National Haemoglobinopathy Registry

Annual Report 2021/2022

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Foreword

It gives me great pleasure to see the annual report of the National Haemoglobinopathy Register for 2021-2022. The NHR continues to serve as an invaluable resource for healthcare professionals, health commissioners and others to ensure that high quality of care is provided to patients with haemoglobin disorders and rare anaemias.

The NHR has undergone significant changes recently. It now reflects the current commissioning structures in NHS England, allowing seamless data collection for the Specialised Services Quality Dashboard under a single NHS number- based patient record. Additionally, new, relevant fields have been included for specific clinical metrics associated with new drugs available under managed access programmes, such as for crizanlizumab. The integration of the newborn outcomes programme within the NHR has been transformative for screening laboratories and community counsellors, with electronic failsafe arrangements via the NHR. Integration of transcranial doppler readings and relevant quality metrics within the NHR has also been a significant milestone for the registry. As before, clear policies outline data requests for research.

The 2021-22 report reflects the hard work that has gone into data entry on the NHR and the tireless effort by the Chair and the steering group in providing us with this overview. There is no doubt that there is further room for improvement in the quality of data in the NHR, as is so clearly outlined in the report. Nonetheless, it is heartening to see that data entry and engagement with the NHR is improving with every passing year, and that the NHR is showing great agility in its capacity to reflect change in clinical practice and to ensure high quality of care for our patients.

The NHR is unique in its scope and quality. I hope current and future clinicians, health commissioners, researchers, industry partners and patients continue to engage with this invaluable resource.

Subarna Chakravorty

King's College Hospital, London

National Specialty Advisor, Haemoglobinopathies

Chapter 1: Introduction

The NHR has been in existence since 2008, initially as an annual record for ensuring that centres could be identified where patients were treated. The original NHR was a database that required consent for patients to be enrolled onto the registry and an annual review data set was completed for patients who were enrolled. Over time as services developed into more formal designations as specialist centres and subsequently the new model of service delivery was developed with the National Haemoglobinopathy Panel (NHP), the Haemoglobinopathy Coordinating Centres (HCC) and their Specialist Haemoglobinopathy Teams (SHT), it was recognised that the NHR needed to transform to meet the needs of the new services.

The NHR was redesigned to become a single patient record based on the NHS number and although an annual review data set is still collected, the NHR can be accessed multiple times to update patients' clinical records as interventions and admissions occur. The record is now a comprehensive record of a patient's treatment and provides data from multiple centres in a single electronic record. The registry collects data to support the Specialised Services Quality Dashboard and all key dashboard data sets for SHT level and most for HCC level are collected on the NHR. This has significantly reduced the burden of data collection on the NHR.

It is important to remember that a registry is only as good as the quality of the data entered on to it and although absolute patient numbers are now far more accurate, the diagnosis, treatments and interventions remain with considerable data gaps. We have a chapter addressing data quality issues and each chapter also includes concerns about completeness of data.

The NHR is an incredibly valuable resource on the state of health of our patients. It can be used to identify potential problems developing as patients age and plan for resources that will be needed to care for them. In order to do this, we need to ensure that we have complete records as far as possible for patients.

I want to thank on behalf of the steering committee all the clinical teams looking after patients with haemoglobinopathies and rare anaemias for their hard work and commitment in ensuring our data is as complete and accurate as possible.

Farrukh Shah

Chair NHR

Chapter 2: PPV Contributions

Author: Funmi Dasaolu

The NHR has integrated in its Steering Committee four Patient and Public Voice (PPV) representatives- two individuals with lived experience of Sickle Cell Disorder, one with lived experience of Thalassaemia, and one representative from a Diamond Blackfan Anaemia patient support group.

Being a patient and public voice representative on the NHR has been an exciting and insightful experience. The fact such roles exist is a testament to how far we as a healthcare community have come. Such roles value the unique contribution and acknowledge the wealth of expertise individuals with lived experience possess. They serve as an opportunity to influence and enhance care and service delivery. Patients are no longer just seen as patients, but there is a great emphasis on partnership and collaboration with individuals who utilise these services.

Moreover, input from PPVs ensure projects and workstreams remain patient focused. Patient representation enables the patient voice to be championed and places patients at the centre of all work, taking into consideration what matters to individuals. Adopting such perspectives enables services to be designed to meet specific needs and address gaps in service provision. As PPVs, our role is to ensure that patients' views are central when difficult discussions are carried out around how and what data is being collected. This is all the more important when considering how data is proposed to be used by different stakeholders. PPVs ensure that the views of patients are not considered as an aside, but rather as a crucial consideration in the balance of decision-making.

Working alongside other PPVs with different conditions has been particularly beneficial to enable a diversity of views to be considered and enables a broader representation of the patient voice. Such views are actively sought and encouraged during meetings. Having a named and dedicated professional overseeing the engagement and work of PPVs has been particularly valuable, especially when there have been concerns or questions regarding specific streams of work.

Given the complexity of work undertaken on the NHR, it can sometimes be difficult to follow discussions and stay abreast of changes and as such we are proposing some changes going forwards. In addition, regular PPV check-ins once every quarter will give us an opportunity to touch base before main meetings and better support the co-ordination of our work. One key aim at present is to revamp and recruit to the vacant PPV posts to support with distribution of workload and broader representation across the conditions included in the NHR. As a collective group of individuals, we are also actively seeking to engage the wider patient community in the work undertaken by the NHR, and are exploring development of a patient app.

In conclusion, the PPV voice being integrated into the NHR is definitely a positive step forward in ensuring that the NHR keeps patients' best interests at heart.

Chapter 3: Thalassemia Report for NHR

Authors: Nandini Sadasivam & Farrukh Shah

This is the first report on data held within the NHR on patients with thalassaemia syndromes which now includes more subcategories of thalassaemia including HbH disease.

As of 31.3.2022 there were 2281 patients registered on the NHR with a diagnosis of thalassemia. Male and female patient numbers were almost equal with 51% female and 48% male respectively. Most of the patients are transfusion dependant beta thalassaemia major (1175) followed by patients with HbH disease. The total number of patients dependant on regular blood transfusion support are 1253 (alpha thalassaemia major, beta thalassaemia major and HbE beta thalassaemia transfusion dependant), although other thalassaemia patients may need transfusion support occasionally). The Alpha thalassaemia major patients have been recorded on the NHR for the first time. Other thalassaemia category of patients includes 97 patients where a diagnosis is not reported. The remaining patients are generally compound heterozygous beta globin variants such as HbC beta thalassaemia or Hb D beta thalassaemia.

Diagnosis	Registered patients
Alpha thalassaemia Major	4
Beta thalassaemia intermedia (excluding HbE thalassaemia)	370
Beta thalassaemia major (excluding HbE Beta thalassaemia)	1175
E Beta thalassaemia (not transfusion dependant)	52
E beta thalassaemia (transfusion dependant)	74
HbH: variant	1
HbH Disease	429
HbH: constant spring	3
Other Thalassaemia	173
Grand Total	**2281**

Table 1- Thalassaemia Diagnoses and Registered Patients

The majority of patients with thalassaemia syndromes in England are of South Asian ancestry at 50.5%. The largest population of patients are of Pakistani heritage, followed by Indian and Bangladesh.

