



# Challenges in drug development for haemoglobinopathies

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<i>INDIRECT INTERESTS:</i>				
6. Principal investigator	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional
7. Investigator	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> optional
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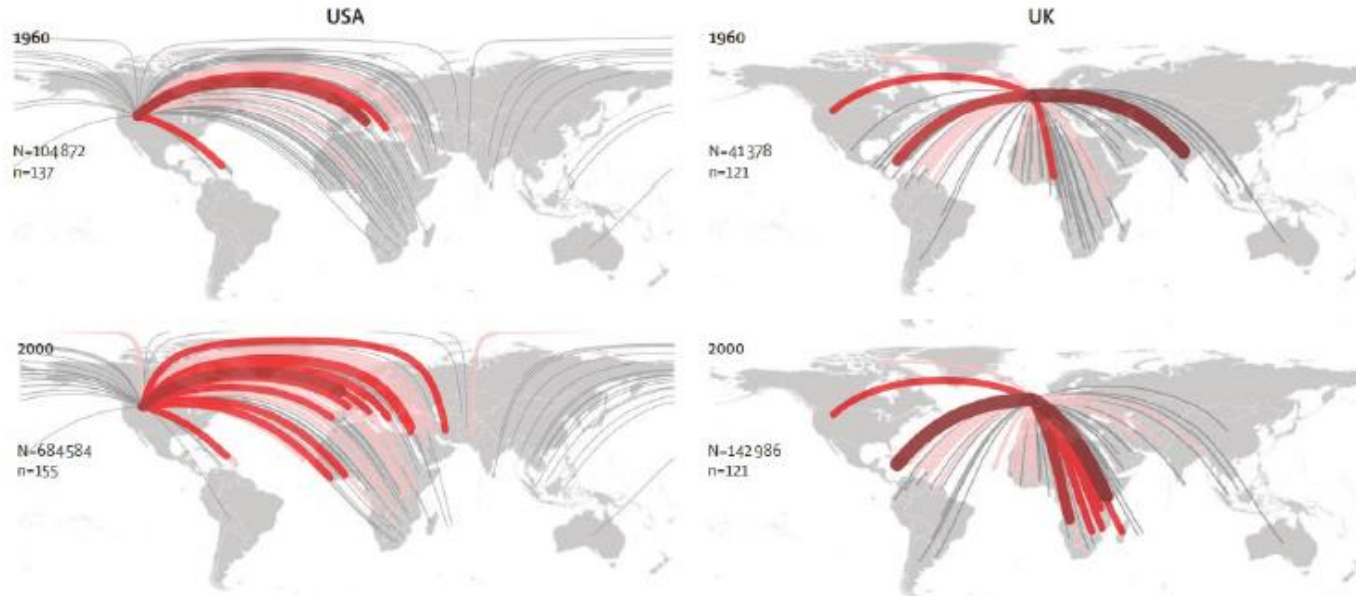
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N.B. I am not receiving any compensation

In recent decades, the globalization of migration has contributed to generate multiethnic European societies.

## Global migration and the changing distribution of sickle haemoglobin: a quantitative study of temporal trends between 1960 and 2000

*Frédéric B Piel, Andrew J Tatem, Zhuojie Huang, Sunetra Gupta, Thomas N Williams, David J Weatherall*



The advancements in clinical trials using new drugs and therapeutic procedures could ameliorate the quality of life of these patients and increase their life expectancy, but....

Hemoglobinopathies are rare and phenotypically diverse.

