulation improvements.

Crizanlizumab, approved by both the FDA and the EMA in 2019 for patients aged 16 years and older²⁹ and administered as an intravenous infusion every 4 weeks, presents major delivery challenges, particularly in lower-level facilities such as district hospitals, which might lack the capacity to provide the high-quality care and monitoring required for intravenous administration.³⁰ The post-marketing confirmatory STAND trial (NCT03814746) did not confirm efficacy, leading the EMA to revoke approval in 2023,³¹ although authorisation remains in the USA. Interpretation of these findings remains debated, and the ongoing SPARKLE trial (NCT06439082) is expected to provide further evidence in adults. Limited real-world evidence from a small single-centre study suggested reduced acute care visits

among adult patients with high baseline hospital use, but treatment persistence was low, with only five of 15 patients remaining on crizanlizumab after 6 months.³² A paediatric safety and dose-finding phase 2 study (SOLACE Kids, NCT03474965) was performed involving children aged 2–17 years, as requested by the EMA, but since the licence was revoked, there was no definitive

Panel 1: Paediatric Drug Optimization for Sickle Cell Disease (PADO-SCD) priority and watch list

PADO-SCD priority list

Short-term (3–5 years) time horizon for development of paediatric formulations

- Hydroxyurea:
 - 500-mg single-scored soluble or single-scored dispersible tablets (preferred and minimum)
 - 100-mg single-scored soluble or single-scored dispersible tablets (preferred)

PADO-SCD watch list

Medium-term and long-term (5–10 years) time horizon for development of paediatric indications and formulations

- Mitapivat
- Etavopivat
- Tebapivat*
- Decitabine plus tetrahydrouridine (NDDec)

*Following phase 2 topline results showing insufficient differentiation from other pyruvate kinase activators, development of tebapivat for sickle cell disease was discontinued by the sponsor (July 2026).

Panel 2: Target product profile for formulations of hydroxyurea (hydroxycarbamide) for the management of sickle cell disease in children

In September, 2025, WHO convened a technical consultation to define the target product profile for paediatric hydroxyurea. This technical consultation was followed by a public consultation, in line with standard WHO procedures for target product profile development. Together, these processes identified clear product development needs and provided guidance on formulation design, regulatory strategies, and other key aspects related to hydroxyurea (appendix pp 5–7).²⁴

The target population was defined as children and adolescents aged 9 months to 19 years with sickle cell anaemia, specifically HbSS and HbSβ0-thalassaemia, in line with WHO recommendations and the strongest available evidence base.¹⁸ The target product profile aligns with WHO guidance that hydroxyurea can be initiated at all facility levels, while setting a minimum expectation of initiation at secondary or referral level with decentralised maintenance when appropriate safeguards are in place.

For formulation design, 100-mg and 500-mg single-scored soluble or dispersible tablets were considered preferred to support initiation and dose adjustment, whereas a 500-mg single-scored soluble or dispersible tablet was considered the minimum acceptable option to promote market viability. Triple-scored 1000-mg tablets were not considered advantageous, given concerns about content uniformity, handling of leftover portions, and poor acceptability even among older children due to tablet size.

Taste masking was considered desirable because hydroxyurea can have a metallic or bitter taste, but it was not retained as a minimum requirement, because no major adherence concerns were reported with existing products.

follow-up study. Given unresolved efficacy concerns,³¹ infusion-based delivery, and much higher cost than hydroxyurea, crizanlizumab was not considered a priority for paediatric development at this stage.

Screening the sickle cell disease pipeline for paediatric impact: feasibility-informed prioritisation of compounds to be promoted for development

The narrow range of available disease-modifying therapies for sickle cell disease, especially for children, affects both the urgency and the standards by which the development pipeline should be judged. New agents are not competing against an abundance of effective alternatives, but against the practical bar set by hydroxyurea—an oral, scalable therapy with a long track record of benefit, especially in children, and an evidence base that extends beyond a single clinical manifestation. Increased understanding of the disease pathophysiology creates new opportunities for additional targets beyond anti-sickling,³³ including downstream targets, such as inflammation, endothelial adhesion, and oxidative stress, thus creating opportunities for further investigation and more treatment options.

Against this backdrop, the pipeline review undertaken to inform PADO-SCD discussions adopted a pragmatic lens (Antwi I et al, unpublished), grounded in what it takes for an intervention to be relevant for the settings where most children with sickle cell disease live.^{17,34} From a policy and practice perspective, compounds that show excellent clinical efficacy could nevertheless prove programmatically fragile if they depend on infusion infrastructure, cold-chain logistics, frequent monitoring, or complex pharmacovigilance that is not feasible at scale. These real-world feasibility considerations directly informed the prioritisation approach: the review concentrated on candidates in phase 2–4 trials with plausible near-term development trajectories, narrowing the field to ten agents for closer examination, and identifying a smaller subset for prioritisation in paediatric investigation on the basis of their likelihood of translating into meaningful paediatric impact.

