Full title: The Sickle Eye Project: Prevalence of visual impairment due to sickle cell retinopathy and maculopathy in the United Kingdom

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The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

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TABLE OF CONTENTS

Key study contacts ---- 3
Study summary ---- 5
1.Introduction ---- 6
1.1 Proliferative sickle cell retinopathy ---- 6
1.2.Sickle cell maculopathy ---- 6
1.3 Current interventions for SCR and maculopathy ---- 6
1.4 Retinal imaging for SCR and maculopathy ---- 7
1.5 Clinical study rationale ---- 8
2.Study Objectives ---- 9
2.1Outcome measures ---- 9
3.Overall study design ---- 12
3.1 Study design ---- 12
3.2 Participants and recruitment ---- 12
3.3 Recruitment and Consent ---- 13
3.4 Eligibility criteria: ---- 13
3.5 Study activities ---- 14
3.5.1 Theoretical framework of acceptability (TFA)-based acceptability questionnaire ---- 14
3.5.2 Pre-validating the questionnaire for acceptability of routine retinal screening in persons with SCD 14
3.5.3 Other study activities ---- 14
4.Image acquisition protocol and transfer of data ---- 18
5.Satistics and data analysis ---- 19
5.1 Data Analysis plan ---- 19
5.2 End of study ---- 20
6.Regulatory reviews and compliance ---- 21
6.1 Ethics approval ---- 21
6.2 Amendments ---- 21
6.3 Data handling and record keeping ---- 21
6.3.1 Source data ---- 21
6.3.2.Case Report Form (CRF) ---- 22
6.3.3 Electronic case report form and data management ---- 23
6.3.4 Data Ownership and Storage ---- 23
6.3.5 Data security ---- 23
6.3.6 Quality control, quality assurance and Monitoring ---- 23
6.3.7. Patient safety and reporting ---- 24
6.3.8 Archiving ---- 24
6.4 Indemnity ---- 24
6.5 Sponsor ---- 24

6.6 Funding ---------- 25
6.7 Data potection and confidentiality ---------- 25
6.8 Post-study care---------- 26
7.Study Management ---------- 27
8.Publication and dissemination Policy ---------- 27
9.Authorship ---------- 27
10.References---------- 28
11.Appendix---------- 30

Study summary

Study Title	**The Sickle Eye Project: Prevalence of visual impairment due to sickle cell retinopathy and maculopathy in the United Kingdom**
Short title	The Sickle Eye Project
Study Design	Cross-sectional, non-interventional study
Study Participants	People with Sickle cell disease
Planned Size of Sample (if applicable)	600 patients with sickle cell disease
Planned recruitment Period	12 months
Research objectives	• Primary objective: To determine the prevalence of visual impairment (best corrected visual acuity ≥ LogMAR 0.3 in at least one eye) due to sickle cell retinopathy (SCR) and/or maculopathy in persons with sickle cell disease (SCD) • Secondary objectives: 1. To determine the prevalence of each stage of SCR and maculopathy and correlation with: i) number of hospital admissions with acute sickle cell episode in the past 12 months, ii) serum HbF level iii) serum Hb level 2. To determine the impact of SCR and maculopathy on vision-related quality of life 3.To determine the acceptability to patients of retinal imaging and routine screening for SCR and maculopathy.

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1. Introduction

1.1 Proliferative sickle cell retinopathy

Sickle-cell disease (SCD) is one of the most common genetic disorders in the UK, with approximately 15000 people affected.[1] It is a debilitating, multisystem disease, associated with episodes of acute illness, progressive organ damage and reduced life expectancy. There are 13 genetic variants of SCD, with HbSS genotype being most common (>70%) and most severe, followed by HbSC genotype. SCD affects predominantly people of African and Afro-Caribbean descent and evidence demonstrates inequalities in healthcare outcomes and access for people with SCD [2]. An all-party parliamentary group inquiry reported low awareness of SCD and its complications among healthcare professionals and underinvestment in sickle cell research[3].

Proliferative sickle cell retinopathy (SCR) is the most common ophthalmic manifestation of SCD and can result in significant sight loss, although the prevalence in the U.K is not currently known. Decades old retrospective and cohort studies from other countries have estimated prevalence of SCR in SCD patients at up to 48% and associated with significant sight loss in up to 12%[4,5]. Importantly, life expectancy for SCD has increased from 14 years in 1973 to >60 years in high-income countries with improvement in management and healthcare delivery[6]. Evidence from cohort studies and large retrospective studies demonstrate increasing incidence of SCR with age[7,8]. As such, we could expect the prevalence of SCR and potentially associated visual impairment, to be currently higher in the UK than previously reported.

Five stages of SCR were described by Goldberg in 1971[9]. These are progressive with stages 1-3 being asymptomatic, stage 3 reflecting the presence of retinal neovascularisation in the far periphery known as seafan neovascularisation, vitreous haemorrhage (bleeding inside the eye) develops in stage 4 and rhegmatogenous and/or tractional retinal detachment in stage 5.

1.2 Sickle cell maculopathy

In addition to the peripheral retina, SCD can also affect the macula (central retina) potentially causing visual loss, known as sickle cell maculopathy. Sickle cell maculopathy (SCM) is defined as patchy areas of severe retinal thinning in the temporal macula. The exact aetiology of macular thinning remains unclear, but it may be related to the temporal macula ending along the horizontal raphe, making it a watershed zone between the vascular arcades of the retinal circulation and thus more susceptible to vascular occlusions[10]. Whilst high-contrast visual acuity was preserved in most patients demonstrated to have SCM in a single centre study[11], irreversible scotoma, decreased retinal sensitivity and visual loss has been described in association with SCM[12,13,14]. Maculopathy was not included in the Goldberg classification as its presence only became more apparent with modern imaging techniques. There is currently no treatment for vision loss due to maculopathy.