A trial that targets a clinical problem occurring in a subgroup restricts the number of eligible participants

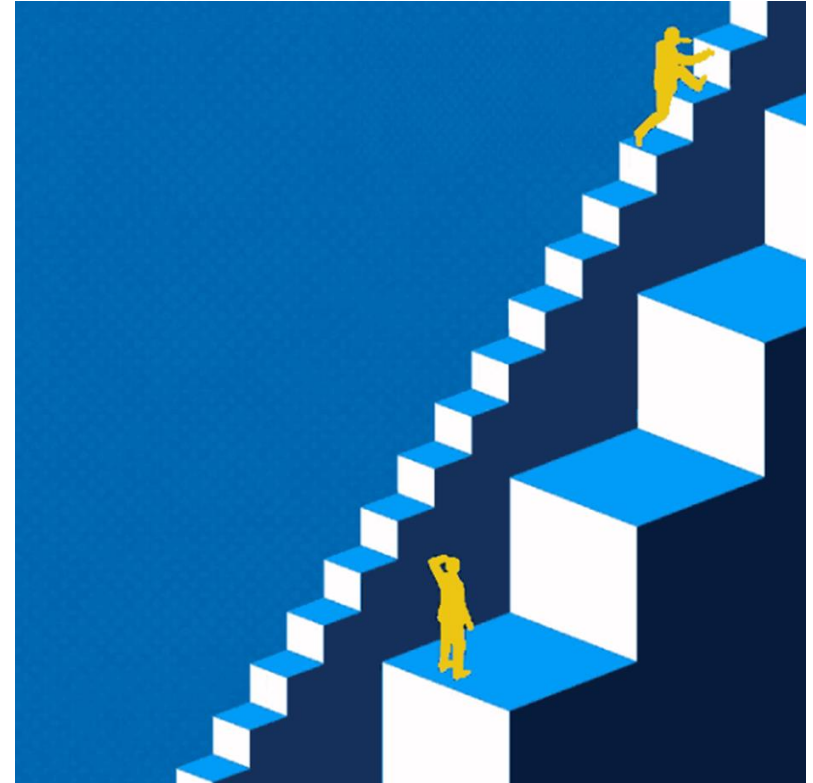
### Limits for CTs

The clinical problem addressed by a specific trial (such as VOC or ACS) may be an acute event with a frequency that is not predictable

Investigators may overestimate the number of participants (feasibility)

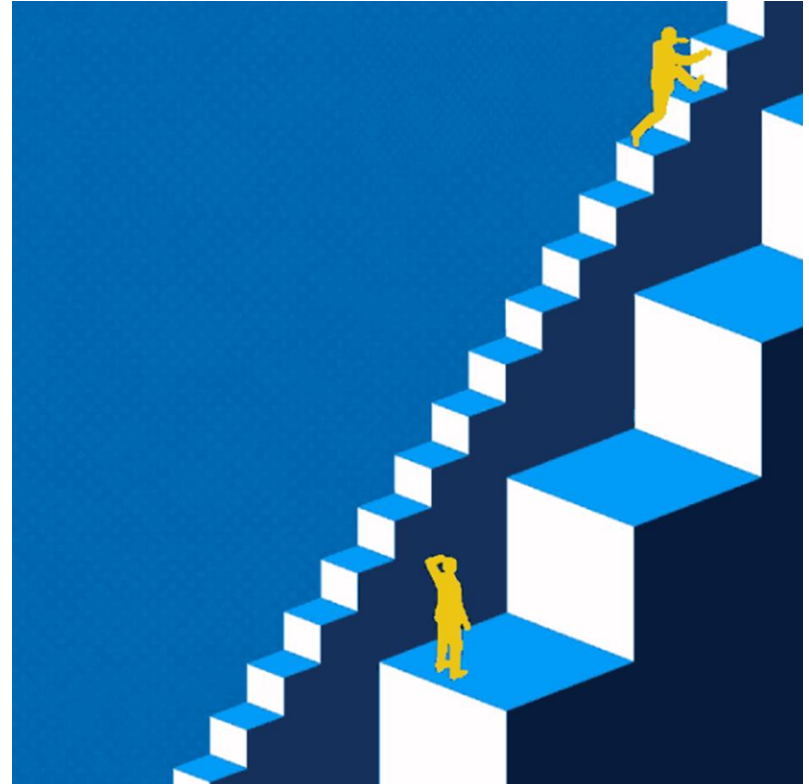
Therapies targeting different pathophysiological mechanisms of SCD:

- modulation of Hb polymerization, erythrocyte dehydration, and Hb oxygen affinity
- prevention of vasal occlusion by inhibiting cell interactions
- prevention of endothelial dysfunction
- modulation of inflammation

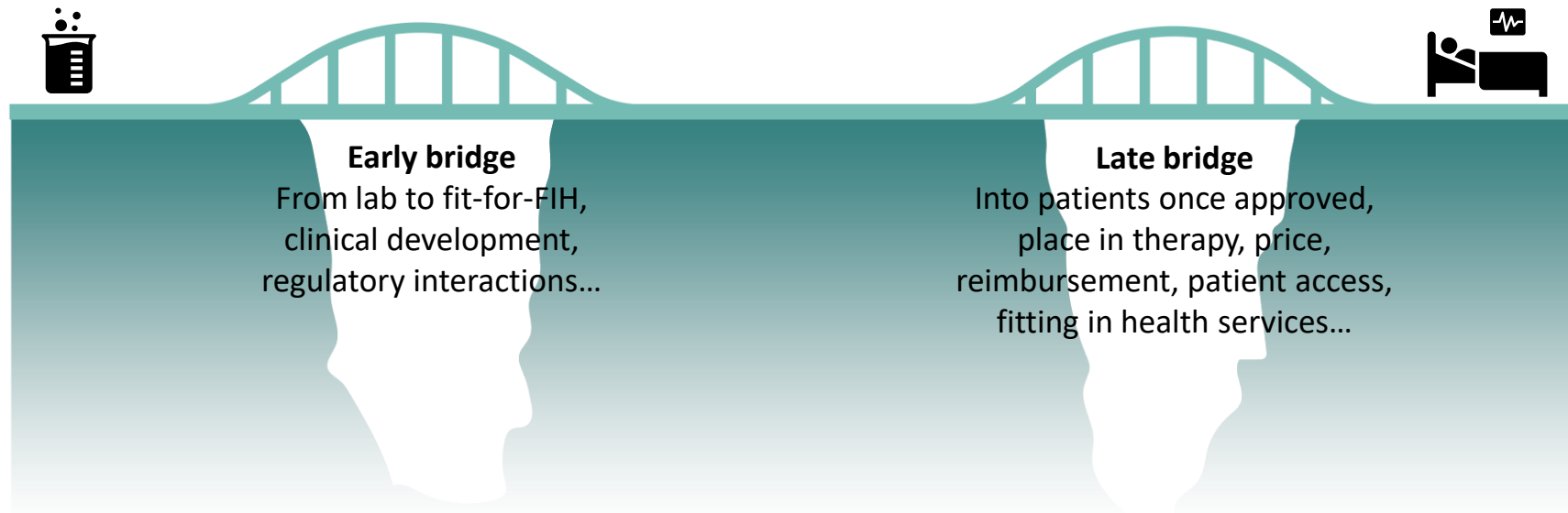


Emerging therapies for thalassaemias based on their pathological target:

- addressing ineffective erythropoiesis and/or hemolysis (TDT and NTDT)
- modifying iron metabolism
- altering globin gene expression