Pyruvate kinase activators—mitapivat, etavopivat, and tebapivat—emerged as the clearest upstream drug class with signals that could plausibly complement, rather than merely substitute, existing standards of care. All three drugs had ongoing trials at the time of the PADO-SCD meeting, including in adolescents (aged 12 years and older [etavopivat, NCT06612268] and aged 16 years and older [mitapivat and tebapivat, NCT05031780 and NCT04536792, respectively]). Etavopivat is currently being evaluated in children aged 6 months and older in a single-arm, open-label phase 1/2 pharmacokinetics and safety study (NCT06198712). No studies in children younger than 16 years have been initiated for mitapivat. The biological rationale of pyruvate kinase activators is compelling: by increasing ATP and reducing 2,3-diphosphoglycerate in red blood cells, they reduce

haemoglobin polymerisation and sickling, thus specifically targeting disease initiation rather than downstream consequences, such as anti-adhesion or anti-inflammatory approaches. Early efficacy data in adults were encouraging for mitapivat. However, despite a substantial increase in haemoglobin, the latest study results did not show significant reductions in vaso-occlusive episodes, underscoring that surrogate endpoints, such as haemoglobin, do not always translate into clinical benefits and the importance of identifying appropriate trial endpoints.^{35,36} Etavopivat also shows haemoglobin improvements, including among paediatric participants aged 12 years and older, and topline results from a phase 3 clinical trial showed both an improvement in haemoglobin and a reduction in vaso-occlusive events.^{37–39} Tebapivat, although at an earlier stage of development, shares the same mechanism of action and therefore had similar therapeutic potential.^{40,41} However, following the announcement of topline results from the phase 2 trial, which did not show sufficient differentiation from other pyruvate kinase activators, the sponsor decided not to pursue further development of tebapivat for sickle cell disease.⁴²

From a policy perspective, the central question is not simply whether pyruvate kinase activators produce favourable short-term laboratory or clinical signals, but whether they can deliver sustained, clinically meaningful benefits across the heterogeneous phenotypes of sickle cell disease—particularly sustained protection against cumulative end-organ damage. Although reduction in vaso-occlusive episodes remains an attractive near-term endpoint, it is also where several sickle cell disease development programmes have faltered, with promising early-phase results not translating into primary endpoints based on vaso-occlusive episode reduction in later-stage trials. If pyruvate kinase activators are positioned primarily as reducers of vaso-occlusive episodes, they could face the same endpoint fragility as highlighted by recent study results.^{35,36} Hospitalisation-related outcomes should also be defined more granularly in studies of vaso-occlusive crises, capturing not only the number of hospitalisations but also total days hospitalised, emergency department visits, and transfusion requirements. Evaluating outcomes using a portfolio of endpoints that better capture haemolysis, endothelial dysfunction, inflammation, and organ injury (ie, accounting for multimorbidity) alongside patient-reported outcomes could advance the field more quickly and reduce the risk of late-phase disappointment.

From a health-system perspective, oral administration of the three pyruvate kinase activators included in the PADO-SCD watch list (panel 1) is advantageous for scale, but dosing frequency might influence adherence (twice per day for mitapivat versus once per day for etavopivat and tebapivat), which can be decisive in routine paediatric care and settings with constrained health-system capacity.

The addition of decitabine plus tetrahydrouridine (NDec) to the PADO-SCD watch list (panel 1) speaks

directly to the strengths and limitations of the current cornerstone therapy, hydroxyurea.⁴³ Although the benefits of hydroxyurea are well established, treatment response remains heterogeneous, and fetal haemoglobin distribution across red cells can remain uneven,⁴⁴ leaving some children insufficiently protected against severe complications. Management requires regular monitoring for toxicity and dose optimisation, which can be challenging to sustain in settings with little clinical monitoring capacity and might contribute to suboptimal dosing and adherence. NDec's appeal is therefore both biological and operational: it targets fetal haemoglobin induction via DNA methyltransferase inhibition, and it is designed for intermittent oral dosing (twice per week), which could reduce pill burden and support adherence—a key implementation issue in chronic paediatric conditions. However, the results of NDec's randomised study have not yet been made available, highlighting the need for evidence to support its efficacy and safety, particularly before testing begins in children.

PADO-SCD discussions acknowledged that combination therapy is likely to be the future standard in sickle

cell disease, much as it is in other chronic, mechanistically complex diseases. Drugs with non-overlapping mechanisms of action can be paired with existing therapies—especially hydroxyurea—to strengthen prevention of both upstream pathophysiology (ie, sickling) and downstream sequelae (eg, hyperinflammation) in sickle cell disease. Pyruvate kinase activators illustrate this potential. With mechanisms distinct from hydroxyurea and generally non-overlapping toxicity profiles, they are well positioned as candidates for combination therapy. Beyond improving haemoglobin concentrations by reducing haemoglobin sickling, pyruvate kinase activators might also help limit cumulative end-organ injury—including stroke, avascular necrosis, and chronic leg ulcers—supporting evaluation not only for prevention of acute events but also for longer-term outcomes, such as cumulative end-organ damage, for evaluation in clinical trials.

In addition to underscoring the urgency of initiating paediatric investigations for compounds on the PADO-SCD watch list—ideally as soon as sufficient adult data become available, typically at the onset of phase 3

Panel 3: Guiding principles for future clinical trials in sickle cell disease: key considerations for policy, trial design, and funding priorities