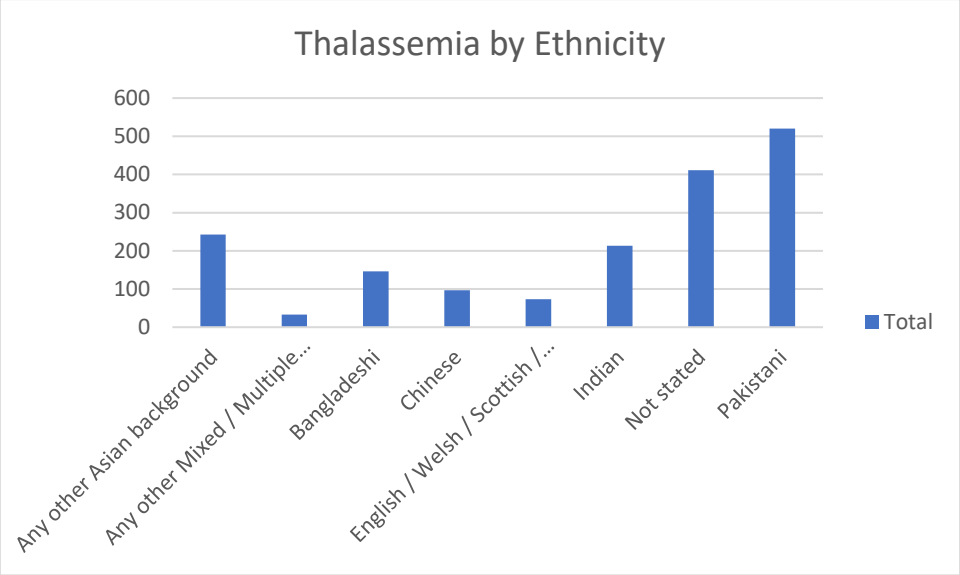


Figure 1 - Thalassaemia by Ethnicity

Ethnicity	Number
African	38
Any other Asian background	243
Any other Black / African / Caribbean background	12
Any other ethnic group	224
Any other Mixed / Multiple ethnic background	33
Any other White background	212
Arab	16
Bangladeshi	146
Caribbean	17
Chinese	97
English / Welsh / Scottish / Northern Irish / British	73
Indian	213
Irish	1
Not stated	411
Pakistani	520
White and Asian	14
White and Black African	2
White and Black Caribbean	9
Grand Total	**2281**

Table 2 - Thalassaemia Patients by Ethnicity Detail

The thalassaemia population remains a young population with the majority of patients below the age of 40 years. Older patients in their 70s and 80s will be those with HbH disease or other compound heterozygous thalassaemia syndromes.

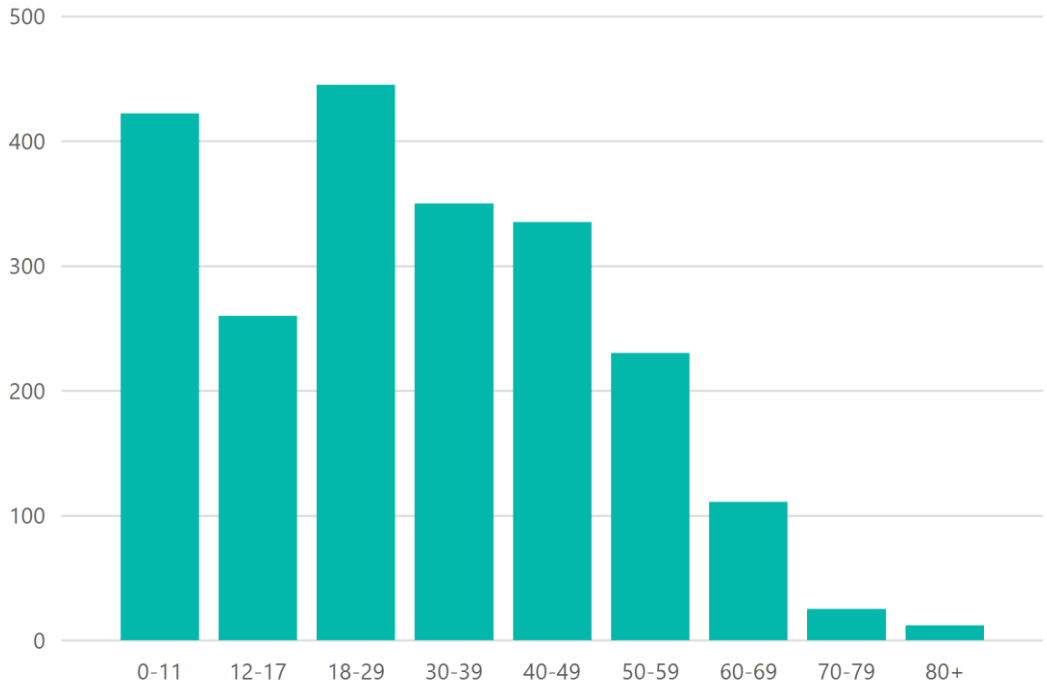


Figure 2 - Thalassaemia Patients by Age Group

Thalassaemia Prevalence across England

The data on the NHR is not accurate for SHTs as all local hospitals have not been mapped to SHTs at the time of the report. The top 10 hospitals for patients with thalassaemia show that the largest population of patients continues be based in cities such as London, Birmingham and Manchester. Recent changes in 2023 to the NHR will allow more accurate data based on SHT to be available for the next annual report.

SHT	Patients
Birmingham Women's and Children's Hospital NHS FT and Sandwell and West Birmingham Hospitals NHS Trust	304
University College London Hospitals NHS Foundation Trust	290
Whittington Health NHS Trust	221
Barts Health NHS Trust	190
Manchester University NHS Foundation Trust	140
Leeds Teaching Hospitals NHS Trust	118
Imperial College Healthcare NHS Trust	91
University Hospitals of Leicester NHS Trust	66
Oxford University Hospitals NHS Foundation Trust	64
North Middlesex University Hospital NHS Trust	62

Table 3 - Thalassaemia Patients by SHT

Annual Review Completion

Annual review fields were completed for the majority of patients although 1040 patients had null entry for both year of review and completed field suggesting the annual review was not undertaken in that year.

Annual Review Complete	Patient numbers
Yes	1230
NULL	1040
No	11

Table 4 - Patient Numbers Completing Annual Review

There were 23 episodes where pregnancy had happened and 19 pregnancies were in female patients and 4 in male patients, however in 225 patients the answer to the question whether the patient had reproduced this year was recorded as unknown status with an even distribution between males and females. It is therefore likely that there were more pregnancies than is recorded on the NHR. This is an important aspect reflecting the ability of patients with good clinical care to have families of their own.

Diagnosis	Female	Male	Total
Beta thalassaemia intermedia (excluding HbE thalassaemia)	5	1	6
Beta thalassaemia major (excluding HbE Beta thalassaemia)	6	2	8
E Beta thalassaemia (not transfusion dependant)	1		1
HbH Disease	7	1	8
Grand Total	**19**	**4**	**23**

Table 5 - Thalassaemia Gender Breakdown

Many centres have reported a lack of psychological support and access to treatment for patients and the annual review addresses the service provision aspects of this. However, there are limitations in data gathering for this in the NHR annual review**.**

79 patients did require and receive psychology support but there were 1078 reports of null and 179 unknown implying the data was not available. The other challenge with this field was the difference between required and received was not clear as the numbers are identical for both questions. One of the goals for future reviews is to ensure this field is correctly responded to so the gap between the need and the ability to provide is clear for colleagues undertaking the annual review.

A total of 85 patients were recorded as deceased on the annual review however for most of these patients the year of annual review was not recorded and likely reflects updating of historical records for patients as they moved into the new platform. During this reporting year 2021/22, 6 deaths were recorded overall, 4 in HbH patients and 2 were transfusion dependant thalassaemia.

Transfusion

Transfusion data is incomplete on the NHR as highlighted by 1252 transfusion dependant patients registered (alpha thalassaemia major, beta thalassaemia major and HbE beta thalassaemia transfusion dependant) but only 646 patients having regular transfusions recorded. Some of these patients are receiving automated exchange and manual exchange transfusions. Collectively assessing the data for only 585 patients on simple top up regimes reported in the NHR excluding manual and automated exchange transfusion patients showed that 9109 transfusion episodes were needed to deliver 20783 units of red cells to patients.