# Evidence from Academic/Pharma industrial research for translation needs to be solid and serve several masters

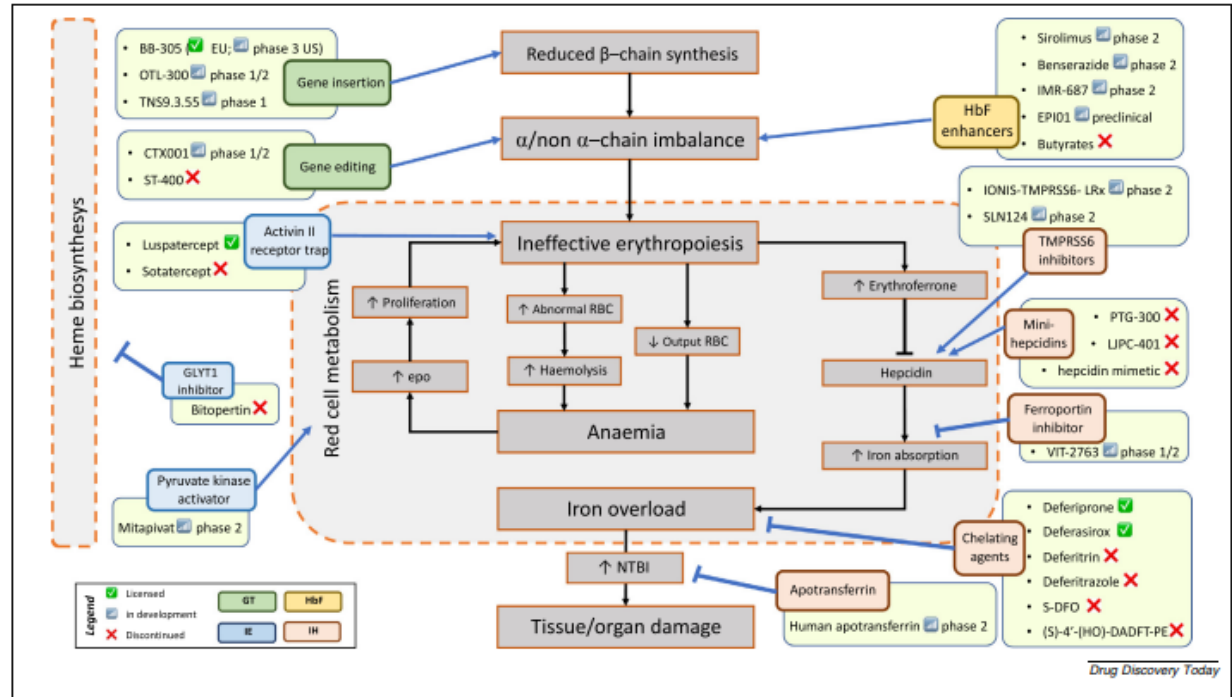


## ODDs have stimulated research efforts in the area of rare diseases

**10 of 28 ODDs for  $\beta$ -THAL**  
(36%) have been discontinued (2 in the preclinical stage and 8 in Phase II);

12 (42%) are active (1 in the preclinical stage, 3 in Phase I and 8 in Phase II).

**Six ODDs, relating to four APIs, are now licensed for the treatment of  $\beta$ -THAL.**

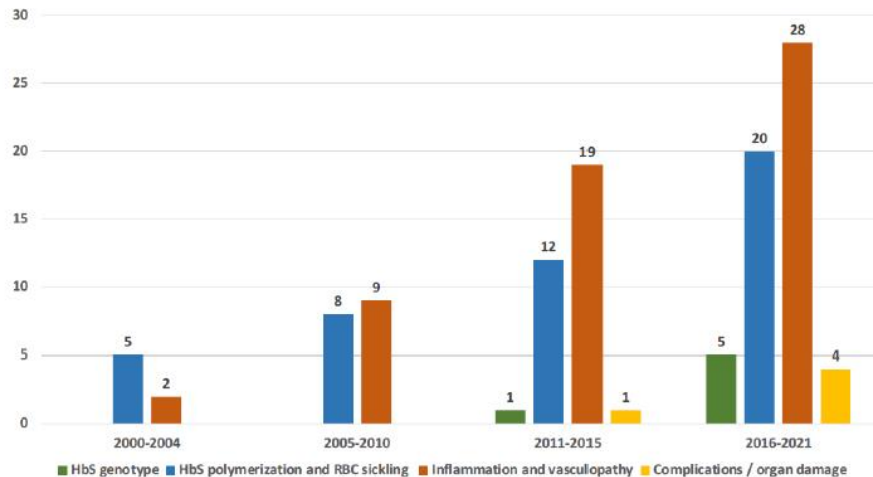


**FIGURE 3**

**Pathophysiology of  $\beta$ -thalassaemia ( $\beta$ -THAL) and therapeutic targets of Orphan Drug Designations (ODDs).** In graph details all ODDs granted in the US and the European Union (EU) from 1983 to 2020; how the respective drugs work; and the outcome of each ODD. Abbreviations: GT, gene therapy; HbF, fetal hemoglobin; IE, ineffective erythropoiesis; IH, iron homeostasis; NTBI, Non-transferrin-bound iron; RBC, red blood cell.