- Therapeutic urgency: the small number of disease-modifying options for children heightens the need for therapies that complement hydroxyurea and address the unmet needs across diverse sickle cell disease phenotypes
- Pragmatic relevance and scalability: prioritise agents that are feasible in settings with constrained health-system capacity and can be delivered at scale, avoiding therapies that require infusion capacity, cold-chain storage, complex logistics, or intensive monitoring
- Endpoint diversification: reduce reliance on pain-related clinical trial endpoints in research of both acute pain and pain-prevention interventions as they capture only a small fraction of the disease burden; validate surrogate biomarkers that target haemolysis, endothelial dysfunction, inflammation, mitochondrial function, end-organ damage, and patient-reported outcomes
- Innovative clinical trial design: use of innovative designs beyond the randomised controlled trial, including adaptive trials, Bayesian and pragmatic designs, N-of-1 studies, digital twin technology, and external control arms, to reduce participant burden, improve feasibility, and accelerate timelines
- Long-term benefit assessment: evaluate sustained, multisystem benefit, including reductions in cumulative end-organ damage and improvement in long-term outcomes, supported by validated biomarkers when relevant (although not appropriate for studies of acute pain)
- Mechanism-aligned endpoints: clinical trial endpoints should reflect biological rationale to ensure meaningful assessment of disease-modifying potential and long-term benefit
- Disease severity classification: develop and apply a classification system for disease severity to support fair comparison of novel treatments, accurate assessment of risks and benefits, and more generalisable results
- Timely paediatric evaluation: policies should support early initiation of paediatric trials—when adult phase 3 studies begin—to reduce delays in evidence generation and access for children
- Inclusive paediatric age ranges: include children as young as age 1 year to accelerate access and evidence generation
- Adherence-friendly dosing: favour once per day or intermittent dosing and minimise pill burden to support adherence in routine paediatric care and settings where sustained patient follow-up is difficult
- Oral administration: prioritise oral agents when possible because of their greater scalability, acceptability, and low health-system burden
- Complementarity with hydroxyurea: prioritise agents with distinct mechanisms of action and non-overlapping toxicity profiles that could be combined with hydroxyurea, enabling stepwise improvement rather than simple substitution
- Combination therapy readiness: regulatory pathways should anticipate multiagent regimens and encourage early exploration of synergistic combinations with non-overlapping toxicity
- Late-phase readiness: funding prioritisation should focus on phase 2–4 drug candidates with realistic near-term pathways to approval, access, and implementation

adult studies—the group emphasised the importance of designing upfront dosing schedules that favour adherence for this population and including children as young as age 1 year in paediatric studies. Panel 3 outlines guiding principles for future clinical trials in sickle cell disease, with a focus on therapeutic urgency, pragmatic feasibility, endpoint diversification, and timely paediatric evaluation.

Gene therapies for sickle cell disease: priorities for equitable adoption in low-income and middle-income countries

Gene therapies are emerging as potentially curative options for sickle cell disease. Although these therapies are still new and definitive long-term evidence of cure is not yet available, patient advocates and clinical experts have described them as transformative therapies with curative intent. As emphasised by key thought leaders in Africa and The *Lancet Haematology* Commission,⁵ the overarching goal is to provide access to definitive or curative therapies for every person living with sickle cell disease, regardless of their geographical location. Achieving this vision requires investments in the research and development of effective and context-appropriate technologies, and implementation protocols for regions with the highest epidemiological burden of sickle cell disease, particularly Africa, where an estimated 75% of affected individuals reside.⁴⁵ Whereas detailed descriptions of gene-therapy platforms have been extensively discussed in the literature,⁵ PADO-SCD discussions focused on the key factors to consider when evaluating approaches to enable adoption in low-income and middle-income countries.

Two gene therapies have been developed and authorised in high-income countries for people aged 12 years and older.⁴⁶ However, to our knowledge, these products have not yet reached any low-income and middle-income countries, and these countries have been largely absent from pivotal clinical trials,⁴⁷ leaving uncertainties regarding efficacy and safety in genetically diverse populations, including African populations. If curative approaches are to be expanded to all patients in need, regardless of geography, progress will be required across a few strategic areas.

The first priority is to include countries with a high burden of sickle cell disease in clinical trials, or at a minimum to ensure they are represented through a robust sample of trial sites.^{48,49} According to the Global Gene Therapy Initiative, a few African countries already have the capacity to deliver ex vivo gene therapy, and these centres could be leveraged in future trials.^{45,49,50} Conducting clinical trials in these settings would not only generate essential context-specific evidence but also help establish or strengthen the infrastructure and regulatory pathways for advanced therapeutics in both research and routine clinical practice, while building a regionally grounded skilled workforce.

A second priority is ensuring that trial populations reflect the age distribution and clinical profile of people

living with sickle cell disease in high-burden settings. Most participants enrolled in randomised controlled trials for sickle cell disease were older than age 12 years, despite more than half of children with sickle cell disease dying before reaching that age.⁴ Generating rigorous data on the efficacy, effectiveness, and safety of gene therapies in paediatric populations—eg, children and adolescents aged 2–11 years—is essential to support translation of research into clinical care and to inform age-appropriate indications and risk–benefit assessments.⁵¹

It remains crucial to invest in research and development, including in basic science technologies such as next-generation gene-editing and gene-addition platforms, particularly in vivo approaches. These advancements might enable safer, more standardised, less resource-intensive delivery protocols. However, ensuring that emerging technologies are available and affordable to those who need them is key.

Affordability must be embedded from the earliest stages of product development.⁵⁰ Two complementary dimensions are crucial. First, strategies to optimise manufacturing costs, including through regional or local production in low-income and middle-income countries, should be actively explored. The very high prices currently observed in high-income countries do not necessarily reflect intrinsic manufacturing costs. As an example, commercial prices for haemophilia B gene therapy are approximately US\$2 million per treatment, compared with real manufacturing costs of about US\$87 000. Although this commercial price refers to an in vivo gene therapy, the magnitude of this difference highlights the substantial scope for rationalising therapy costs.⁵² In low-income and middle-income country settings, costs could be further reduced through access to lower-cost labour and raw materials, including viral vectors.⁵³ Additionally, the lower cost of lifelong replacement therapy in these settings should be factored into gene therapy pricing.