Patients had an array of red cell antibodies reported on the NHR despite Rh and Kell group matching which is widely undertaken in the UK. The commonest antibodies identified were Anti E and Anti-c.

Description	Count of Antibody Specificity
Anti-A1	1
Anti-Bgb	2
Anti-c	10
Anti-Cw	8
Anti-D	9
Anti-E	26
Anti-f [ce]	1
Anti-Fyb	1
Anti-Jk3	1
Anti-Jka	4
Anti-Jkb	3
Anti-K	16
Anti-Kpa	14
Anti-Lea	1
Anti-Leb	2
Anti-Lua	8
Anti-M	3
Anti-S	2
Pan-reactive antibody	3
Specificity Not Determined	28
Unassigned Antibody Identity	1
Grand Total	**144**

Table 6 - Count of Antibody Specificity

Management of Iron Overload

Chelation therapy was recorded for 702 patients, and they were on a range of treatment regimes.

423 were taking Deferasirox monotherapy, 115 on desferrioxamine monotherapy,69 on deferiprone monotherapy and 95 patients were on combination regimes. This data is under reported as the number of transfusion dependant patients is considerably higher, and it is also expected that non transfusion dependant patients will be on iron chelation regimes intermittently to manage iron overload.

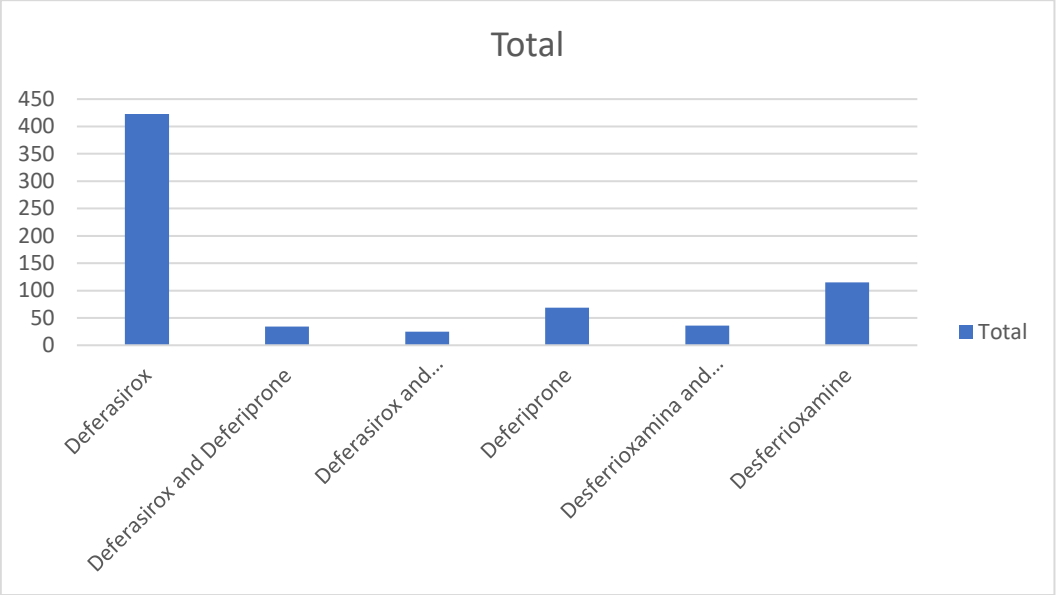


Figure 3 - MRI assessments for iron overload

Cardiac Assessments

327 patients underwent MRI assessments for iron overload during 2021/22. The majority of patients had no cardiac iron overload and the average cardiac T2* was 33.6 ms with 18 patients with a cardiac T2* less than 10 ms (average 7.4ms). Ejection fraction if reported by MRI were in the normal range. The ejection fraction was lower in patients where an ECHO was undertaken suggesting this is more likely to be undertaken in acute settings where patients present with cardiac symptoms.

Liver Iron Assessments

416 patients had a liver iron assessment undertaken during the annual review year 2021/22. Of these, 140 were a liver T2* assessment and 276 were Ferriscan liver iron assessment. The average liver iron by Ferriscan was 6.9 mg/g/dw with those with a liver iron quantification by liver T2* the average T2* was 8.7ms.

These liver iron values show that for the vast majority of patients the liver iron is well controlled.

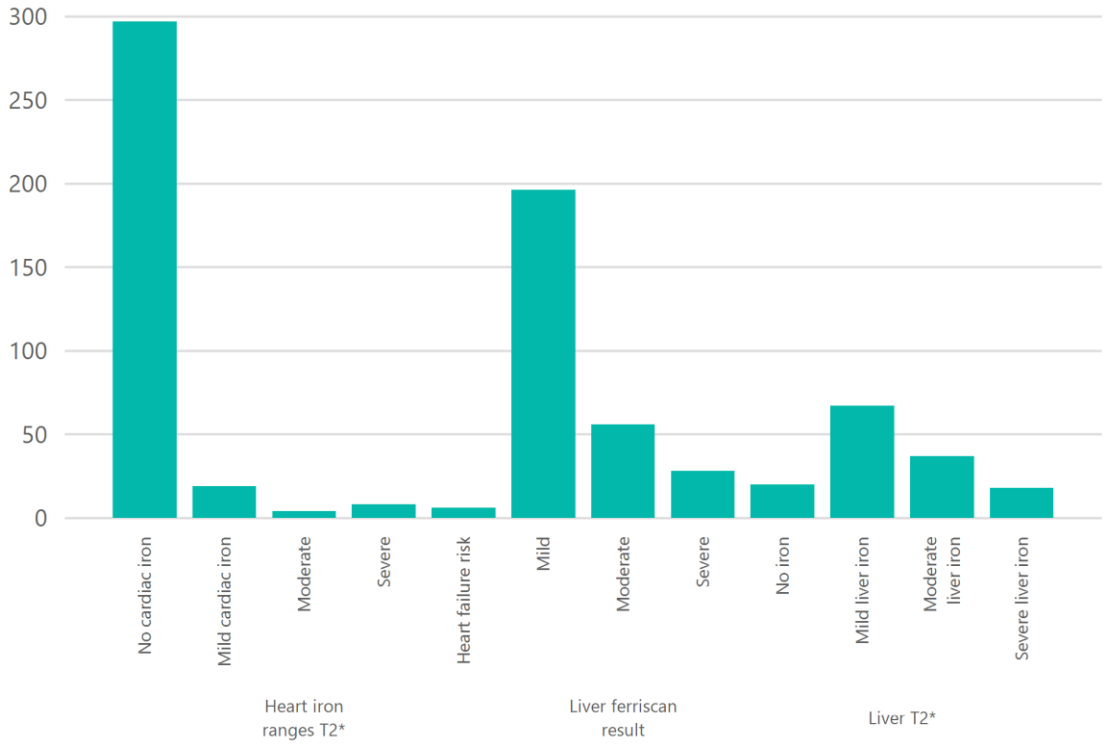


Figure 4 - Liver Iron Numbers

There is likely to be under reporting of MRI data on the NHR in the context of the total number of patients with transfusion dependence and the guideline recommendations that liver iron should be assessed annually and cardiac T2* 1-2 yearly depending on the severity of the cardiac iron burden.

Bone Density Imaging

A total of 40 patients had bone density scans reported during the 2021/22 reporting period. 12 had normal bone density with 14 having osteopenia and 14 having osteoporosis in the scans.

Comorbidities

In total 1245 comorbidities have been recorded with 11 serious adverse events at the time of the data collection.