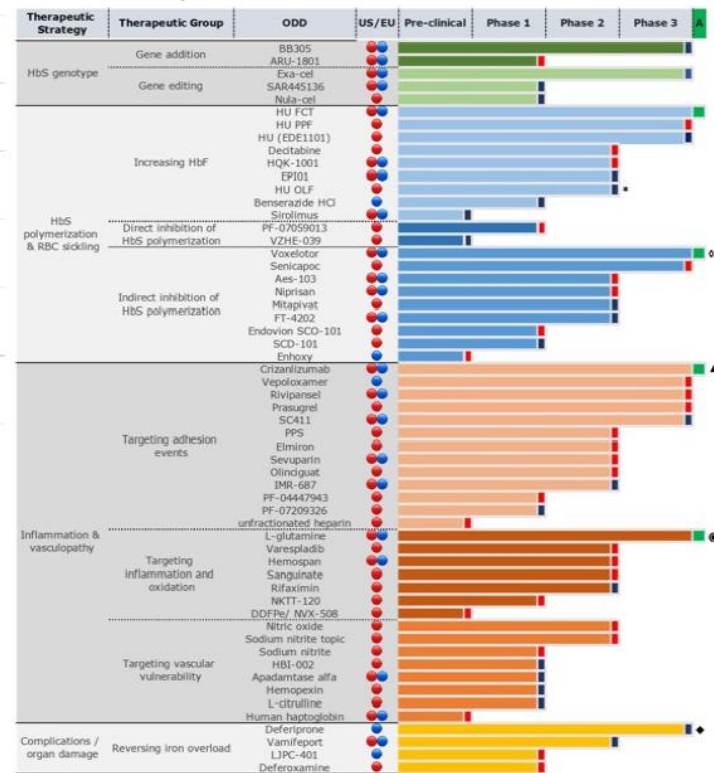
## ...and for SCD



- 20 years of sickle cell orphan drug development has ~12% success rate, with highest rates when targeting early pathophysiological steps.
- Failure rates for lack of efficacy were highest in late stages of drug development when vaso-occlusive crisis was the key clinical endpoint.

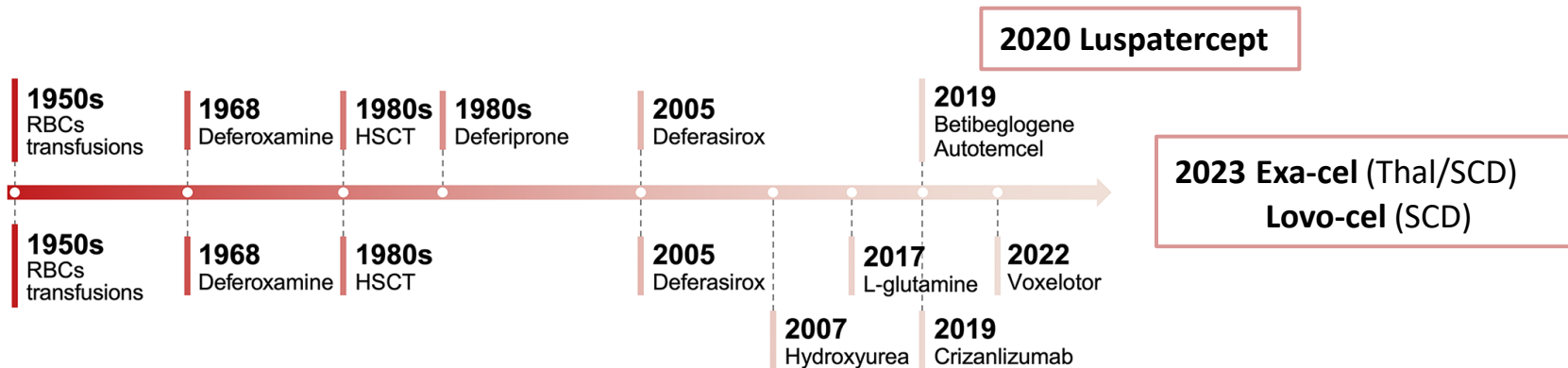
## Successes and pitfalls in orphan drug development for sickle cell disease