As new therapies are developed in high-income countries, the pathways to regulatory approval in low-income and middle-income countries, and the role of bridging studies to enhance regulatory reliance and efficiency will need to be clarified. Additionally, strengthening the capacity of national regulatory agencies to assess complex gene therapy dossiers, approve these treatments, and ensure post-marketing safety monitoring is necessary.⁵⁴ Much progress has already been made toward regulatory harmonisation in Africa through the establishment of the African Medicines Agency, which provides a strong foundation for coordinated review and reliance frameworks.

Taken together, these considerations underscore that gene therapy, particularly in vivo, could offer an opportunity not only to advance the technological frontier of care resulting in potential cure, but also to reconfigure access and financing models so that high-value interventions can be delivered at scale, including in settings constrained by geography, infrastructure, and cost.

Identifying appropriate endpoints and optimising trial design in sickle cell disease: a call to action

Despite advances in sickle cell disease management in recent years and a strong pipeline of compounds currently under investigation, several essential research gaps remain and urgently need to be addressed. PADO-SCD discussions aligned with the American Society of Hematology's research priorities, highlighting the need for further work in pain management, organ complications, sickle cell trait research, gene therapy and novel therapeutics, expansion of transplant options, digital health and registries, and the reduction of health disparities.⁵⁵ To keep pace with the rapidly evolving treatment landscape, the field must now prioritise the identification of appropriate clinical trial endpoints, the optimisation of study design, and broader therapeutic evaluation that includes paediatric populations alongside adults. Furthermore, clinical trials in sickle cell disease should be prioritised on the African continent, where most people with the condition live.

Traditional trial endpoints, such as vaso-occlusive episode frequency, transfusion dependence, and hospitalisation rates, although of some value, capture only a fraction of the disease burden and are fraught with limitations, because they are influenced by care-seeking behaviour, socioeconomic factors, and institutional variability in admission criteria.^{56,57} Severity of sickle cell disease is often defined by the frequency or duration of vaso-occlusive episodes. This metric has served as the foundation for clinical trial eligibility and regulatory approval for most therapies approved by the FDA. However, frequency or duration of vaso-occlusive episodes is a narrow and inadequate measure of the overall disease burden,⁵⁷ a concern that became the focus of a recent American Society of Hematology workshop in December, 2025.⁵⁸ To better measure therapeutic impact, future research should focus on harmonising and validating objective, biologically informed endpoints that reflect haemolysis, inflammation, endothelial activation, mitochondrial function, and cumulative end-organ damage, as suggested by recent consensus recommendations.⁵⁵ Notably, the use of non-clinical endpoints should be grounded in robust validation of their relationship with patient-relevant outcomes. Parallel emphasis is needed on patient-reported outcomes^{59–61} that quantify daily pain interference, fatigue, functional limitations, and mental health, although they might not be ideal endpoints for studies of acute vaso-occlusive episodes.^{62,63} Organ-specific subclinical markers such as neuroimaging changes, kidney function trajectories, cardiopulmonary testing, and digital monitoring of pain and physical activity are also needed, particularly those that can detect benefit long before overt clinical deterioration occurs.^{57,61,64}

As emerging gene-based^{65,66} and disease-modifying therapies enter the pipeline, endpoints must also adapt to

capture long-term engraftment, genomic stability, fertility preservation, durability of response, and reversal or stabilisation of chronic organ damage. Optimising clinical trial design is another central priority. Historically, sickle cell disease trials have been hindered by small sample sizes, heterogeneous disease presentation, logistical challenges,^{67,68} and few clinical research facilities in regions with high disease prevalence.^{64,69} Challenges with pain-related endpoints in acute vaso-occlusive episode studies are becoming more apparent now that enrolment limitations have been overcome through research networks such as the Pediatric Emergency Care Applied Research Network.^{56,70} As of July, 2026, no drug has received FDA regulatory approval to shorten the duration of acute vaso-occlusive complications, highlighting the complex pathophysiology of acute pain in sickle cell disease.⁵⁷ Ultimately, reconsideration of optimal outcomes for clinical trials for sickle cell disease-related vaso-occlusive episodes is warranted. The field must therefore collaborate to define and validate surrogate endpoints that better reflect underlying disease biology and long-term benefit. Although the 2019 American Society of Hematology–FDA consensus workshop established a comprehensive set of recommendations for clinical trial endpoints,^{61,64} meaningful progress has stalled, and the field remains effectively at an impasse. A coordinated stakeholder initiative that brings together clinicians, scientists, regulators, and individuals living with sickle cell disease as a working group is essential. Biopharmaceutical partners should also be closely engaged in this effort to ensure alignment on priorities and to support the development of studies that are not only more purposeful, but also more feasible and efficient to conduct. Without a strategic push forward, there is a severe risk of delaying important innovation at a time when new therapies could transform outcomes.