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1.3 Current interventions for SCR and maculopathy

Laser photocoagulation is currently the only intervention with high-level evidence of safety and efficacy in the management of stage 3 SCR[15,16]. Laser photocoagulation has an indirect effect as it destroys the ischaemic retina responsible for production of vascular endothelial growth factor (VEGF) that triggers the proliferation of new blood vessels. This technique is commonly used in the treatment of diabetic retinopathy and widely available in the U.K. For SCR, there has been a paucity of randomized controlled trials (RCT) of intervention, with only 2 RCTs evaluating laser treatment for stage 3, and both conducted over 30 years ago. In the first randomized controlled trial of laser, Jampol et al[15] compared laser treatment to observation in a randomized controlled trial of 167 eyes and reported 3.4% developed vitreous haemorrhage (stage 4 SCR) in the laser-treated arm versus 27.5% in the observation arm whilst 1% developed visual loss in the laser-treated arm versus 5% in the observation arm. Faber et al subsequently reported similarly positive results[16]; with a Cochrane review of the safety and efficacy data of laser treatment for stage 3 SCR concluding that laser treatment reduces the risk of visual loss at mean follow-up of 1 year and is protective against the development of vitreous haemorrhage[17]. However, the RCTs and other case series also reported spontaneous regression of stage 3 in up to 30% of eyes[7,17]. In addition, these RCTs evaluating laser treatment are more than 30 years old and laser technology as well as the systemic management of SCD has improved significantly in that time.

Alternatively, stage 3 and 4 SCR can be managed with intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy. Over the last 16 years, intravitreal anti-VEGF have become common place in ophthalmic practice with many licensed indications including age-related macular degeneration and diabetic retinopathy. As VEGF is implicated in SCR[18], the use of intravitreal anti-VEGF therapy is scientifically rational, and evidence of regression and resolution has been demonstrated in case series of eyes with stage 3 and 4 SCR[19]. Additionally, angiopoietin-1 and angiopoietin-2 have also been implicated in the pathophysiology of SCR[20]. In June 2022, NICE approved Faricimab, an intravitreal bi-specific monoclonal antibody that inhibits VEGF and angiopoietin-2 for the treatment of wet-age related macular degeneration and diabetic macular oedema[21, 22]. No RCTs have been conducted comparing intravitreal anti-VEGF therapy or anti-angiopoietin-2 to laser therapy or observation.

The main therapeutic intervention for stage 4 and 5 SCR is vitrectomy. Vitrectomy is a surgical intervention that involves removal of the vitreous (including blood if stage 4 SCR) and repositioning of the retina to its proper position against the back of the eye (when there is retinal detachment as in stage 5). Despite significant advances in modern surgical techniques, visual outcomes for stage 4 or 5 SCR remain poor, with final visual acuity post-surgery often significantly below driving vision,[23] so early detection of SCR remains an opportunity to prevent sight loss.

There is also the potential for systemic treatment of SCD to influence the progression of SCR and/or maculopathy. Hydroxycarbamide is the gold standard treatment for prevention of painful crises in SCD and has

been proven to reduce hospital admissions in patients with SCD[24]. Hydroxycarbamide induces fetal hemoglobin production (HbF) thereby decreasing sickle hemoglobin erythrocyte polymers, haemolysis, and painful vaso-occlusive crisis. Rigorous investigation over the past 30 years has demonstrated the efficacy of hydroxycarbamide in reducing disease complications, health care utilization, and costs for patients with SCD. However, compliance rates are well established to be low and linked to a variety of reasons including fear of side effects, stigma and low health literacy[25]. Although there are no prospective studies that evaluate the efficacy of hydroxycarbamide on reducing the incidence of SCR, large retrospective studies have highlighted the protective effect of hydroxycarbamide on SCR and maculopathy[26,27]. These studies suggest hydroxycarbamide, by elevating levels of HbF, can significantly reduce the odds of developing SCR and reduce the progression of sickle maculopathy. There is also emerging evidence that the severity of SCR and maculopathy correlates with severity of systemic anaemia associated with SCD[28,.29]. As such, retinal screening may improve compliance with hydroxycarbamide if evidence confirming protective retinal effects are corroborated. Retinal screening may also highlight the need for escalations of management to the haematologist.

1.4 Retinal imaging for SCR and maculopathy

Retinal imaging has undergone revolutionary advancement in the past 20 years. Ultrawide field fundus photography detects SCR more reliably than traditional eye examination or imaging.[30] The widespread availability and use of optical coherence tomography (OCT) (and OCT-angiography in some centres), which are rapid, non-invasive imaging tools that produce detailed images of the macular and associated vascular plexuses means we can now detect damage to the macular otherwise undetected using traditional methods. These tools are now used routinely and extensively in the management of various high-volume eye diseases across the country including age-related macular degeneration, diabetic eye disease and patients with visual symptoms from SCR or maculopathy and are likely to be acceptable to all patients with SCR. The combination of Ultrawide field colour, OCT and OCTA will provide the best method for detecting vision-threatening retinal changes in sickle cell disease and detecting change over time.