Enrico Costa,<sup>1</sup> Antonella Igrò,<sup>2</sup> Mariane de Montalembert,<sup>3</sup> Hubert G. M. Leufkens,<sup>4</sup> Russell E. Ware,<sup>5</sup> and Lucia De Franceschi<sup>1</sup>



# Milestones in the development of treatments for THAL and SCD

## $\beta$ -thalassemia



## Sickle Cell Disease



1

# Challenges

## TRIAL POPULATION

**Regulatory perspective:** For clinical research results to be generalizable, the enrolled participants in the research study should reflect the population affected by the condition or those for whom the treatment or intervention is intended.



**Haemoglobinopathies have substantial genotypic and/or phenotypic heterogeneity.** Different phenotypes may present with involvement of different organ systems, with different severity or rate of deterioration. In addition, metabolism and interindividual response variability seem linked to genetics of poorly characterized enzymes and differences between races cannot be excluded (*Pharmacogenomics J.* 2018 Dec;18(6):730-739. doi: 10.1038/s41397-018-0045-1).

**Impact on representativeness of early clinical data**

# Clinical trials

- In accordance with principles of guidelines for specific therapeutic area
- For EMA scientific advice (or MAA national advice)
- RCT preferable over SATs but may not be feasible

## Efficacy primary endpoints

- established and validated disease-specific endpoints accepted
- non-validated clinical or biomarker endpoint would have to be validated before being accepted in a clinical trial
- need for long-term follow-up for efficacy/safety also to assess durability of effect (i.e., ATMP)



# In the era of gene therapy and gene editing as a potential cure

## Primary endpoints

- Primary endpoint
  - Thalassaemia: T112 = achieving transfusion independence, i.e. proportion of patients with weighted average Hb  $\geq$  9 g/dl without transfusion for at least 12 consecutive months any time after CTX001 infusion
  - Sickle cell disease: VF12 = being VOC free, i.e. proportion of patients that did not experience severe vaso-occlusive crisis for at least 12 months after CTX001 infusion

## Specific clinical endpoints of cure related to SCD phenotype

### VOC



#### PROS:

- Tracking the frequency and severity of VOCs (in terms of hospitalization and opioid use)
- Development of prior pharmacological therapies exclusively utilized VOC as a clinical efficacy endpoint

#### CONS:

- Focus on VOC did not capture the full extent of disease symptomatology and complications and slowed the development of new therapies
- Most SCD patients (94.8%) have infrequent VOCs requiring hospitalization (< 3 annually) and are excluded from VOC-focused trials
- SCD patients can have lifelong complications in addition to pain (i.e., anaemia)

**management of uncertainties**

**Full MA**

Voxelotor	Crizanlizumab
<p>The <u>primary efficacy endpoint of Hb response (percentage of subjects achieving a &gt;1 g/dL increase in Hb from baseline at Week 24), together with secondary endpoint (change from baseline in Hb and clinical measures of haemolysis at Week 24)</u>, served as the basis for the marketing authorization of voxelotor in the EU for <u>the treatment of haemolytic anaemia</u> due to SCD in adults and paediatric patients 12 years of age and older.</p>	<p>For crizanlizumab, the <u>primary efficacy endpoint</u> was <b>the annual rate of sickle cell related pain crises (SCPC or VOC)</b>. The <u>key secondary efficacy endpoint</u> was the <b>annualised rate of days hospitalised</b>. At time of its approval in the EU, data supporting the effects of crizanlizumab <u>were not considered comprehensive</u> due to some uncertainty about the size of crizanlizumab's effect. The medicine was therefore granted a <b>marketing authorisation on condition</b> that the company provided data from the STAND (CSEG101A2301) study in order to confirm the efficacy and safety of the medicine.</p>
<p><u>Voxelotor received a full marketing authorisation valid throughout the EU on 14 February 2022.</u></p>	<p><u>Crizanlizumab: revocation of EU marketing authorisation due to lack of therapeutic efficacy (03/08/2023).</u></p>

