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The Innovation-Affordability Trade-off of Exagamglogene Autotemcel (Casgevy) for Severe Sickle Cell Disease in NHS England

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Abstract. Severe sickle cell disease is often accompanied by pain and multiorgan damage, thus placing a heavy burden on the patients, their families and the National Health Service (NHS). Exagamglogene autotemcel (exa-cel; Casgevy) offers a new option: a single, autologous CRISPR-Cas9-edited cell therapy that aims to reactivate fetal haemoglobin and prevent severe vaso-occlusive crises. However, the £1.651 million list price, resource-intensive treatment path and uncertain lifetime benefit are problems for a tax-funded healthcare system. This paper conducts a focused narrative review and a case study of the NICE technology appraisal TA1044 to explore why exa-cel was recommended via managed access rather than for routine NHS use. Evidence from the CLIMB SCD-121 trial shows a promising short-term clinical response, but its single-arm design, limited follow-up, and the risks of myeloablative conditioning remain important sources of uncertainty. NICE's decision does not rule out innovation; rather, it is concerned that the modelled cost-effectiveness relies too heavily on assumptions about durability, mortality, quality of life and future healthcare consumption. Therefore, managed access is a reasonable temporary compromise to provide access for eligible patients while further evidence is gathered.

Keywords: Exagamglogene autotemcel, sickle cell disease, gene editing, cost-effectiveness, NHS England

1. Introduction

Sickle cell disease (SCD) is a genetic disorder of the blood that results in abnormal haemoglobin, haemolysis, anaemia and vaso-occlusion. For people with severe disease, the burden extends beyond individual hospital admissions, encompassing severe pain, disruption to education or work, anxiety about future crises, and gradual organ damage. English real-world data show that people who have had recurrent vaso-occlusive crises (VOCs) experience significantly higher mortality and healthcare utilisation than matched controls [1]. Families also bear substantial costs; UK and French caregivers have reported a lower quality of life, financial pressure and reduced work efficiency [2].

Based on the above, exagamglogene autotemcel (exa-cel), also known as Casgevy, is a typical scientific achievement. It involves editing a patient's own haematopoietic stem cells using CRISPR-Cas9, followed by a single infusion after myeloablative conditioning. The Medicines and Healthcare

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products Regulatory Agency (MHRA) authorised it in 2023, but regulatory approval establishes acceptable quality, safety and efficacy; it does not by itself establish value for money or guarantee routine NHS funding [3]. NICE subsequently recommended exa-cel with managed access for a defined population rather than routine use [4].

This paper examines the reasons NICE recommended managed access rather than routine NHS use and assesses how exa-cel's clinical benefits, high upfront cost, implications for health inequalities and long-term uncertainty should inform future funding decisions.A focused narrative review is combined with a case study of NICE appraisal TA1044, drawing on peer-reviewed clinical and economic research and official UK and European regulatory sources.

2. Clinical need and the therapeutic value of exa-cel

2.1. Disease burden and limitations of current care

Recurrent VOCs are common in severe SCD and generally require early pain relief or hospitalisation. In a linked English database study, 1,117 patients with recurrent VOCs had a mean of 5.84 crises per patient-year and significantly higher inpatient, outpatient and prescription use than matched controls. Their death rate was about five times higher than that of controls, but the retrospective design and manufacturer's sponsorship require caution in interpretation [1]. Over time, people with severe SCD may develop a range of complications, including acute coronary syndrome, stroke, kidney damage, chronic pain, and premature mortality. Recently, English studies have also shown that complications are associated with substantially higher annual direct healthcare costs [5].

Organised care can reduce harm but seldom eliminates the daily uncertainty of illness. Hydroxycarbamide, transfusion programmes, pain management, and infection prevention are important components of current care; however, problems with adherence, adverse effects and different responses limit their effectiveness in preventing serious illness. Allogeneic haematopoietic stem cell transplantation can be curative, but access is limited by the requirement of a suitable donor and by risks such as graft-versus-host disease, graft failure and transplant-related toxicity. Therefore, NICE's eligible population focuses on individuals aged 12 and older with severe sickle cell disease and recurrent vaso-occlusive crises who are suitable for stem cell transplantation but lack a matched related donor [4]. The comparison is not between Exa-cel and Perfect Care; rather, it is between intensive, uncertain intervention and a life with a heavy disease burden.

2.2. Mechanism and treatment pathway

Exa-cel is an autologous, ex vivo gene-edited cell therapy. CD34+ haematopoietic stem and progenitor cells are collected from the patient and edited at the erythroid-specific enhancer of BCL11A. Reducing BCL11A activity in erythroid cells increases the production of fetal haemoglobin. Fetal haemoglobin does not sickle in the same way as haemoglobin S and can therefore reduce vaso-occlusion [6, 7]. Because the cells are autologous, exa-cel avoids the need for donor matching and the risk of graft-versus-host disease, but it does not simplify the treatment pathway.