Comorbidity	Number
Bacterial infection	9
Cardiorespiratory	70
Endocrine	257
Genitourinary	24
Haematological	0
Hepatobiliary	14
Neurological disorders	16
Obstetric/ gynaecological	1
Orthopaedic	194
Other	555
Serious Adverse Events	11
Viral infection	94
Grand Total	**1245**

Table 7 - Comorbidities

These events ranged from complications occurring many years prior such as diabetes and endocrine complications. It is likely that as the new platform has gained functionality clinical teams have added historical complications as part of base line documentation. This is likely to continue for a few years as patients' records are brought up to date.

During the financial year 2021/22 a total of 86 comorbidities were recorded. This included 4 serious adverse events all of which were deaths between 1/4/2021 and 1/4/2022. There were 30 viral infections with 1 report each of hepatitis B and other viral illness and 28 of COVID-19 infections. 26 complications were recorded as other not listed above. 13 patients had orthopaedic complications 8 of which were either osteoporosis/osteopenia with the remainder fractures. The remaining 16 complications were a mixed cohort of endocrine, bacterial infection, liver disease and thromboembolic problems.

Data on comorbidities is significantly under reported both historically and currently. COVID-19 data entry was good as clinical teams were contributing to a COVID-19 study for patient outcomes and many sites ensured that the data was entered into the NHR.

Comorbidity	Number in financial year 2021/22	Sub type
Bacterial infection	2	Not specified
Cardiorespiratory	3	2 VTE and 1 asthma
Endocrine	3	2 NIDDM, 1 hypothyroidism
Genitourinary	1	
Haematological	0	
Hepatobiliary	3	2 fatty liver, 1 fibrosis
Neurological disorders	1	seizure
Obstetric/ gynaecological	0	
Orthopaedic	13	5 fractures,
Other	26	
Serious Adverse Events	4	deaths
Viral infection	30	28 COVID-19 infection
Grand total	**86**	

Table 8 - Comorbidities by Subtype

Data Challenges

The data entered on the NHR for thalassaemia is increasing in amount but remains limited. It is clear that many centres are not able to enter a comprehensive set of data for their patients especially results of imaging and type of chelation regime the patient is taking. Chelation regimes in particular change over time and this is likely to only be entered accurately in centres with good data manager support.

One of the most critical aspects of data accuracy is ensuring the correct diagnosis is assigned to the patient. Part of the future work will include communication with sites where the diagnosis appears to be inaccurate to ensure these errors are corrected.

Chapter 4: Sickle Cell Disease

Author: Sanne Lugthart

Patient Cohort Changes 2021 - 2022

From April 2021 until March 2022 financial year there were 15,481 patients with Sickle Cell Disease registered on the NHR. During this year, 27 emigrated from England, 514 patients deceased and 200 babies with Sickle Cell Disease (SCD) disease where born. The analysis was performed on 14,940 patients.

Haemoglobinopathy Coordinating Centres and Specialist Haemoglobinopathy Teams

The numbers of patients registered per HCC are shown in Figure 5 and Table 9. Table 10 includes the patient numbers per SHT. There are 1,520 patients in the registry that are not registered under a HCC or SHT.

Patient characteristics

The age categories from the remaining 14,940 patients are shown in Figure 6. Most patients (58%) are between the age of 0 to 29 years. Sex distribution is nearly equal; 7,927 females (53%), 7008 males (47%) and 5 patients are unclassified. The majority of sickle cell disease patients were homozygous sickle cell disease (HbSS) (64%), followed by HbSC (28%) as shown in Figure 7. Most patients fall under the Black / African / Caribbean / Black British ethnicity group (82%) (Figure 8).

Treatment types

There are 19,090 treatment inputs made into the NHR. Unfortunately, the search options within the treatment types are slightly limited, as each treatment entry was a free text box. This means that per patient medication has been manually entered by a health care professional into the NHR. There are 3,012 patients (20%) registered who are on Hydroxycarbamide and 2,816 (18%) are still taking this in 2021-2022. Of the 30 patients taking Voxelotor in February 2023, 16 patients have started Voxelotor during 2021-2022 financial year. From March 2023, 113 patients are registered to be on Crizanlizumab and 40 of those have started therapy in 2021-2022.

Please note that all medication input per patient is not fully reliable as all medication is included in one free text box.

Transfusion

There are 979 patient receiving transfusions; 740 regular red-cell exchanges, 22 manual exchanges and 217 patients receive top-up transfusions.

Comorbidities

The list of comorbidities is long and in some cases no entry date is given. Between 2021 and 2022, 1,241 comorbidities were registered into the NHR. The majority (n=401) were ‘simple veno-occlusive crises’, 248 patients contracted a COVID-19 infection, 47 were registered as deceased. A selection of comorbidities is shown in Table 11.

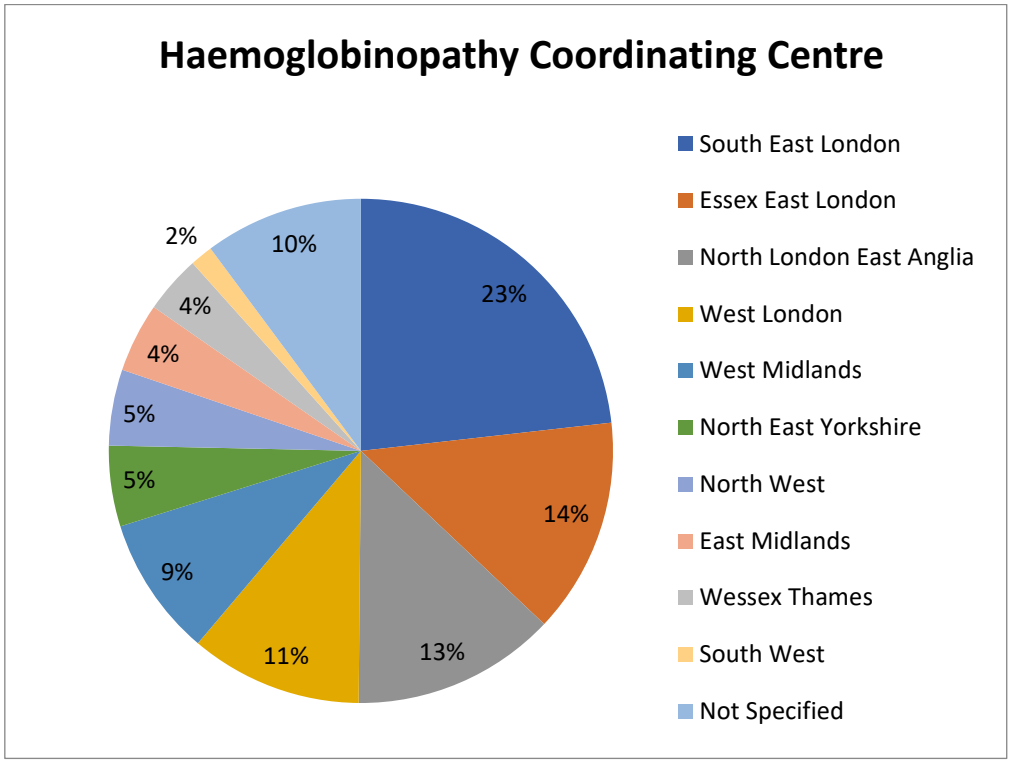
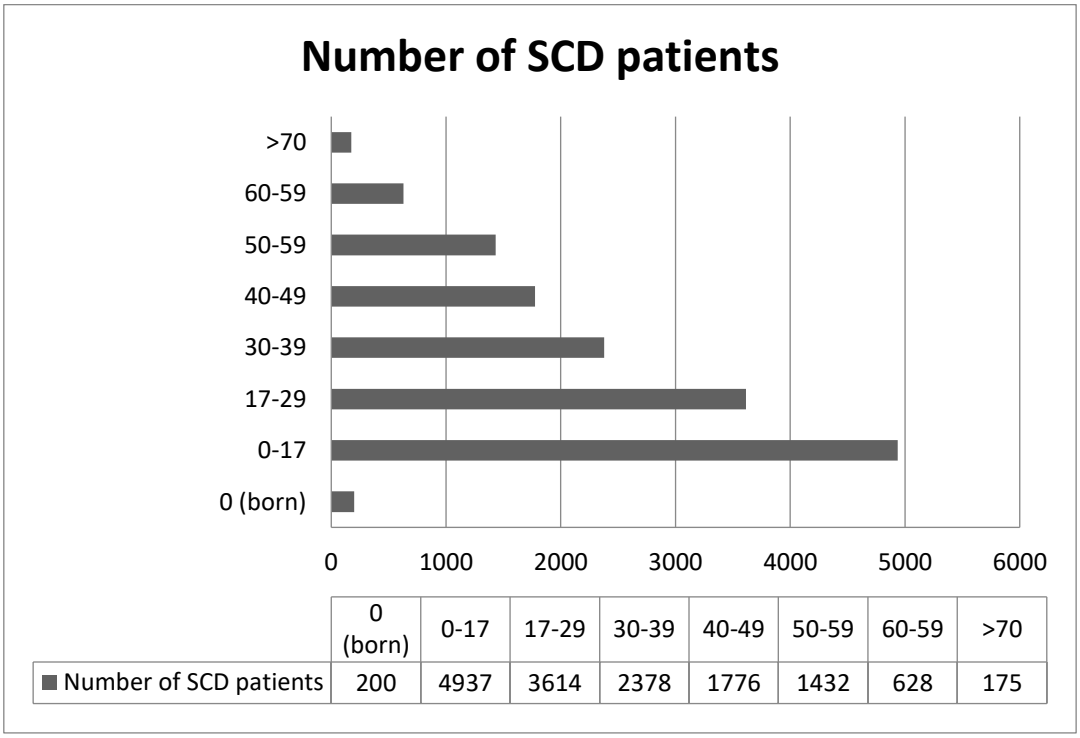