Prospective longitudinal cohort and registry studies, community-engaged research infrastructure, and strategic biomarker collection will be essential to strengthen trial readiness and deepen mechanistic understanding.⁵⁵ Research should therefore emphasise the use of innovative designs beyond the randomised controlled trial, including adaptive trials, Bayesian designs, N-of-1 studies,⁷¹ digital twin technology, and external control arms, to reduce participant burden, improve feasibility, and accelerate timelines. Pragmatic trials and real-world data could complement traditional randomised clinical trials by enhancing generalisability, particularly for therapies with long-term or organ-protective mechanisms that require extended follow-up.⁵⁵ Furthermore, strengthening community-based research capacity and embedding equity into site selection, eligibility criteria, and engagement strategies are essential to ensure diverse and representative enrolment.⁷²

Few compounds in late-phase clinical development as of July, 2026, are being investigated in children,^{73–75} despite sickle cell disease being a lifelong condition

with early-onset morbidity. Paediatric research should be prioritised to allow timely evaluation of new small-molecule agents, biologics, and gene-based interventions within paediatric-appropriate safety and ethical frameworks. This research includes developing age-specific endpoints, incorporating caregiver-reported outcomes, and studying developmental effects on growth, neurocognitive function, fertility, and long-term organ health. Strengthening newborn screening-linked networks^{76,77} and establishing longitudinal paediatric cohorts⁷⁸ will help create trial-ready populations that can accelerate the evaluation of new therapies. Affordable novel therapies beyond curative therapies are also needed, because access to such therapies will be out of reach for many patients,¹⁰ particularly those in settings with populations facing high barriers to care and experiencing the highest burden of disease.

Collectively, these priorities must align closely with the evolving therapeutic pipeline, which includes gene editing, stem cell-based approaches, and multiple disease-modifying agents, ensuring that endpoints are sensitive to mechanism-specific benefits, designs are flexible enough for rapidly advancing technologies, and paediatric access is embedded early in development. This integrated approach will accelerate the translation of scientific advances into meaningful and equitable improvements in outcomes for all individuals living with sickle cell disease.

Conclusions

PADO-SCD outcomes highlighted both the urgency of expanding therapeutic options for children with sickle

cell disease and the need to anchor innovation in equity, feasibility, and public health relevance. Although the current pipeline of compounds under investigation for sickle cell disease is robust, the range of available treatment options remains strikingly poor, underscoring the continued importance of advancing new therapeutic candidates alongside improving access to existing ones. Hydroxyurea remains the only widely scalable disease-modifying therapy with a strong paediatric evidence base, yet formulation and access barriers continue to constrain its impact in high-burden settings.

The prioritisation of age-appropriate hydroxyurea formulations, together with selected pipeline candidates for early paediatric development, therefore reflects a pragmatic strategy that balances scientific promise with real-world needs. At the same time, potentially curative therapies are becoming more visible, with gene therapy products already commercially available in some high-income settings. However, the prospect of a cure must not be allowed to justify delaying investment in pragmatic disease-modifying therapies that could benefit far more children in the near term.

Coordinated action across the product life cycle, such as that facilitated by WHO and its Global Accelerator for Paediatric Formulations Network partners, will need to intersect global efforts in introducing and scaling-up human genomics and precision medicine tools.⁷⁹ Optimisation of clinical trial design and endpoints, proactive acceleration of clinical development programmes, fostering of regulatory efficiency, and ensuring access when solutions are developed will be essential to translate scientific progress into meaningful gains in survival and quality of life.

Contributors

TM coordinated the overall writing process, with substantial original drafting of specific sections by NOYJr, JSH, CRM, GS, and JM. MP and WMW supervised the writing of the manuscript, reviewed, and provided feedback in relevant sections. All authors participated in the PADO-SCD process and the target product profile development process, reviewed the manuscript throughout, and provided relevant feedback.

Declaration of interests

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Search strategy and selection criteria

The content and discussions of the Paediatric Drug Optimization for Sickle Cell Disease (PADO-SCD) meeting were informed by a comprehensive review of WHO resources on sickle cell disease, complemented by materials from partners, including an overview of available hydroxyurea formulations compiled by Médecins Sans Frontières. A systematic literature review was outside the scope of this exercise. Instead, we identified key background materials through targeted searches using terms relevant to the meeting objectives and through proactive outreach to PADO-SCD participants with expertise in specific areas, who were invited to share relevant literature and resources. To identify disease-modifying therapies for sickle cell disease that were still under investigation and not yet included in WHO recommendations, a structured pipeline review of products in phase 2–4 development was carried out. On July 2, 2025, we searched the WHO International Clinical Trials Registry Platform and AdisInsight to identify investigational therapeutics in phases 2, 3, or 4 using the following search terms in various combinations: "sickle cell" OR "sickle cell disease" OR "drepanocytosis" OR "drepanocytose" OR "anémie falciforme" OR "Hb-SS disease" OR "Hemoglobin S Disease" OR "Hemoglobin SS" OR "HbS disease" OR "HbSS". We also conducted targeted literature searches and contacted product developers as needed to clarify development timelines, formulation plans, or unpublished updates. Eligible therapies were assessed with a multiattribute prioritisation framework that considered clinical efficacy, safety, paediatric feasibility, formulation considerations, implementation factors, and potential public health relevance. The final integrated dataset was cleaned, standardised, and used to inform downstream analysis and meeting deliberations.