Patients are mobile and undergo apheresis for cell manufacturing and quality control before myeloablative busulfan conditioning and reinfusion. Then they need to be admitted for haematological recovery and extended observation. Conditioning has the risk of serious cytopenias, infection and infertility; manufacturing failure or delay may leave patients without treatment after an extended preparation period. Therefore, the European Medicines Agency has classified Casgevy as a medicine

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that can prevent painful crises through edited cells, rather than as an easy-to-obtain gene correction [3]. Although exa-cel offers the prospect of reducing disease burden, the treatment pathway remains complex and demanding.

2.3. Clinical benefits, safety and remaining uncertainty

The first CLIMB SCD-121 study was an open-label, single-arm, phase 3 trial for young people aged 12-35 with severe sickle cell disease. Out of the 30 evaluable participants for the primary endpoint, 29 (97%) were free from severe VOCs for at least 12 consecutive months; all 30 were free from hospitalisation due to severe VOCs for at least 12 months [6]. These findings have potential clinical applications. Avoiding a crisis will save time, energy and the morale of the old ways. The results also indicate that reactivating fetal haemoglobin can provide molecular editing for real-world applications of patients.

However, the evidence base remains insufficient to establish the long-term clinical and economic benefits of the treatment. The trial was small, lacked a control group and had limited follow-up. Adverse events were generally related to busulfan conditioning and autologous transplantation, but rare or delayed harm could not be ruled out. Long-term registries are thus tracking treated patients and their outcomes after allogeneic transplantation [3, 6]. Despite these limitations, ExaCel has shown some short-term clinical benefits, so we must weigh this strong observed efficacy against the uncertainty of long-term effects.

3. NICE appraisal and managed NHS access

3.1. Approval, eligibility and the treatment offer

In November 2023, the MHRA authorised the first CRISPR-based medicine in the UK under a licence [3]. NICE then had a different task: to determine whether the NHS should pay for exa-cel and under what conditions. In February 2025, NICE proposed extending the managed access list to include eligible persons aged 12 and above [4]. Delivery requires specialist expertise and infrastructure for collection, conditioning, infusion and long-term follow-up [4]. This is different. Marketing authorisation determines if a medicine can be used; health technology assessment determines whether the expected health benefits justify the resources diverted from other parts of the NHS.

3.2. Price, resources and the reason for managed access

The published list price for exa-cel is £1.651 million per dose, excluding the additional costs of mobilisation, apheresis, conditioning, hospitalisation, and follow-up. A confidential commercial arrangement reduces the cost to the NHS, so the public list price cannot be considered the actual acquisition cost [4]. Even with a discount, the initial budget impact is concentrated, and many of the claimed savings and health benefits will occur much later. This is typical of cell and gene therapies: a large potential lifetime value needs to be built on the basis of evidence obtained over a relatively short period [8].

NICE determined that exa-cel was not suitable for general use because the evidence of cost-effectiveness remained too uncertain, especially at the upper end of plausible estimates. However, the technology showed potential, and some of this uncertainty could be reduced through further data collection. Therefore, managed access allows for treatment under agreed-upon conditions and

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collection of outcome data [4]. It is not a weaker type of normal approval. It is a conditional funding mechanism that offers two options: stronger evidence may support the continuation of use, or disappointing durability and resource results will weaken the case.

4. Cost-effectiveness and long-term uncertainty

4.1. Qalys, icers and opportunity cost

NICE generally expresses health benefits in terms of quality-adjusted life years (QALYs) and compares incremental costs with incremental QALYs using an incremental cost-effectiveness ratio (ICER). This system does not assign a simple monetary value to an individual life. Instead, the relevant question is how much health benefit the NHS can generate from allocating limited resources to exa-cel, and what health benefits might be forgone elsewhere. For exa-cel, the model credits avoided crises, reduced long-term complications, improved quality of life and possible survival gains, and then offsets these benefits with acquisition and treatment costs. Weighting of severity may give more weight to the gains of people with serious illnesses, but the problem of opportunity cost has not been solved.

The numerical UK results are partially confidential due to the commercial discount. This limits public scrutiny and makes the assessment more dependent on NICE's interpretation of the evidence, rather than on a publicly reproducible ICER. A US model may be useful for understanding model structure, but it cannot be transferred directly to England because treatment prices, usual care costs, discounting and decision thresholds differ [9]. A defensible NHS analysis should be based on the English care pathway.

4.2. Sources of economic uncertainty

Durability is the central uncertainty. If the edited stem cells continue to produce fetal haemoglobin and prevent severe VOCs over the patient's lifetime, a substantial initial payment may be offset by many years of avoided medical expenditure. If protection decreases, or if late complications occur despite fewer crises, both QALY gains and avoided costs may be lower than projected. Mortality modelling is also relatively sensitive due to the short follow-up time of the trial. Extrapolation must connect intermediate outcomes to distant life expectancy, and small changes in that relationship can materially alter the ICER.