Figure 5 - Distribution of patient numbers across 10 HCCs in England.

Over 50% of patients with SCD are under a centre in the London area, the remaining HCCs oversee the care of SCD patients elsewhere.



	0 (born)	0-17	17-29	30-39	40-49	50-59	60-59	>70
Number of SCD patients	200	4937	3614	2378	1776	1432	628	175

Figure 6 - Age distribution Sickle Cell Disease patients actively registered in NHR during 2021 and 2022.

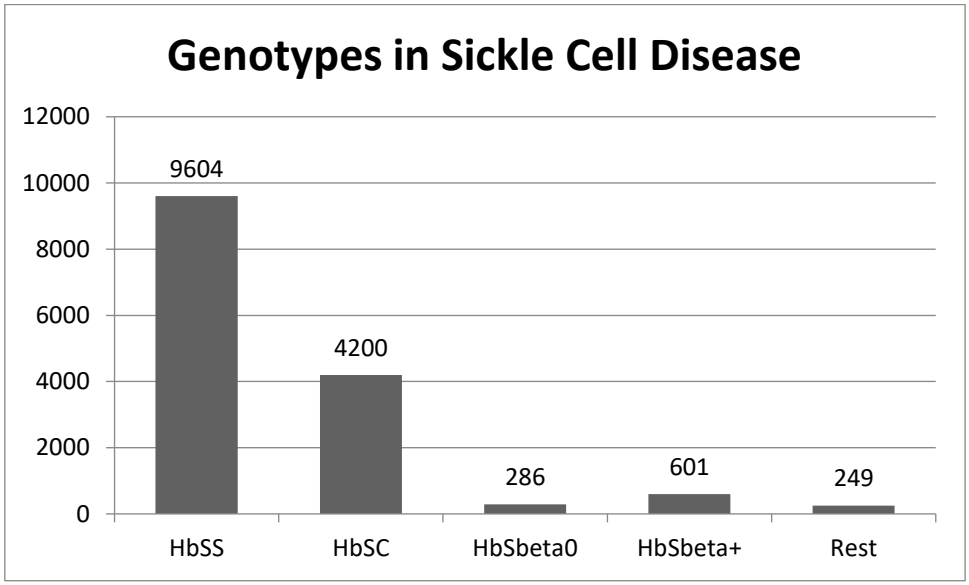


Figure 7 - SCD genotype distribution registered in NHR between 2021 and 2022.

The less common genotypes are classified in the Rest group such as HbS D Punjab and HbS Lepore.

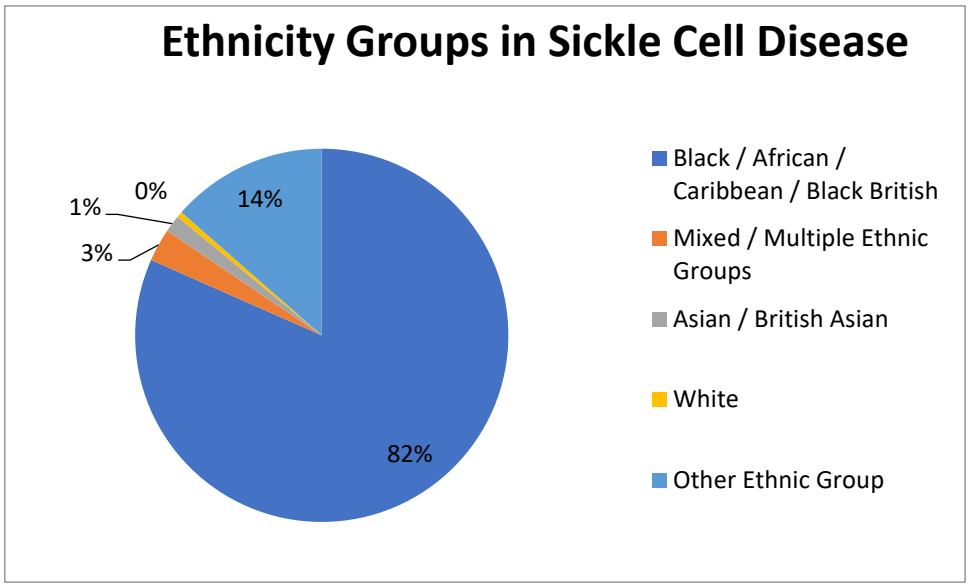


Figure 8 - Ethnicity group distribution in Sickle Cell Disease.

Haemoglobinopathy Coordinating Centre	n=
South East London	3468
Essex East London	2067
North London East Anglia	1956
West London	1651
West Midlands	1340
North East Yorkshire	773
North West	729
East Midlands	664
Wessex Thames	554
South West	218
Not Specified	**1520**

Table 9 - Allocation of patients per Haemoglobinopathy Coordinating Centre (HCC) for 2021-2022.

There are 10 Sickle HCCs in England. A group of patients has not yet been allocated an HCC and are classified as 'not specified'.

There are 24 SHTs in England but some centres split adult from paediatrics on the NHR and hence data for 27 centres is presented in the table below. A group of patients has not yet been allocated an SHT and are classified as 'not specified'.