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References

- Kato GJ, Gladwin MT, Steinberg MH. Deconstructing sickle cell disease: reappraisal of the role of hemolysis in the development of clinical subphenotypes. *Blood Rev* 2007; **21**: 37–47.
- Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. *Lancet* 2010; **376**: 2018–31.
- Ilesanmi OO. Pathological basis of symptoms and crises in sickle cell disorder: implications for counseling and psychotherapy. *Hematol Rep* 2010; **2**: e2.
- Thomson AM, McHugh TA, Oron AP, et al, and the GBD 2021 Sickle Cell Disease Collaborators. Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000–2021: a systematic analysis from the Global Burden of Disease Study 2021. *Lancet Haematol* 2023; **10**: e585–99.
- Piel FB, Rees DC, DeBaun MR, et al. Defining global strategies to improve outcomes in sickle cell disease: a *Lancet Haematology* Commission. *Lancet Haematol* 2023; **10**: e633–86.
- Williams TN. Sickle cell disease in sub-Saharan Africa. *Hematol Oncol Clin North Am* 2016; **30**: 343–58.
- Adeloye D, Auta A, Ale BM, Thompson JY, Rudan I, and the Global Health Epidemiology Research Group (GHERG). Prevalence estimates of sickle cell disease among children and adolescents in sub-Saharan Africa: a systematic review and modelling analysis. *Lancet Child Adolesc Health* 2026; **10**: 438–47.
- Chaturvedi S, DeBaun MR. Evolution of sickle cell disease from a life-threatening disease of children to a chronic disease of adults: the last 40 years. *Am J Hematol* 2016; **91**: 5–14.
- Ware RE, de Montalembert M, Tshililo L, Abboud MR. Sickle cell disease. *Lancet* 2017; **390**: 311–23.
- Rai P, Ataga KI. Using disease-modifying therapies in sickle cell disease. *Hematology (Am Soc Hematol Educ Program)* 2023; **2023**: 519–31.
- Kinney TR, Helms RW, O'Branski EE, et al, and the Pediatric Hydroxyurea Group. Safety of hydroxyurea in children with sickle cell anemia: results of the HUG–KIDS study, a phase I/II trial. *Blood* 1999; **94**: 1550–54.
- Wang WC, Ware RE, Miller ST, et al, and the BABY HUG investigators. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *Lancet* 2011; **377**: 1663–72.
- Rankine-Mullings AE, Nevitt SJ. Hydroxyurea (hydroxycarbamide) for sickle cell disease. *Cochrane Database Syst Rev* 2022; **9**: CD002202.
- Lobo CL, Pinto JFC, Nascimento EM, Moura PG, Cardoso GP, Hankins JS. The effect of hydroxycarbamide therapy on survival of children with sickle cell disease. *Br J Haematol* 2013; **161**: 852–60.
- Mlyuka HJ, Kilonzi M, Mutagonda RF, et al. Barriers and facilitators of availability of hydroxyurea for sickle cell disease in Tanzania: a qualitative study of pharmaceutical manufacturers, importers, and regulators. *Healthcare (Basel)* 2022; **10**: 2223.
- Okocha EC, Gyamfi J, Ryan N, et al. Barriers to therapeutic use of hydroxyurea for sickle cell disease in Nigeria: a cross-sectional survey. *Front Genet* 2022; **12**: 765958.
- Mahadevia H, Ponvilawan B, Madan U, Sharma P, Qasim H, Shrestha A. A review on disease modifying pharmacologic therapies for sickle cell disease. *Ann Hematol* 2025; **104**: 881–93.
- WHO. WHO consolidated guidelines for the management of common childhood illness: management of sickle-cell disease in children and adolescents. Geneva: World Health Organization. 2026. <https://www.who.int/publications/i/item/9789240122666> (accessed Aug 11, 2026).
- WHO. Paediatric drug optimization for sickle cell disease: meeting report, 8–10 September 2025. Geneva: World Health Organization. 2026. <https://www.who.int/publications/i/item/B09861> (accessed Aug 3, 2026).
- WHO. Paediatric drug optimization standard procedure. Geneva: World Health Organization. 2021. <https://iris.who.int/server/api/core/bitstreams/3654862c-2a89-41ca-a850-6118ffaf535a/content> (accessed May 6, 2026).
- WHO. Global Accelerator for Paediatric Formulations Network (GAP-f). 2026. <https://www.who.int/initiatives/gap-f> (accessed May 6, 2026).