1.5 Clinical study rationale

There is no reliable estimate of the burden of sight loss due to SCR and maculopathy in the UK or the number of people with different stages of SCR and maculopathy. This lack of data makes planning configuration and delivery of appropriate services for eye health in SCD difficult and could lead to unwarranted variation

There is also no national screening guideline or programme for early detection of SCR in the U.K. The National Institute for Health and Care Excellence (NICE) recommends that people with SCD should be evaluated by an ophthalmologist every 2-3 years if they have no evidence of retinopathy and people with retinopathy should be reviewed at least annually[31]. However, only 40% of eye departments provide routine retinal screening for SCR in a recent feasibility survey of eye departments in the UK (Dinah, 2022, unpublished) due to lack of consensus

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on appropriate intervention to prevent progression. In centres providing screening there is variation in how this is undertaken between clinical examination and type of retinal imaging used. Our study will determine the proportion of vision loss due to SCR and maculopathy in the U.K. We will also determine the distribution of the stages of SCR and maculopathy and correlation with severity of SCD. SCR and maculopathy screening are easily incorporated into existing diagnostic clinic pathways for retinal diseases. However, there is a need to establish any benefit of screening and the acceptability to patients with SCD.

We do not currently know what the prevalence of sight loss due to SCR and maculopathy is, nor the potential for preventing sight loss by implementing a national screening programme. The traditional approach of face to face clinic appointment can also make compliance difficult in a working age population with many health demands. The use of imaging could provide a more flexible approach to access, through diagnostic centres as has been introduced in Newcastle where virtually all the sickle cell patients under the care of haematology have now had their eyes imaged.

Our patient and public involvement (PPI) group informed us of their lack of awareness of the potential effects of SCD on vision. They described the difficulties associated with vision loss including the increased vulnerability associated with loss of driving license in the context of living with SCD, days off work associated with vitreous haemorrhage impacting their financial well-being and livelihoods and difficulty engaging in vision-related tasks at work and university. One of the members of our PPI group told us they would have been compliant with their systemic medication if they knew it could help preserve their sight and the others agreed this could be a motivating factor for many people with SCD.

2.Study Objectives

The Sickle Eye Project includes an internal pilot phase, which is the first 4 months of the recruitment period, to assess recruitment and trial processes.

The objectives of the internal pilot are:

1. To open 6 sites by the end of the pilot phase
2. 95% of the expected monthly recruitment is achieved by the end of the pilot phase
3. Adherence to imaging protocol in ≥90% of cases
4. 95% of recruited participants with completed NEI VFQ 25 questionnaire

Main study primary objective: To determine the prevalence of visual impairment (best corrected visual acuity ≥LogMAR 0.3 in at least one eye) due to SCR and/or maculopathy in persons with SCD

Main study secondary objectives:

1. To determine the prevalence of each stage of SCR and maculopathy and correlation with:

i) number of hospital admissions with acute sickle cell episode in the past 12 months, ii) serum HbF level iii) serum Hb level

2. To determine the impact of SCR and maculopathy on vision-related quality of life.

3.To determine the acceptability to patients of retinal imaging and routine screening for SCR and maculopathy.

2.1 Outcome measures

Internal pilot outcomes

The following progression criteria using a red/amber/green traffic light system will be used to inform whether we progress to the main trial:

Site opening progress

Green: 6 sites are open to recruitment

Amber: 3 -5 sites are open to recruitment

Red: 2 or fewer sites or more are open to recruitment

Recruitment progress

Green: Recruitment of >120 at end of pilot phase

Amber: Recruitment of $\leq$ 120 but ≥ 79 patients at end of pilot phase

Red: Recruitment of <79 patients at end of pilot phase.

Fidelity check demonstrating adherence to image acquisition protocol

Green: Adherence to image acquisition protocol in ≥90% of cases.

Amber: Adherence to image acquisition protocol in ≥80%

Red: Adherence to image acquisition protocol in <80% of cases

Completion of the NEI VFQ-25

100% of recruited participants completing the NEI VFQ-25

Green: ≥95% of recruited participants with completed NEI VFQ-25

Amber: ≥80% of recruited participants with completed NEI VFQ-25

Red: <80% of recruited participants with completed NEI VFQ-25

If at the end of the pilot phase the thresholds are at amber or red for any of the progression decision points, the Co-Investigator Group, which includes a lived experience expert as co-applicant will review and provide remedial action that would allow progression to the main trial to the Funder. If there are no obvious remedial actions that can be taken, the Co-Investigator group will discuss stopping the trial with the Funder.

Main study primary outcome

1. The prevalence of visual impairment due to SCR or maculopathy (defined as best corrected visual acuity LogMAR ≥ 0.3 in at least one eye) in a representative sample of the UK population with SCD

Secondary outcomes

1. The prevalence of each stage of SCR and presence of maculopathy by age and genotype

2. The correlation of each stage of SCR and maculopathy to severity of SCD as determined by number of hospital admissions in the preceding 12 months/serum HbF/ serum Hb.

3. The impact of SCR and presence of maculopathy on vision-related quality of life.

4. The acceptability to patients of routine retinal imaging for SCR and maculopathy

5. The development of updated consensus definitions and a modernized classification system for SCR and maculopathy, leveraging the increased insight into retinal tissue anatomy and vascular blood flow afforded by contemporary imaging technologies

3.Overall study design

3.1 Study design

This is a cross-sectional, non-interventional study. Potential participants will be introduced to the study by their haematologist, who will also provide them with the participant information sheet. Identification of potential participants in the haematology clinic is important to prevent ascertainment bias and sample a representative

sample of people with SCD. All patients with SCD are offered regular specialist follow-up by a haematologist in the UK. The national haemoglobinopathy registry record for 2021 reported 12904 people with SCD confirming that an overwhelming proportion of SCD patients are under specialist care in the UK. Informed consent will be obtained from willing participants by the ophthalmology team either in the eye department or over the telephone. Informed consent will be obtained prior to the collection of any data. Once consented, participants will have best corrected visual acuity (BCVA) with habitual correction and pinhole measured, a slit lamp examination of the anterior segment and fundus, spectral-domain optical coherence tomography (SD-OCT), optical coherence tomography-angiography (OCT-A) and ultra-widefield fundus photography performed in the eye department. Subsequently, the participant will have the NEI VFQ-25 questionnaire and the acceptability of retinal screening questionnaire administered.