SHT	n=
Barts Health NHS Trust	1691
Birmingham Women's and Children's Hospital NHS FT and Sandwell and West Birmingham Hospitals NHS Trust	1321
King's College Hospital NHS Foundation Trust	1302
Guy's and St Thomas' NHS Foundation Trust	1127
Lewisham and Greenwich NHS Trust	713
North Middlesex University Hospital NHS Trust	711
University College London Hospitals NHS Foundation Trust	656
Manchester University NHS Foundation Trust	622
St Georges Healthcare NHS Foundation Trust	601
Imperial College Healthcare NHS Trust	538
London Northwest University Healthcare NHS Trust	500
Oxford University Hospitals NHS Foundation Trust	448
Leeds Teaching Hospitals NHS Trust	415
Whittington Health NHS Trust	396
University Hospitals of Leicester NHS Trust	388
Homerton Healthcare NHS Foundation Trust	360
Croydon Health Services NHS Trust	304
Nottingham University Hospitals NHS Trust	276
University Hospitals Bristol & Weston NHS Foundation Trust	217
The Newcastle Upon Tyne Hospitals NHS Foundation Trust	173
Addenbrooke's Hospital Cambridge (Cambridge University Hospitals NHS Foundation Trust)	170
Royal Liverpool and Broadgreen University Hospitals NHS Trust and Alder Hey Children's NHS Foundation Trust	157
Sheffield Teaching Hospitals NHS Foundation Trust	120
University Hospital Southampton NHS Foundation Trust	112
Sheffield Children's NHS Foundation Trust	71
University Hospital of Wales (Cardiff and Vale University Health Board)	58
Sandwell Hospital - Paediatrics	16
Not Specified	1477

Table 10 - Allocation of patients per Specialist Haemoglobinopathy Team (SHT) for 2021-2022

Comorbidities registered in 2021-2022	n=
Acute chest syndrome	90
Simple VOC	411
COVID-19 infection	248
Avascular necrosis	22
Splenic sequestration	12
Stroke (ischemic/haemorrhagic)	12
Priapism	26
Retinopathy (any grades)	27
Delayed Haemolytic Transfusion Reaction	9
Deceased	47
Complication not listed	181
Deep venous thrombosis	7
Pulmonary embolus	7

Table 11 - Comorbidities registered in NHR between April 2021 until March 2022 for SCD patients.

This list only includes a selection of the most common and related co-morbidities.

Chapter 5: Transcranial Doppler (TCD) Screening in Sickle Cell Disease Quality Assurance Programme

Contributors: Professor Baba Inusa, Soundrie Padayachee

Background

Variations in delivery of TCD screening of children with sickle cell disease training were addressed as part of the HCC Service Specification. The NHP together with the NHR have been responsible for developing and overseeing the development of the TCD quality assurance programme. At present the following progress has been made.

Progress

- Regional TCD leads (either a vascular scientist or a clinician) have been appointed to look after TCD practice in each HCC, ensuring that each HCC is adequately staffed for TCD screening and QA standards are met.
- The current provision of TCD screening across the Network has been established.
- TCD Standard Operating Procedures has been reviewed across the Network and a standardised approach has been agreed by all HCC TCD leads
- Quality Assurance: the first stage QA has been performed across the Network to establish:
  a. TCD Instrumentation
  b. SOP and HCC STOP classification
- Quality Assurance for the following is in progress:
  a. TCD Practitioners scanning portfolio
  b. Annual review of TCD skills and practitioner scan portfolio
  c. Competent practitioners to be added to the National register

- TCD QA Reports will be generated from NHR data from 2022 to describe:
  a. Annual review of practitioners scan numbers and TCD skills
  b. Annual review of STOP distribution
  c. Reviews of TCD velocity optimization
  d. Time averaged maximum mean velocity distribution (using normal MCA velocities) within each HCC
- Criteria for QA evaluation will be applied to these reports to identify any indications of poor scanning, incorrect STOP classification or inappropriate surveillance intervals and clinical pathway.

TCD Dashboard

Data fields included:

- Middle cerebral artery velocity and depth
- Anterior cerebral artery velocity and depth
- Terminal internal carotid artery velocity and depth
- Posterior cerebral artery velocity and depth
- STOP classification
- Scan quality
- Practitioner ID
- SHT and HCC

To 31st March 2022, TCD data from over 2000 scans has been entered on the registry. Some of the SHTs show low scan numbers which are being reviewed. It is expected these were recorded in hospital records and not transferred to the NHR. It is expected that TCDs will be formally recorded by all sites for patients who meet eligibility criteria on the NHR for 2022/23.

National Haemoglobinopathy Registry: TCD category standardisation and terminology

The TCD dashboard on the NHR has standardised categories and terminology.

NORMAL - All TAMMV less than 170 cm/sec.

CONDITIONAL - A TAMMV of at least 170 cm/sec but less than 200 cm/sec in one or more of the three designated vessels.

ABNORMAL - TAMMV of at least 200 cm/sec in any one of the MCA, ACA or TICA.

LOW VELOCITIES - TAMMV <70cm/s .

ASYMMETRY OF >50% in one or more of the three designated vessels.

NON-DIAGNOSTIC - Velocity not measurable due to patient compliance or poor imaging window. Repeat scan if poor compliance.

INADEQUATE - A study that does not provide readings from right and left MCA/ICA/ACA would be classified as inadequate however, if one vessel is clearly abnormal this should be scanned.

DNA - patient did not attend for scan.

NONE - TCD not available in clinic.

Quality Assurance: Phase 1 - preliminary reports from HCCs

Two questionnaires were circulated to TCD leads in October 2020; the first focussed on TCD instrumentation mode and general safety checks. The second focussed on TCD practitioners, registration, surveillance population and STOP classification. TCD screening was delivered at 26 Hospitals across the 10 HCCs, data has been received from 14 hospitals across 5 of the HCCS, namely North West, East Midlands, South East London & the South East, West London, Wessex & Thames Valley. Below is a **preliminary** summary of the information collected so far, a more detailed analysis will be completed once data is received from all hospitals across the 10 HCCs.

Instrumentation

	SCD HCC	TCD modes
1	NORTH WEST	Imaging
2	NE YORKSHIRE	x
3	E MIDLANDS	Imaging & non-imaging
4	W MIDLANDS	x
5	E LONDON & ESSSEX	x
6	SE LONDON & SE	Imaging & non-imaging
7	W LONDON	Imaging
8	N CENTRAL LONDON & E ANGLIA	x
9	WESSEX & THAMES VALLEY	Imaging & non-imaging
10	SOUTH WEST	

Table 12 - SCD HCC TCD Modes

A review of Network practice showed that the majority of hospitals use imaging TCD.

- Three HCCs provided both imaging and non-imaging TCD. Non-imaging TCD can often prove successful when imaging TCD has failed due to a poor window. HCCs should use this resource in their HCC to scan patients with limited imaging TCD scans, before requesting MRA.
- The five HCCs that responded all met the QA instrumentation requirements (electrical safety and service).
- STOP velocity thresholds were consistent across the Network.
- All centres obtained signals from the MCA, ACA, BIF, TICA and PCA regularly.
- Some centres also obtained signals from the basilar and extracranial ICA.

Practitioners

	SCD HCC	Practitioners	On Register
1	NORTH WEST	4	2
2	NE YORKSHIRE	6	2
3	E MIDLANDS	4	1
4	W MIDLANDS	3	2
5	E LONDON & ESSSEX	6	4
6	SE LONDON & SE	9	5
7	W LONDON	12	5
8	N CENTRAL LONDON & E ANGLIA	5	1
9	WESSEX & THAMES VALLEY	3	3
10	SOUTH WEST	3	1
	Total	**53**	**26**

Table 13 - Practitioners by SCD HCC

53 practitioners were confirmed across the Network, 26 were on the Forum TCD Register. All SCD TCD practitioners should be entered on the Register. Regional TCD Leads will be responsible for evaluating staff and confirming entry requirements for joining the Register.

STOP Classification

Scan data was received from 5 HCCs but some hospitals within these HCCs have not submitted data. 21 hospitals out of the 29 listed submitted data.