- WHO. Target product profiles, preferred product characteristics and target regimen profiles. 2025. <https://www.who.int/our-work/science-division/research-for-health/optimizing-research-processes/product-profiles> (accessed May 6, 2026).
- Clinton Health Access Initiative. Breaking through barriers: how US\$ 1 tests and affordable treatment are transforming sickle cell disease care. 2025. <https://www.clintonhealthaccess.org/blog/breaking-through-barriers-how-us1-tests-and-affordable-treatment-are-transforming-sickle-cell-disease-care> (accessed May 6, 2026).
- WHO. Target product profile for formulations of hydroxyurea for the management of sickle cell disease in children. Geneva: World Health Organization. 2026. <https://www.who.int/publications/i/item/B09727> (accessed Aug 11, 2026).
- US Food and Drug Administration. Full prescription information [Endari]. 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/208587s004bl.pdf (accessed May 6, 2026).
- Niihara Y, Miller ST, Kanter J, et al, and the Investigators of the Phase 3 Trial of l-Glutamine in Sickle Cell Disease. A phase 3 trial of l-glutamine in sickle cell disease. *N Engl J Med* 2018; **379**: 226–35.
- European Medicines Agency. Withdrawal of application for the marketing authorisation of Xyndari (glutamine). Amsterdam: European Medicines Agency. 2019. https://www.ema.europa.eu/en/documents/medicine-qa/questions-and-answers-withdrawal-application-marketing-authorisation-xyndari-glutamine_en.pdf (accessed July 7, 2026).
- Elenga N, Loko G, Etienne-Julian M, Al-Okka R, Adel AM, Yassin MA. Real-world data on efficacy of L-glutamine in preventing sickle cell disease-related complications in pediatric and adult patients. *Front Med (Lausanne)* 2022; **9**: 931925.
- Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. *N Engl J Med* 2017; **376**: 429–39.
- Kanter J, Ataga KI, Bhasin N, et al. Expert consensus on the management of infusion-related reactions (IRRs) in patients with sickle cell disease (SCD) receiving crizanlizumab: a RAND/UCLA modified Delphi panel. *Ann Hematol* 2024; **103**: 1909–17.
- Abboud MR, Cançado RD, De Montalembert M, et al. Crizanlizumab with or without hydroxyurea in patients with sickle cell disease (STAND): primary analyses from a placebo-controlled, randomised, double-blind, phase 3 trial. *Lancet Haematol* 2025; **12**: e248–57.
- Cheplowitz H, Block S, Groesbeck J, Sacknoff S, Nguyen AL, Gopal S. Real-world data of crizanlizumab in sickle cell disease: a single-centre analysis. *J Hematol (Brossard)* 2023; **12**: 105–08.
- Colombatti R, Jastaniah W, Makani J, Andemariam B. Sickle cell disease. *Lancet* 2026; **407**: 1095–111.
- Kuriri FA. Hope on the horizon: new and future therapies for sickle cell disease. *J Clin Med* 2023; **12**: 5692.
- Idowu M, Otieno L, Dumitriu B, et al. Safety and efficacy of mitapivat in sickle cell disease (RISE UP): results from the phase 2 portion of a global, double-blind, randomised, placebo-controlled trial. *Lancet Haematol* 2025; **12**: e35–44.
- Agios. Press release. Agios announces topline results from RISE UP phase 3 trial of mitapivat in sickle cell disease. Nov 19, 2025. <https://investor.agios.com/news-releases/news-release-details/agios-announces-topline-results-rise-phase-3-trial-mitapivat> (accessed May 6, 2026).
- Novo Nordisk. Company announcement. Novo Nordisk: etavopivat is the first in a new class of drugs to meet both co-primary endpoints in the phase 3 HIBISCUS trial, substantially reducing vaso-occlusive crisis events and improving haemoglobin response in sickle cell disease. April 20, 2026. <https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=916533> (accessed May 6, 2026).
- Saraf SL, Hagar R, Idowu M, et al. Multicenter, phase 1 study of etavopivat (FT-4202) treatment for up to 12 weeks in patients with sickle cell disease. *Blood Adv* 2024; **8**: 4459–75.
- Inati A, Ogutu B, Clary ELJ, et al. Etavopivat in adolescents with sickle cell disease: emerging safety and efficacy findings from the first cohort of the ongoing phase 1/2 hibiscus kids study. *Blood* 2025; **146** (suppl 1): 618.