In some departments, it may be more appropriate for the haematology team to share brief details about the study, including the study leaflet with potential participants. Interested participants can be sent the participant information sheet ahead of their eye clinic appointment.

The NEI VFQ-25 questionnaire can be administered over the telephone either at the time of consent or after the visit to the eye department. The acceptability of retinal screening questionnaire has to be administered after the retinal imaging has been performed.

If the NEI VFQ-25 is completed over the telephone, this must be done ±28 days of the eye clinic visit for examination and retinal images.

The research team will also complete an electronic case report form recording basic demographic history such as: Year of birth, Sex, Sickle genotype, Number of hospital admissions with acute sickle crisis, medical history, current medications and interventions for SCD, previous history of stage 4 or 5 sickle cell retinopathy, ocular comorbidities, previous ocular interventions and most recent serum haemoglobin (Hb) and serum haemoglobin F (HbF) within 3 months of study entry.

3.2 Participants and recruitment

Haematology teams in participating sites will inform consecutive patients with SCD ≥ 16 years about the study and refer to the ophthalmology unit for routine retinal screening. In units where patients have already been referred for screening but are awaiting appointments in the ophthalmology department can also be recruited in the ophthalmology department. In the ophthalmology department, patients with SCD who meet the study inclusion criteria will be invited by the clinical team to take part. Participating Trusts have been selected as they already offer or are willing to offer routine eye screening for SCD patients as part of standard of care and confirmed to have ultra-widefield fundus imaging and spectral domain OCT.

We have used the 2021 national haemoglobinopathy registry (NHR) report to identify centres treating patients with SCD in England. Eligible centres had to meet the following criteria:

1. At least 60 patients with SCD on the registry
2. Ultra-wide field fundus photography
3. Spectral domain OCT imaging
4. A routine screening programme for SCR in place or willing to institute one
5. Capacity and willingness to participate in the present study

3.3 Recruitment and Consent

600 individuals who have been diagnosed at any point with SCD will be identified from up to 16 geographically dispersed participating NHS Trusts across the UK.

Individuals identified to be eligible will be approached in clinic by their consultant haematologist or a member of their clinical team, who will explain the background, aims and nature of the project, and provide further information about the project in an accessible format (participant information sheet; PIS). Potential participants can also be identified from the ophthalmology waiting list if they have been referred as part of a routine screening programme from haematology. An invitation letter informing potential participants due to attend a sickle cell clinic can be sent out with appointment letters so that they are aware of the study before attending the clinic.

Interested participants will be invited to attend the eye clinic where they will be consented and research activities will occur. For those who do not speak English or would benefit from translation services, this will be funded by the study. Informed consent can also be obtained over the telephone. Potentially eligible participants who have previously given consent to contact for any research can be approached by the research team by telephone and if willing to consider participating, the PIS can be posted to them. There will be an opportunity to discuss the study before consent is obtained in the eye clinic or by telephone, and it will be made clear that the individual is free to withdraw from the study at any point.

Telephone consent

Participants can provide consent verbally to a member of the research team over the telephone. Before taking consent the member of the local research team will ensure that they have a witness present who can verify that informed consent was taken. The member of the local study team acting as a witness does not need to be named on the Delegation Log. The member of the local research team who is taking remote consent will read each of the statements on the ICF to the potential participant and will insert their initials in each of the associated boxes to confirm that the participant agrees with the statement. After consent has been taken the witness will

countersign the informed consent form (ICF) and a copy of the completed form sent to the participant. The method by which this was done will be recorded at the end of the consent form. A copy of the ICF will be placed in the participant's notes which will record the name of the person taking the consent, the witness, and the date this was done. Oral confirmation of ongoing consent to participate in the Sickle Eye Project should be sought from the participant when they present for their procedure, and this should be recorded in the participant's medical notes

3.4 Eligibility criteria:

Inclusion criteria

- Willingness to participate
- Ability to provide informed consent
- Age 16 years or older
- Diagnosis of SCD of any genotype

Exclusion criteria

- Inability to consent
- Poor image quality
- Age <16 years
- Sickle cell trait only

3.5 Study activities

3.5.1 Theoretical framework of acceptability (TFA)-based acceptability questionnaire

The theoretical framework of acceptability (TFA) was developed in response to recommendations that acceptability should be assessed in the design, evaluation and implementation phases of healthcare interventions[32]. The TFA consists of seven component constructs (affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness, and self-efficacy) that can help to identify characteristics of interventions that may be improved. Using this robust framework, a validated generic TFA-based questionnaire[33] was developed as an adaptable tool to measure acceptability across various healthcare interventions.

3.5.2 Pre-validating the questionnaire for acceptability of routine retinal screening in persons with SCD

We have adapted the generic TFA questionnaire with insights from our PPI group pilot, expert clinical opinion and literature review. The first draft of the adapted TFA questionnaire has been discussed with our PPI consisting of 10 patients with lived experience of SCD, who also helped us to develop the study design. This

feedback was incorporated and shared with the PPI group and a further group of 10 patients attending retinal screening clinics for SCD at 2 eye units in the UK to check comprehensibility and comprehensiveness. The final version of the questionnaire incorporates this input from patients and medical experts managing patients with SCD.