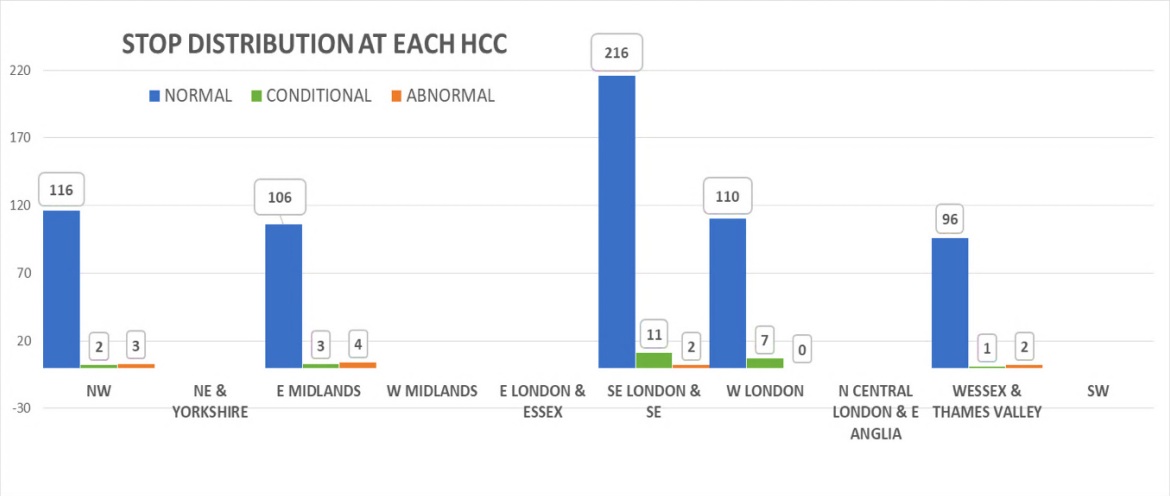


Figure 9 - STOP Distribution at each HCC

	SCD HCC	Number on surveillance	Abnormal or conditional STOP
1	NORTH WEST	121	4.1
2	NE YORKSHIRE	-	-
3	E MIDLANDS	113	6.2
4	W MIDLANDS	-	-
5	E LONDON & ESSSEX	-	-
6	SE LONDON & SE	229	5.7
7	W LONDON	117	6.0
8	N CENTRAL LONDON & E ANGLIA	-	-
9	WESSEX & THAMES VALLEY	99	3 .0
10	SOUTH WEST	-	-
	Total	**679**	**5%**

Table 14 - Surveillance and Abnormal STOP by SCD HCC

The preliminary figures from those centres who responded indicate that 679 patients were on surveillance - however this figure will be greater once all centres have responded. The incidence of abnormal or conditional STOP classifications at each HCC ranged from 3.0-6.2%.

In Progress

A comprehensive evaluation of STOP classifications, practitioner competency and instrumentation across the Network will be available once all data has been received from all HCCs.

TCD data reported on NHR post implementation to 31st March 2022:

Data from the NHR post implementation shows that uptake of scan reporting on the NHR is being undertaken by the majority of SHTs but not all centres have recorded scans for their patients during the 2021/22 year.

SHT	Patients	TCD Scans
Barts Health NHS Trust	325	396
Manchester University NHS Foundation Trust	187	207
Birmingham Women's and Children's Hospital NHS FT and Sandwell and West Birmingham Hospitals NHS Trust	184	196
St Georges Healthcare NHS Foundation Trust	141	192
North Middlesex University Hospital NHS Trust	138	182
Lewisham and Greenwich NHS Trust	127	134
Leeds Teaching Hospitals NHS Trust	113	133
Guy's and St Thomas' NHS Foundation Trust	94	121
Oxford University Hospitals NHS Foundation Trust	92	96
University Hospitals of Leicester NHS Trust	91	93
University Hospitals Bristol & Weston NHS Foundation Trust	62	71
Nottingham University Hospitals NHS Trust	55	59
Royal Liverpool and Broadgreen University Hospitals NHS Trust and Alder Hey Children's NHS Foundation Trust	55	58
University College London Hospitals NHS Foundation Trust	56	57
Croydon Health Services NHS Trust	46	48
Sheffield Children's NHS Foundation Trust	41	47
The Newcastle Upon Tyne Hospitals NHS Foundation Trust	42	46
Addenbrooke's Hospital Cambridge (Cambridge University Hospitals NHS Foundation Trust)	36	39
London Northwest University Healthcare NHS Trust	19	25
University Hospital Southampton NHS Foundation Trust	8	8
King's College Hospital NHS Foundation Trust	5	5
Homerton Healthcare NHS Foundation Trust	3	4
Sheffield Teaching Hospitals NHS Foundation Trust	2	2
Whittington Health NHS Trust	2	2
Imperial College Healthcare NHS Trust	1	1
Total	**1925**	**2222**

Figure 10 - TCD scans with a scan date between 01-Apr-2021 and 31-Mar-2022.

STOP Category for scans reported:

For centres that did enter their scan results for patients, the majority have normal TCD criteria and the number of conditional and abnormal criteria are relatively proportionate. As the TCD QA process started in 2022/23 this will provide more assurance on the quality of the scans undertaken.

SHT	STOP category	Patients	TCD scans
Barts Health NHS Trust	Normal	281	305
	Conditional	29	49
	Abnormal	4	4
	Non Diagnostic	18	19
	Not entered	19	19
	SHT total	**325**	**396**
Manchester University NHS Foundation Trust	Normal	173	175
	Conditional	2	2
	Abnormal	3	3
	Non Diagnostic	8	8
	Not entered	19	19
	SHT total	**187**	**207**
Birmingham Women's and Children's Hospital NHS FT and Sandwell and West Birmingham Hospitals NHS Trust	Normal	177	183
	Conditional	5	5
	Abnormal	2	3
	Non Diagnostic	5	5
	SHT total	**184**	**196**
St Georges Healthcare NHS Foundation Trust	Normal	111	115
	Conditional	6	11
	Abnormal	3	6
	Non Diagnostic	8	8
	Not entered	36	52
	SHT total	**141**	**192**
North Middlesex University Hospital NHS Trust	Normal	116	138
	Conditional	17	23
	Abnormal	4	6
	Non Diagnostic	8	9
	Not entered	6	6
	SHT total	**138**	**182**
Lewisham and Greenwich NHS Trust	Normal	112	118
	Conditional	5	5
	Abnormal	4	4
	Non Diagnostic	4	4
	Not entered	3	3
	SHT total	**127**	**134**

Leeds Teaching Hospitals NHS Trust	Normal	105	109
	Conditional	10	15
	Abnormal	3	3
	Non Diagnostic	5	5
	Not entered	1	1
	SHT total	**113**	**133**
Guy's and St Thomas' NHS Foundation Trust	Normal	88	95
	Conditional	11	18
	Abnormal	1	3
	Non Diagnostic	4	5
	SHT total	**94**	**121**
Oxford University Hospitals NHS Foundation Trust	Normal	88	90
	Conditional	3	3
	Non Diagnostic	3	3
	SHT total	**92**	**96**
University Hospitals of Leicester NHS Trust	Normal	84	85
	Conditional	2	2
	Abnormal	1	1
	Non Diagnostic	4	4
	Not entered	1	1
	SHT total	**91**	**93**
University Hospitals Bristol & Weston NHS Foundation Trust	Normal	58	60
	Conditional	1	1
	Abnormal	1	5
	Non Diagnostic	5	5
	SHT total	**62**	**71**
Nottingham University Hospitals NHS Trust	Normal	54	56
	Conditional	2	2
	Abnormal	1	1
	SHT total	**55**	**59**
Royal Liverpool and Broadgreen University Hospitals NHS Trust and Alder Hey Children's NHS Foundation Trust	Normal	46	46
	Conditional	2	3
	Non Diagnostic	6	6
	Not entered	3	3
	SHT total	**55**	**58**
University College London Hospitals NHS Foundation Trust	Normal	42	42
	Non Diagnostic	1	1
	Not entered	14	14
	SHT total	**56**	**57**
Croydon Health Services NHS Trust	Normal	36	37
	Conditional	7	7
	Abnormal	3	4
	SHT total	**46**	**48**