Quality-of-Life Estimates Also Count. Patients may experience substantial relief after treatment, but utility estimates need to reflect the full treatment pathway, including pre-treatment disease, conditioning, recovery, possible infertility, residual complications, and the psychological benefit of reduced uncertainty. Caregiver spillovers are real but should be quantified carefully rather than applied uniformly across technologies [2]. Cost assumptions are also relatively large. Avoided admissions and complications resulted in savings, but specialist capacity, extended hospital stays, fertility preservation and long-term monitoring added to the cost of the vial.

Finally, discounting reduces the present value of benefits that will occur in the future relative to costs. It is not only a technical problem but also shows that current expenditures do not match the future uncertain benefits. Cell and gene therapies are outside the scope of traditional evidence because manufacturing, payment and clinical risk occur at different times [8]. The economic case for exa-cel is therefore not disproved; it is highly conditional. Strong short-term efficacy cannot, by itself, validate all the lifetime assumptions required for routine funding.

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5. Discussion: balancing innovation, affordability and equity

5.1. Upfront cost, NHS opportunity cost and health inequalities

Analysis of affordability alone cannot cover all the advantages that older models lack. People of African and Caribbean descent are disproportionately affected by severe SCD due to historical underdiagnosis of pain and unequal access to specialist medical services. Freedom from recurrent crises may enable some patients to return to education or work, participate more fully in family life, and plan for the future with less disruption from hospitalisation. Equity will be used to give more weight to the severity of SCD and to meet the needs of an underserved population.

However, the unmet clinical needs of patients must be considered alongside the resource constraints faced by the healthcare system. Funds committed to exa-cel cannot simultaneously cover nursing, diagnostics, mental health services and treatments for other NHS patients. Therefore, a justifiable equity judgment should protect the underserved SCD population and the health-of-nations for all patients in the NHS. Exa-cel has demonstrated promising short-term clinical outcomes; however, limited evidence on treatment durability and long-term safety means that its longer-term value remains uncertain. In general, a premium is only likely to be required for serious illnesses that need extended medical treatment; otherwise, it would not be necessary. Private discounts may be the result of negotiation, but it is unknown how much public funds have been saved.

5.2. Managed access and future reassessment

Where the short-term effectiveness is clear but evidence of long-term benefits and cost-effectiveness is lacking, managed access provides an expedient funding path. Exa-cel is highly suitable for this mechanism because withholding a potentially life-saving therapy will immediately cause harm to eligible patients, and several main uncertainties, such as duration, late complications, mortality, quality of life, treatment failure and NHS resource use, can be reduced through organised follow-up. However, a comprehensive real-world evidence base is required for meaningful reassessment. If the registry overrepresents patients with favourable responses and underreports manufacturing failures, treatment discontinuations, or poor outcomes, selection and reporting biases may reduce the reliability of the reassessment. Therefore, data collection should include patient-reported outcomes, laboratory tests and the experiences of all patients in the treatment process, including those who do not receive a successful infusion.

Institutional Risks also affect managed access. Temporary funding may lead to a situation where, after building specialist capabilities and making patients accustomed to the treatment, it is difficult to stop even if the evidence later shows that it is less effective than expected. Reassessment could therefore lead to price renegotiation, narrower eligibility, or suspension of routine commissioning. The 2026 manual by NICE shows a net health benefit of £25,000 and £35,000 per QALY [10], but this later system does not cover the original 2025 TA1044 decision. The new threshold will change the above estimates; otherwise, strong evidence or a reasonable price must be provided. The most justifiable structure is to tie payment to continuous access of the predetermined results, require all-encompassing long-term follow-up, and prevent managed access from becoming a way to obtain permanent funds.

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6. Conclusion

NICE recommended managed access over routine NHS use because exa-cel has shown excellent results but also has some problems. The CLIMB SCD-121 trial showed that almost all evaluable participants were free from severe VOCs for at least 12 consecutive months, and this result could have a significant impact on the lives of patients who have been repeatedly disrupted by pain and hospitalisation. However, the data came from a small, uncontrolled study and had a much shorter follow-up period than the lifetime horizon used in the economic model. The £1.651 million list price, additional transplantation costs and confidential discount further complicate public assessment of value.

Therefore, managed access is a reasonable current compromise. It addresses clinical need without claiming that short-term effectiveness has resolved uncertainties about durability, safety, mortality, and cost-effectiveness. It is also more ethically balanced than either unrestricted use or a total ban; patients can access it, and the NHS will continue to assess routine funding based on new evidence.

Future reassessment will focus on sustained freedom from serious diseases, long-term organ damage, survival, fertility and other limiting factors, the quality of life for patients and caregivers, treatment failures and full utilisation of NHS resources. Although the 2026 revision of NICE's general cost-effectiveness framework may change the calculation method, it will not be the sole reason. Routine funding will be most justifiable if enduring benefits are shown and the final price fairly distributes the risks. The key lesson from Casgevy is that responsible innovation requires neither unchecked enthusiasm nor excessive caution; it requires learning while safeguarding both current patients and the wider health system.

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