**CMA &  
confirmatory  
trial**



# ASH-FDA consensus recommendations for SCD endpoints & Lancet Haematology Commission

- The ASH and FDA developed consensus recommendations for trial endpoints, resulting from the SCD Clinical Endpoints Workshop.
- Recommendations were focused on endpoints in PROs, pain, specific clinical endpoints related to SCD phenotype, and endpoints in low-resource settings (Farrell et al. *Blood Adv.* 3 (23) (2019) 4002–4020; Farrell et al. *Blood Adv.* 3 (23) (2019) 3982–4001).
- "Defining global strategies to improve outcomes in sickle cell disease: a Lancet Haematology Commission" (<https://www.thelancet.com/commissions/sickle-cell-disease>).

(Lancet Haematology July 2023)

## Global strategies to improve outcomes in sickle cell disease

The Lancet Haematology Commission highlights multiple concerns associated with sickle cell disease (SCD), grouped into five categories:

Epidemiology	Screening and gene editing	Substituted and emerging treatments	Cellular therapies	Transfusions and supportive care
<ul style="list-style-type: none"> <li>United availability of the individual epidemiological data</li> <li>Large numbers of people with SCD are neglected in high-prevalence countries</li> </ul>	<ul style="list-style-type: none"> <li>A lack of evidence screening policies and guidelines is</li> <li>Highly diverse countries</li> <li>A lack of consistent and sufficient funding is</li> <li>High-prevalence countries</li> <li>A lack of targeted newborn screening programmes in low-income and middle-income countries (LMICs)</li> </ul>	<ul style="list-style-type: none"> <li>A need for comprehensive national SCD programmes</li> <li>Poor management of vaso-occlusive pain crises and other acute events</li> <li>Poor access to safe blood transfusions</li> <li>Poor access to affordable hydroxyurea</li> </ul>	<ul style="list-style-type: none"> <li>Limited awareness of curative therapies</li> <li>Limited access to allogeneic haematopoietic stem-cell transplantation</li> <li>Limited access to autologous haematopoietic stem-cell transplantation for gene therapy in high-income countries (HICs)</li> <li>A lack of investment in the development of in vivo gene therapy</li> </ul>	<ul style="list-style-type: none"> <li>Poor established or available transfusion services or criteria to train health-care professionals in managing patients with SCD, particularly in LMICs</li> <li>A lack of funding for training and educating health-care providers worldwide</li> </ul>

SCD is a long-neglected condition. Improving outcomes will require substantial financial and political commitment, but doing so will positively impact the lives of millions of patients and families worldwide.

The Commission makes 12 key recommendations for achieving this:

1. Enable routine collection of comparable epidemiological data across all countries by 2025
2. Ensure that testing is available for all babies worldwide by 2025
3. Make hydroxyurea accessible and affordable to all people with SCD by 2025
4. Improve blood transfusion supply and safety by 2025
5. Balance participation of LMICs in SCD clinical trials for new therapies by 2025
6. Accelerate the development of effective and affordable therapies to achieve safe and accessible cures by 2040
7. Make current estimates of the global burden of SCD by 2050
8. Make national governments accountable through monitoring of public health interventions implementation and progress
9. Inform populations affected by SCD about reproductive risks and choices. Tailor information to cultures and religion
10. Provide access to minimum specific health care to all people with SCD no matter where they live
11. Educate health-care professionals and the general public about SCD and its management
12. Prioritise funding for SCD research through dedicated calls

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These goals are all achievable, but are not without challenges:

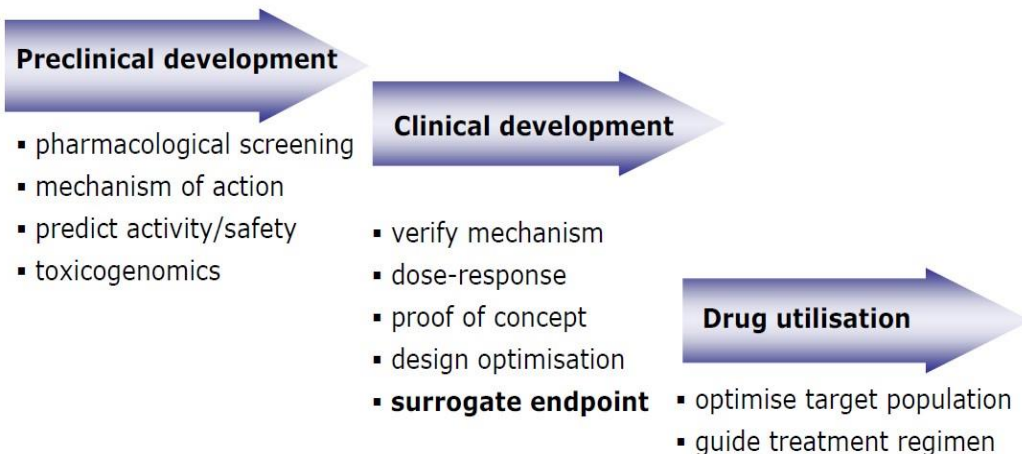
- SCD is probably the most common, serious inherited disease in the world. It is also one of the top 10 causes of non-communicable death globally.
- Whereas the majority of leading causes of death are decreasing, this number of deaths due to SCD is increasing globally.
- Despite this, there are fewer than five effective disease-modifying agents and less, and most people with SCD in the world do not have access to any of these.

**Read the full Commission and all related content at [thelancet.com/commissions/sickle-cell-disease](https://www.thelancet.com/commissions/sickle-cell-disease)**

THE LANCET Haematology

The best science for better lives

## Qualification Advice & Opinion - Novel methodologies



- **Identification and Development of Biomarkers** (as intermediate endpoint or surrogate endpoints in clinical trials).
- **Long-term endpoints concerning organ function** (e.g., cardiac, pulmonary, endocrine, renal, neurological, bone and splenic function).
- **PROs** can be determined with patient and caregiver input using validated measures.

**High standards of evidence in the interest of patients and society: a joint effort**

## Post-Authorisation, Registry Data

**Due to the rare nature of the disease and patient availability for clinical studies, efficacy/safety data could be limited to pre-approval. Therefore, additional data may need to be collected in the post-marketing through dedicated PASS/PAES and/or Registries**

Information obtained from Registries play an important role at every stage of drug development, from drug discovery to the design of clinical studies intended to support MA of a drug and beyond into the post marketing period.

Three main areas for which RWD analyses can support EMA committees' decision-making



1

### Understand the clinical context

Disease epidemiology

Clinical management

Drug utilisation

2

### Support the planning and validity

Design and feasibility of planned studies

Representativeness and validity of completed studies

3

### Investigate associations and impact

Effectiveness and safety studies

Impact of regulatory actions

## WE CAN DO MORE...

- Increase the synergy between European research teams working on the pathophysiology of THAL/SCD at preclinical levels and the subsequent clinical development (i.e., initial orphan designations, protocol assistance, COMP, SAWP).
- Involve a larger number of patients in clinical trials (i.e.,  $\alpha$ -thalassaemia major or intermedia, HbS/C, HbS/ $\beta$  etc.).
- Data on new therapies regarding children are currently limited and access to new therapeutic approaches in children is often delayed since most clinical trials involve only adults at first. This should be carefully considered.
- Generate common action at the European level to ensure optimal care of THAL/SCD patients (especially for those who do not currently have access to specialist clinical services in many parts of Europe).