- 40 Xu JZ, Philips BJ, Kiriza NK, et al. Tebapivat improves red cell deformability and decreases sickling in patients with sickle cell disease: a phase 1 trial substudy. *Eur J Haematol* 2026; **116**: 98–100.
- 41 Xu JZ, Novelli EM, Ribeil J-A, et al. Results from a phase 1 study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of tebapivat (AG-946) in patients with sickle cell disease. *Blood* 2024; **144** (suppl 1): 2496.
- 42 Agios. Agios provides update on phase 2 trial of tebapivat in sickle cell disease. July 21, 2026. <https://investor.agios.com/news-releases/news-release-details/agios-provides-update-phase-2-trial-tebapivat-sickle-cell> (accessed Aug 5, 2026).
- 43 Molokie R, Lavelle D, Gowhari M, et al. Oral tetrahydrouridine and decitabine for non-cytotoxic epigenetic gene regulation in sickle cell disease: a randomized phase 1 study. *PLoS Med* 2017; **14**: e1002382.
- 44 Khandros E, Steinberg MH. One cell at a time: HbF distribution in sickle cell disease. *Blood Adv* 2026; **10**: 1278–80.
- 45 Bukini D, Makani J, McCune J, et al. Consensus-driven target product profiles for curative sickle cell disease gene therapies. *Mol Ther Methods Clin Dev* 2024; **32**: 101287.
- 46 US Food and Drug Administration. Approved cellular and gene therapy products. <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products> (accessed May 6, 2026).
- 47 Adair JE, Androski L, Bayigga L, et al. Towards access for all: 1st working group report for the Global Gene Therapy Initiative (GGTI). *Gene Ther* 2023; **30**: 216–21.
- 48 Moshi G, Sheehan VA, Makani J. Africa must participate in finding a gene therapy cure for sickle-cell disease. *Nat Med* 2022; **28**: 2451–52.
- 49 Doxzen KW, Adair JE, Bazzo YMF, et al. The translational gap for gene therapies in low- and middle-income countries. *Sci Transl Med* 2024; **16**: eadn1902.
- 50 Makani J, Bukini D, Malangahe S, et al. Access to gene therapy for sickle cell disease in Africa. *EBioMedicine* 2025; **115**: 105713.
- 51 Jeyaraj R, Brown LK, Jagadisan B, et al. Safety of in vivo gene therapy in children: mechanisms and management of liver injury. *Lancet Child Adolesc Health* 2026; **10**: 448–61.
- 52 Bolous NS, Chen Y, Wang H, et al. The cost-effectiveness of gene therapy for severe hemophilia B: a microsimulation study from the United States perspective. *Blood* 2021; **138**: 1677–90.
- 53 Harlow EM, Adair JE. Make gene therapies more available by manufacturing them in lower-income nations. *Nature* 2024; **631**: 502–04.
- 54 Olaghery J, Williams DA, Farrar J, et al, and the Reagan–Udall Foundation for the FDA. Scientific advancements in gene therapies: opportunities for global regulatory convergence. *Biomedicine* 2025; **13**: 758.
- 55 American Society of Hematology. Sickle cell disease research priorities 2024 update. https://www.hematology.org/-/media/hematology/files/research/scd-research-priorities_2024-update_18sept24_final.pdf (accessed May 6, 2026).
- 56 Rees CA, Hatabah D, Korman R, et al, and the Pediatric Emergency Care Research Network (PECARN). Hospital variations in time-to-crisis-resolution among children and adolescents with sickle cell disease. *Am J Hematol* 2026; **101**: 206–12.
- 57 Ataga KI. The challenge of clinical end points in sickle cell disease. *Blood* 2023; **142**: 2047–54.
- 58 American Society of Hematology. Scientific workshops. <https://www.hematology.org/meetings/annual-meeting/schedule-and-program/programs/friday-scientific-workshops> (accessed July 24, 2026).
- 59 Bakshi N, Liu Z, Gillespie S, et al. Patient-reported outcomes in children with sickle cell disease at presentation for an acute pain episode. *Blood Adv* 2023; **7**: 5103–07.
- 60 Singh SA, Bakshi N, Mahajan P, Morris CR. What is the future of patient-reported outcomes in sickle-cell disease? *Expert Rev Hematol* 2020; **13**: 1165–73.
- 61 Farrell AT, Panepinto J, Carroll CP, et al. End points for sickle cell disease clinical trials: patient-reported outcomes, pain, and the brain. *Blood Adv* 2019; **3**: 3982–4001.
- 62 Brousseau DC, Scott JP, Badaki-Makun O, et al, and the Pediatric Emergency Care Applied Research Network (PECARN). A multicenter randomized controlled trial of intravenous magnesium for sickle cell pain crisis in children. *Blood* 2015; **126**: 1651–57.
- 63 Morris CR, Hatabah D, Korman R, et al. Arginine therapy for pain in sickle cell disease: a phase-2 randomized, placebo-controlled trial. *Am J Hematol* 2025; **100**: 1119–31.
- 64 Farrell AT, Panepinto J, Desai AA, et al. End points for sickle cell disease clinical trials: renal and cardiopulmonary, cure, and low-resource settings. *Blood Adv* 2019; **3**: 4002–20.
- 65 Ballantine J, Tisdale JF. Gene therapy for sickle cell disease: recent advances, clinical trials and future directions. *Cytotherapy* 2025; **27**: 826–34.
- 66 Leonard A, Tisdale JF. A new frontier: FDA approvals for gene therapy in sickle cell disease. *Mol Ther* 2024; **32**: 264–67.
- 67 Dampier CD, Smith WR, Kim HY, et al, and the Investigators of the Sickle Cell Disease Clinical Research Network (SCDCRN). Opioid patient controlled analgesia use during the initial experience with the IMPROVE PCA trial: a phase III analgesic trial for hospitalized sickle cell patients with painful episodes. *Am J Hematol* 2011; **86**: E70–73.
- 68 Dampier CD, Smith WR, Wager CG, et al, and the Sickle Cell Disease Clinical Research Network (SCDCRN). IMPROVE trial: a randomized controlled trial of patient-controlled analgesia for sickle cell painful episodes: rationale, design challenges, initial experience, and recommendations for future studies. *Clin Trials* 2013; **10**: 319–31.
- 69 Ally M, Balandya E. Current challenges and new approaches to implementing optimal management of sickle cell disease in sub-Saharan Africa. *Semin Hematol* 2023; **60**: 192–99.
- 70 Estep JH. MAGiC: VOC remains but kids with SCA appear. *Blood* 2015; **126**: 1637–38.
- 71 Augustine EF, Yu TW, Finkel RS. N-of-1 studies in an era of precision medicine. *JAMA* 2024; **332**: 1386–87.
- 72 Lee LH, Whisenton LH, Bengier J, Lanzkron S. A community-centered approach to sickle cell disease and clinical trial participation: an evaluation of perceptions, facilitators, and barriers. *Blood Adv* 2021; **5**: 5323–31.
- 73 Chudleigh J, Follett A, Mcfarlane-Griffith E, et al. Exploring how children and young people with sickle cell disease and their families want to be involved in research: a qualitative study. *Health Expect* 2025; **28**: e70242.
- 74 Hirschfeld S, Lagler FB, Kindblom JM. Prerequisites to support high-quality clinical trials in children and young people. *Arch Dis Child* 2021; **106**: 423–28.
- 75 Lagler FB, Hirschfeld S, Kindblom JM. Challenges in clinical trials for children and young people. *Arch Dis Child* 2021; **106**: 321–25.
- 76 Green NS, Zapfel A, Nnodu OE, et al. The Consortium on Newborn Screening in Africa for sickle cell disease: study rationale and methodology. *Blood Adv* 2022; **6**: 6187–97.
- 77 Therrell BL Jr, Lloyd-Puryear MA, Ohene-Frempong K, et al, and the faculty and speakers at the First Pan African Workshop on Newborn Screening, Rabat, Morocco, June 12–14, 2019. Empowering newborn screening programs in African countries through establishment of an international collaborative effort. *J Community Genet* 2020; **11**: 253–68.
- 78 Chang M, Semakula D, Little JA, et al. Grandchildren of GRNDaD: Shifts in disease-modifying therapy at the adolescent transition in sickle cell disease. *Br J Haematol* 2025; **207**: 1070–75.
- 79 Ambrosino E, Abou Tayoun AN, Abramowicz M, et al. The WHO genomics program of work for equitable implementation of human genomics for global health. *Nat Med* 2024; **30**: 2711–13.

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