3.5.3 Other study activities

Best corrected visual acuity (BCVA) with habitual correction and pinhole

This is a measure of the primary outcome. BCVA will be assessed using the Early Treatment of Diabetic Retinopathy Study vision chart chart in a 4 meter lane under routine clinic conditions as part of routine clinical care as usually conducted. Participants will be invited to bring their most up to date correction to the study visit. BCVA will be recorded with their habitual correction and pinhole in LogMAR. **Refraction by an optometrist is not required**

Slit lamp biomicroscopy and dilated funduscopy

Slit lamp biomicroscopy allows the ophthalmologist to microscopically examine the eye for any abnormalities or problems. Dilated funduscopy allows better evaluation of the lens and vitreous. This will be performed to document other ocular causes of visual impairment such as corneal scars, cataracts and vitreous haemorrhage.

Spectral domain OCT

Spectral domain OCT (SD-OCT) is the current reference standard for diagnosing and monitoring progression of various macular diseases. It is non-invasive and rapid, often taking less than 15 seconds to capture a detailed assessment of the macular. It captures the cross-sectional morphology of retinal structures and allows detailed assessment of anatomical layers affected by the disease. In sickle cell maculopathy, there is evidence of retinal thinning, with the temporal retina being most commonly affected. All images will be assessed by the ophthalmology team and management instituted as per standard of care. The interpretation of the images will be documented in the study case report form

OCT angiography

OCT-Angiography (OCT-A) is now often routinely performed as part of routine clinical care and provides depth-resolved visualisation of the superficial and deep capillary plexuses. By allowing depth-resolved visualization of the macular vascular network with high resolution, optical coherence tomography angiography (OCTA) recently detected much more macular vascular alterations than previously detected using just OCT and provided additional features, including enlargement and irregularities of the foveal avascular zone (FAZ), hairpin venular loops, and areas of flow loss responsible for irreversible macular thinning[34]. All images will be assessed by the

ophthalmology team and management instituted as per standard of care. The interpretation of the images will be documented in the study case report form

Ultra-widefield fundus photography

Ultra-widefield fundus photography captures an image covering more than 80% of the retina. It allows the observer to assess the retina, associated blood vessels and optic nerve. This is particularly of benefit in sickle cell retinopathy, where the initial stages of proliferative retinopathy occur in the far periphery and can be missed if the periphery is not carefully assessed. In the UK, Optos imaging and the Zeiss Clarus are the most commonly used ultra-widefield imaging systems. All units included in this study will be using either the Optos or the Clarus. Whilst there is evidence that un-dilated ultrawide field fundus photography can be of utility in screening for sickle cell retinopathy with a specificity of 100% compared to dilated funduscopy examination in one study, the sensitivity was 69.2%[35]. Therefore, for the purpose of this study, ultra-widefield fundus photography will be performed with a dilated pupil. All images will be assessed by the ophthalmology team and management instituted as per standard of care. The interpretation of the images will be documented in the study case report form

NEI-VFQ 25

The NEI-VFQ 25 is a validated 25 item questionnaire comprising of 11 subscales on different aspects of vision-related functioning (VRQoL), quality of life and 1 item on general health. It is the most commonly used patient reported outcome measure in retinal research and trials. It is designed to assess the influence of visual impairment on vision-related function and multiple dimensions of VRQoL. This instrument has evidence of good psychometric properties, including reliability and construct validity, assessed using classical test theory in a mixed population of patients with various eye diseases and visual impairment.

Due to the proliferation of diagnostic hubs in the NHS, the NEI-VFQ-25, which can take up to 15 minutes to complete may limit recruitment at some sites. As such, we will monitor the impact of completing this questionnaire on recruitment through our monthly investigators meeting for the first 3months of recruitment. Feedback from Principal Investigators on the impact of the NEI-VFQ 25 on recruitment will determine whether to switch to the EQ-5D with vision bolt-on.

EQ-5D with vision bolt-on

The 5 level EQ-5D is a widely used preference-based health related quality of life instrument with one question for each of 5 core dimensions of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. To capture the effect of conditions that affect sensory functions or cognition that may not

be adequately captured by the instrument, additional dimensions, known as 'bolt-ons' were developed. The vision bolt-on has demonstrated enhanced sensitivity, construct validity and responsiveness to change in populations with vision problems[36,37]. Importantly, EQ-5D with vision bolt-on comprises of 6 questions which can be rapidly completed by participants

Study activity	**Personnel**	Baseline	±28 days
Eligibility criteria check	Haematology team	x	
Patient information sheet	Haematology team Or Ophthalmology team	x	
Informed consent	Ophthalmology team	x (Can be completed by telephone)	
BCVA with habitual correction and pinhole	Ophthalmology team	x	
Slit lamp biomicroscopy and dilated funduscopy	Ophthalmology team	x	
OCT	Ophthalmology team	x	
OCT-A	Ophthalmology team	x	
Ultrawide field fundus photography	Ophthalmology team	x	
***NEI-VFQ 25**	Ophthalmology team	x (Can be completed by telephone)	x

***Acceptability Questionnaire**	Ophthalmology team	x (Can be completed by telephone after retinal imaging and within 14 days)	x
Clinical assessment of images	Ophthalmology	x	
Completion of case report form	Ophthalmology/haematology team	x	x
Transfer of images	Ophthalmology team	x	x

4.Image acquisition protocol and transfer of data

Imaging acquisition will be performed by trained staff at each recruitment site. As this is a pragmatic study, and the imaging to be acquired are standard of care in NHS eye departments, standards for training and experience of staff performing the imaging acquisition function will be the ones applicable at each recruitment site as per local Standard Operating Procedures.

The Moorfields Reading Centre will provide supporting material of educational and advisory character for acquisition of high-quality imaging from the Sickle Eye Project participants. It will also provide detailed, yet simple and intuitive instructions for imaging file export and direct upload to the Moorfields Grading Portal Web-based Application.

For details on the process of User activation, including Users with the Uploader role, and User Management, please see relevant provisions of the 'Data Protection and Information Security' section.

For each patient, imaging from the three following modalities will be obtained, and transferred to the Moorfields Reading Centre. Imaging from both eyes will be obtained:
- Optical Coherence Tomography scan (TopCon 3D-2000, Heidelberg Spectralis or Zeiss Cirrus).

Recommended parameters: Macula Centre 6x6 mm Raster Scans.

- Optical Coherence Tomography Angiography where available (TopCon Triton, Heidelberg Spectralis OCT-2, Zeiss Angioplex)

Recommended parameters: Macula Centre 6x6 OCT Angiography mode
- Wide Field Imaging (Optos California or Zeiss Clarus)

Recommended parameters for wide field imaging: Instructions will be provided to assist Imaging acquisition staff with obtaining clear view of the Fundus, including the extreme periphery through imaging acquisition at the central and 4 peripheral positions of gaze (up, down, right, left) and the avoidance of 'eyelash' artifacts that interfere with Fundus view in Optos Ultra-Wide Field Imaging.

The images being transferred to Moorfield hospital will be link anonymised with no patient identifiers. The link key will remain with each recruiting site and will not be shared with the sponsor site.

Bi-directional communication between recruitment sites and the Moorfields Reading Centre will be possible through the interactive Moorfields Grading Portal. A granular Audit Log will record all study-related activity, including who, where and when each activity was performed.

5. Statistics and data analysis

The primary analysis will be to calculate the prevalence of sickle cell retinopathy/maculopthy-related vision loss together with its 95% confidence interval (CI) to illustrate the uncertainty in the estimate. It is anticipated the prevalence will be approximately 10% based on data from Saidkasimova et al[34]. With 554 subjects the prevalence can be estimated with a 95% confidence interval with a 5% width e.g. expected to be from 7.5% to 12.5%. The sample size (N) was chosen to satisfy this 5% width, given the confidence interval is expected to be p +/- 1.96*sqrt(p*(1-p)/n), where p=0.1. To obtain this number of evaluable subjects we estimate approximately 600 subjects will have to be enrolled, this allows for a drop-out rate of just under 10%.

A sample size of 600 will also allow accurate estimates of the stages of SCR and maculopathy occurrence to be obtained. For example, the following CIs are based on a French retrospective cohort of 942 patients[11] :

	%	N	95%CI	width
Stage 0	30%	166	(23%-37%)	14%
Stage 1-2	40%	222	(34%-46%)	13%
Stage 3	20%	110	(13%-27%)	15%
Stage 4	5%	28	(8%-20%)	12%
Stage 5	5%	28	(8%-20%)	12%
	100%	554		

Other endpoints also include the calculation of the prevalence of each stage of SCR by age bracket and genotype. Sample size relevance in these circumstances can be illustrated by considering a hypothetical outcome. For example, under the null hypothesis there would be no association between prevalence and age, and given the hypothetical distributions of stage, and age below, it can be shown that the estimated correlation (Spearman Rank) has a greater than 3 SE difference (from zero) with 554 cases. This suggests powering is adequate for associations of this size, by the 'rule of three', for 85% power (Zbeta=1) and 5% sig level (Zalpha=1.96).

		Age Group							
									rate
N		*3.1%*	*7.4%*	*8.2%*	*14.0%*	*16.9%*	*21.7%*	***9.7%***	**overall**
	Stage/Age	**16-25**	**26-35**	**36-45**	**46-55**	**56-65**	**66+**		
	5	1	5	6	6	5	2		
SCR	4	2	5	5	8	6	3		
	3	23	28	28	20	12	4		
	1-2	46	56	55	39	23	8		
	0	24	42	40	27	19	6		
		96	*136*	*134*	*100*	*65*	*23*	554	

Spearman Rank -0.14 (95%CI:-0.23 to -0.06), p=0.001

5.1 Data Analysis plan

The primary analysis is to estimate the prevalence of SCD-related vision loss. In addition to the calculated value, a corresponding 95% confidence interval will be obtained to illustrate its associated uncertainty. We will also calculate prevalence of each stage of SCR and maculopathy by age bracket and genotype. The unit of analysis will be the eye with the worse SCR stage, or randomly chosen eye if both are of the same stage. The chi-square test for trend will be used if groups are ordinal. The Kruskal-Wallis test (categorical factors) or Spearman rank (ordinal factors) will be used when comparing SCR stage between groups, as above.

The association between SCD severity (as assessed by number of hospital admissions in past year and haemoglobin and haemoglobin F level within 3 months) with SCR stage and presence of sickle maculopathy will be examined using Spearman Rank or Pearson product correlation. Multivariable analysis such as logistic regression will be undertaken to assess the simultaneous effects of multiple factors on stage of SCR and presence of maculopathy. The correlation between NEI VFQ-25 global score and acceptability with best

corrected visual acuity, SCR stage and presence of maculopathy will also be assessed using Spearman rank correlation.

5.2 End of study

The end of trial will be 9 months after the last participant completes the study procedures. This will allow sufficient time for the completion of protocol procedures, data collection and data input and cleaning. The study team will notify the REC and Sponsor that the trial has ended within 90 days of the end of trial. Where the study has terminated early, the chief investigator will inform the REC within 15 days of the end of study. The Sponsor and CI will provide the REC with a summary of the study report within 12 months of the end of trial.

6. Regulatory reviews and compliance

6.1 Ethics approval

The project will meet the requirements and principles set by General Data Protection Regulations 2018 and the European Medicines Agency (GCP Guidelines).

No study activity will take place prior to all the approvals being in place from the relevant agencies, and permission to carry out the research has been received from the local R&I office.

The Investigators will obtain HRA and REC approval and receive local R&I capacity and capability at London North West University Healthcare NHS Trust and other participating sites. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 (incl. later revisions) and any other relevant ethical guidance. Any subsequent changes to the study conduct, design or management will be notified to original approving R&I Department and any other relevant regulatory authority via a substantial amendment.

6.2 Amendments

If there is any amendment to be made, this will not be instigated until it has been approved by the appropriate regulatory bodies, and confirmation has been received that their support is continued. Notice of any amendments to the protocol will be submitted to the HRA, REC and local R&I office, following discussion within the team. Amendments to any documents will be clearly identified by the version number and date.

The Chief Investigator will ensure that an annual report will be sent to the ethics committee within 30 days of the anniversary of permission being given. A final report will be submitted within one year of the end of the study, complete with the results and any publications. All correspondence with the REC will be retained and filed within the master site file.

6.3 Data handling and record keeping

6.3.1 Source data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained.

Table 1: Source data for Sickle Eye Project

Data	Source
Imaging	The source is the original imaging, usually as an electronic file. The clinical interpretation of the images will be summarised on an eCRF. This will be transferred to the Moorfields Reading Center electronically.
Demographic and clinical data	The original clinical notes are the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g. phone calls), must be documented in the source documents. Information will be recorded on electronic CRFs hosted on secure servers at Moorfield Eye Hospital (MEH) servers. Original paper CRFs, where used, will be kept at site.
Recruitment	The original record of consent is the ATHENA consent form. This should be kept in the Investigator site file
Drop Out	Where a participant expresses a wish to withdraw, the conversation must be recorded in the source data

Hospital source data will comprise of (but is not limited to) the hospital notes/electronic patient records and case report forms. Hospital source data is kept as part of the participants' medical notes generated and maintained at site.

6.3.2.Case Report Form (CRF)

An electronic case report form (eCRF) will be completed for each individual participant. Paper CRF forms will be provided to aid the collection of trial data if required and where the team is having difficulty completing the eCRF directly online. Sites should retain records of the paper CRFs, and these should be transcribed onto the eCRF. The original paper CRF, if used, should be filed in the Investigator Site File and archived along with the site study documents. Data reported on each form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs/ eCRFs will be trained by the sponsor site to adhere to standard formats. Protocol and GCP non-compliances should be added to a Protocol Deviation Log, held by the site, and reported to the Sponsor site - when the research site becomes aware of the incident and as per the GCP requirements. In all cases it remains the responsibility of the site's PI or their delegate to ensure that the CRF/eCRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the site's PI or their delegate on the paper CRF if used.

6.3.3 Electronic case report form and data management

The **Moorfields Grading Portal (MGP)** allows secure upload and sharing of de-identified (pseudonymised) imaging and clinical data contributed by recruitment and data sites to the Moorfields Reading Centre (www.readingcentre.org), to deliver Reading Centre services. MGP serve as the eCRF and image upload tool for this study. This database will be hosted on Moorfields Eye Hospital servers.

6.3.4 Data Ownership and Storage

The data uploaded to the MGP will be provided by GCP-trained NHS staff contributing to clinical trials and other Ophthalmology Research. The Study Sponsor is the Data Controller and data use is strictly specified by the Study Protocol and the permissions provided by Research Participants through offering Informed Consent. The data uploaded to the MGP does not contain any personal identifiable information. Information Governance and Data Protection is the primary responsibility of the Data Controller and research sites are responsible for their own data protection under the requirements of GDPR 2018 and GCP.
Logical Information location: Moorfields Virtual Private Cloud hosted by Amazon Web Services (AWS) and secure Reading Centre servers.

Physical information location: AWS eu-west 2 (London) and Moorfields Ophthalmic Reading Centre on-premises servers.

6.3.5 Data security

All data will be handled in accordance with the General Data Protection Regulations (GDPR) and Data Protection Act 2018. The data uploaded to the MGP are stored in secure, monitored servers. All MEH clinical trial databases are part of the MEH disaster recovery strategy and have a 5-day Recovery Time Objective. Where data is transferred electronically to MEH this will be in accordance with the GDPR and UK Data Protection Act 2018, as well as MEH Information Security Policy and Trust Information Governance Policy. There will be a documented record of any data transfer regarding the trial management. Access to trial data stored in MEH servers will be granted to authorised representatives from the Sponsor, host institution and other relevant bodies to permit trial-related monitoring, audits and inspections in line with participant consent.

6.3.6 Quality control, quality assurance and Monitoring

The study may be subject to inspection and audit by the R&I Department of London North West University Healthcare NHS Trust under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care.

Monitoring

The study project manager will be in regular contact with the site research teams to check on progress and address any queries that they may have. The project manager will check CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent queries requesting missing data or clarification of inconsistencies or discrepancies

6.3.7. Patient safety and reporting

The safety profile for this trial population is well characterised, established and all tests are currently carried out within the NHS as part of standard care. As such the reporting of non-serious and serious adverse events are not required for this study.. If any SAEs do occur whilst the patient is at their assessment, the PI or delegate must record this in the patient's medical notes. The PI or delegate does not need to report any SAEs to the trial office.

6.3.8 Archiving

It is the responsibility of the PI or a delegated person at each site to ensure all essential trial documentation and source documents (e.g. signed ICFs, Investigator Site Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for a minimum of 10 years. As Sponsor, LNWH will archive the Trial Master File for a minimum of 10 years. Archiving will be authorised by LNWH (Sponsor) following submission of the end of trial summary report. To enable evaluations and/or audits from LNWH (Sponsor), the investigator agrees to keep records, including the identity of all participants (sufficient information to link records, e.g., CRFs and hospital

records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of tests performed and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer. If the investigator becomes unable for any reason to continue to retain trial records for the required period (e.g., retirement, relocation), LNWH (Sponsor) should be prospectively notified. The trial records must be transferred to a designee acceptable to LNWH, such as another investigator, another institution, or to an independent third party arranged by MEH. Investigator records must be kept for a minimum of 10 years after completion or discontinuation of the trial or for longer if required by applicable local regulations. The investigator must obtain LNWH written permission before disposing of any records, even if retention requirements have been met. The Sponsor will be responsible for archiving the Trial Master File and databases, in line with the Sponsor SOP for archiving non-regulated studies. The sites will be responsible for archiving the site file in line with their local SOP for storage. Destruction of essential documents will require authorisation from the Sponsor

6.4 Indemnity

London North West University Healthcare NHS Trust and all participating NHS sites hold negligent harm and non-negligent harm insurance policies which apply to this study.

6.5 Sponsor

London North West University Healthcare NHS Trust will act as the sponsor for this study.

6.6 Funding

This work has been funded by NIHR RFPB Grant (Ref: NIHR204961) and an unrestricted grant from Roche Pharmaceuticals. The views expressed are those of the authors and not necessarily those of the NIHR, the department of health and social care or Roche Pharmaceuticals.

6.7 DATA PROTECTION AND PATIENT CONFIDENTIALITY

All investigators and study staff will comply with the General data protection Regulations 2018.

All research using patient data must follow UK laws and rules.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the trial through assignment of a unique patient identification number. All patient medical information associated with the trial is confidential and may be used and disclosed only as permitted by the Informed Consent Form signed by the patient.

LNWH Data Protection Officer:

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent amendments). The data collected will be processed by London North West University Healthcare NHS Trust. London North West University Healthcare NHS Trust are the data controllers. Where appropriate our Data Protection Officer Nuala Brodie-Buchan will be consulted.

Participants will always be identified using their unique trial identification number in any correspondence between the lead site (LNWH) and local centres.

The Investigator must maintain documents not for submission to LNWH (eg participant identification logs) in strict confidence. In the case of specific issues and/or queries resulting from audits/monitoring, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected. Representatives of the study team and Sponsor may be required to have access to participants' notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times. The participants will provide consent for reading centre experts to be sent their tests linked by their unique trial ID number.

Data Protection

Data controller: London North West University Healthcare NHS Trust

Data processor: Moorfields Ophthalmic Reading Centre & Clinical AI Lab, Moorfields Eye Hospital NHS Foundation Trust

The Moorfields Reading Centre has implemented automated daily backup for the entire AWS VPC database. These backups are encrypted (AES 256) and managed by AWS RDS service. Standard daily backups are retained for 30 days and allow for both individual file and full instance restores. The retention period can be customized with a minimum of 7 days.

Long-term storage of data takes place in secure, on-premises servers at the Moorfields Reading Centre.

The database, itself, is encrypted using AES256 at rest. This includes all underlying storage for DB instances, its automated backups, read replicas, and snapshots. Data in transit within the VPC is encrypted. Data storage is encrypted at AES256 when at rest and in transit. All data is only accessible within the VPC.

Identifiable patient data will not be accessed outside the direct care/site-level research team at any stage of the project. All images will be pseudonymised and no personal data will be included on the images. No personal identifiers will be sent to the Reading Centre and a unique identification code will be assigned to each image. This log of subject codes will be kept at each recruitment site but not shared with the Reading Centre.

The eCRF will not bear the subject's name or other personal identifiable data. A Study ID will be used for identification on the eCRFs. A separate log file which links the study ID and the patient's details, screening log and recruitment information will be kept on a protected NHS computer at recruitment sites.

The Moorfields Reading Centre complies fully with the Data Protection Legislation (including the "General Data Protection Regulation" or "GDPR") and the Data Protection Act 2018.

6.8 Post-study care

All participants will continue to receive standard medical care as provided by the NHS following participation in the clinical study. There are no interventions that participants will be prevented from accessing after their participation in the study has been completed.

7. Study Management

The study management group (SMG) will take responsibility for the day-to-day management of the study and consists of the Chief Investigator, co-applicants, statisticians and project manager. The role of this group is to monitor all aspects of the conduct and progress of the study and ensure that the protocol is adhered to by all participating sites and take appropriate action to safeguard participants and the quality of the study itself. They will meet at least once a month.

The co-investigator group consists of all members on the grant and will review, troubleshoot and plan strategically.

8. Publication and dissemination Policy

Results of this trial will be submitted for publication in a high-impact peer reviewed journal. The manuscript will be prepared by the CI and authorship will be determined by the Sickle Eye Project publication policy. Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the TMG prior to wider circulation. Manuscripts must be submitted to the TMG in a timely fashion and well in advance of being submitted for publication to allow time for review and resolution of any outstanding issues. The study question is important and has the potential to change clinical practice. This view has been validated by the health professionals and extensive patient engagement work across the country. Methods to ensure rapid clinical impact once the results are available include: submitting the study findings to the Scientific committee in charge of generating guidelines by the Royal College of Ophthalmologists, production of lay information for dissemination via patient charities and organisations and dissemination at ophthalmology and haematology national and international conferences. In addition to this, in consultation with the investigators and appropriate journal, a press release will be issued to media upon publication of the results.

9. Authorship

All researchers who have been involved in the project will have authorship of the paper and responsibility for the review and dissemination of the results. Determination of authorship will be determined by the Sickle Eye Project publication policy

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