Sheffield Children's NHS Foundation Trust	Normal	31	31
	Conditional	4	9
	Non Diagnostic	7	7
	SHT total	**41**	**47**
The Newcastle Upon Tyne Hospitals NHS Foundation Trust	Normal	39	41
	Conditional	1	1
	Non Diagnostic	2	2
	Not entered	2	2
	SHT total	**42**	**46**
Addenbrooke's Hospital Cambridge (Cambridge University Hospitals NHS Foundation Trust)	Normal	34	35
	Conditional	3	3
	Not entered	1	1
	SHT total	**36**	**39**
London Northwest University Healthcare NHS Trust	Normal	17	20
	Abnormal	1	1
	Non Diagnostic	3	4
	SHT total	**19**	**25**
University Hospital Southampton NHS Foundation Trust	Normal	7	7
	Non Diagnostic	1	1
	SHT total	**8**	**8**
King's College Hospital NHS Foundation Trust	Normal	4	4
	Conditional	1	1
	SHT total	**5**	**5**
Homerton Healthcare NHS Foundation Trust	Normal	3	3
	Non Diagnostic	1	1
	SHT total	**3**	**4**
Sheffield Teaching Hospitals NHS Foundation Trust	Normal	2	2
	SHT total	**2**	**2**
Whittington Health NHS Trust	Not entered	2	2
	SHT total	**2**	**2**
Imperial College Healthcare NHS Trust	Normal	1	1
	SHT total	**1**	**1**
Total		**1925**	**2222**

Figure 11 - TCD scans by SHT and Stop Category between 01-Apr-2021 and 31-Mar-2022

Self-reported assessment of quality for scans reported

Operators have been reporting on the quality of the TCD scan as part of the quality assurance and most scans have been reported as good or average. There will be more work undertaken to improve on the not entered figures so a more accurate quality assessment can be made.

SHT	Scan quality	Patients	TCD scans
Barts Health NHS Trust	Good	166	196
	Average	79	85
	Poor	15	17
	Non Diagnostic	5	5
	Not entered	87	93
	SHT total	**325**	**396**
Manchester University NHS Foundation Trust	Good	153	156
	Average	21	21
	Poor	3	3
	Non Diagnostic	6	6
	Not entered	21	21
	SHT total	**187**	**207**
Birmingham Women's and Children's Hospital NHS FT and Sandwell and West Birmingham Hospitals NHS Trust	Good	137	142
	Average	19	19
	Poor	6	6
	Non Diagnostic	1	1
	Not entered	28	28
	SHT total	**184**	**196**
St Georges Healthcare NHS Foundation Trust	Good	69	75
	Average	12	12
	Poor	2	2
	Non Diagnostic	7	7
	Not entered	68	96
	SHT total	**141**	**192**
North Middlesex University Hospital NHS Trust	Good	108	142
	Average	18	19
	Poor	12	13
	Not entered	8	8
	SHT total	**138**	**182**
Lewisham and Greenwich NHS Trust	Good	94	99
	Average	1	1
	Poor	2	2
	Non Diagnostic	1	1
	Not entered	31	31
	SHT total	**127**	**134**
Leeds Teaching Hospitals NHS Trust	Good	8	9
	Poor	2	2
	Not entered	104	122
	SHT total	**113**	**133**

Guy's and St Thomas' NHS Foundation Trust	Good	78	96
	Average	11	11
	Poor	9	9
	Non Diagnostic	3	3
	Not entered	2	2
	SHT total	**94**	**121**
Oxford University Hospitals NHS Foundation Trust	Good	77	80
	Average	6	6
	Poor	3	3
	Non Diagnostic	1	1
	Not entered	6	6
	SHT total	**92**	**96**
University Hospitals of Leicester NHS Trust	Good	19	19
	Average	50	50
	Poor	15	16
	Non Diagnostic	3	3
	Not entered	5	5
	SHT total	**91**	**93**
University Hospitals Bristol & Weston NHS Foundation Trust	Good	38	40
	Average	1	1
	Poor	2	2
	Non Diagnostic	4	4
	Not entered	22	24
	SHT total	**62**	**71**
Nottingham University Hospitals NHS Trust	Good	47	51
	Average	3	3
	Poor	2	2
	Not entered	3	3
	SHT total	**55**	**59**
Royal Liverpool and Broadgreen University Hospitals NHS Trust and Alder Hey Children's NHS Foundation Trust	Good	42	45
	Average	2	2
	Poor	4	4
	Non Diagnostic	1	1
	Not entered	6	6
	SHT total	**55**	**58**
University College London Hospitals NHS Foundation Trust	Good	1	1
	Average	2	2
	Poor	1	1
	Not entered	53	53
	SHT total	**56**	**57**

Croydon Health Services NHS Trust	Good	34	35
	Average	2	2
	Poor	9	9
	Not entered	1	2
	SHT total	**46**	**48**
Sheffield Children's NHS Foundation Trust	Good	21	25
	Average	1	1
	Poor	1	1
	Non Diagnostic	2	2
	Not entered	18	18
	SHT total	**41**	**47**
The Newcastle Upon Tyne Hospitals NHS Foundation Trust	Good	13	15
	Non Diagnostic	1	1
	Not entered	29	30
	SHT total	**42**	**46**
Addenbrooke's Hospital Cambridge (Cambridge University Hospitals NHS Foundation Trust)	Good	31	34
	Poor	2	2
	Not entered	3	3
	SHT total	**36**	**39**
London Northwest University Healthcare NHS Trust	Good	14	18
	Average	1	1
	Poor	4	5
	Non Diagnostic	1	1
	SHT total	**19**	**25**
University Hospital Southampton NHS Foundation Trust	Good	5	5
	Average	1	1
	Poor	1	1
	Non Diagnostic	1	1
	SHT total	**8**	**8**
King's College Hospital NHS Foundation Trust	Good	4	4
	Not entered	1	1
	SHT total	**5**	**5**
Homerton Healthcare NHS Foundation Trust	Good	3	4
	SHT total	**3**	**4**
Sheffield Teaching Hospitals NHS Foundation Trust	Not entered	2	2
	SHT total	**2**	**2**
Whittington Health NHS Trust	Not entered	2	2
	SHT total	**2**	**2**
Imperial College Healthcare NHS Trust	Good	1	1
	SHT total	**1**	**1**
Total		**1925**	**2222**

Figure 12- TCD Scans and Scan Quality between 01-Apr-2021 and 31-Mar-2022

Data Quality Issues

TCD data on the NHR is of high quality but the limitation is that all centres have not currently reported data on to the NHR. The expectation is that this will improve considerably during 2022/23 and a robust QA system will be implanted to ensure that centres not reporting TCD results are supported to ensure that data is entered.

Chapter 6: Rare Inherited Anaemias (RIAs)

Authors: Noemi Roy

Introduction

One of the new aspects of the NHR is the systematic inclusion of rare inherited anaemias (RIAs) in the NHR. This will allow a better understanding of the prevalence and distribution of RIAs across the country, as well as give an indication of how well managed patients are according to type of RIA. All data described in this report refer to patients registered on to the NHRv2 by 31st March 2022. For future Annual Reports, it is hoped to utilise data generated from the RIA Annual Reviews. Current Annual Review field are not specific to RIAs but data from this report will inform the design of RIA-specific AR fields. In future we would anticipate an improved registration of RIA patients in each centre, and improved completion rate of Annual Reviews by centres for all patients with RIAs. In addition, the data from future, more complete RIA Annual Reviews should allow improved determinations of real-world incidence and prevalence of each of the RIAs, as current reported data in the scientific literature vary and are likely to be inaccurate due to the rarity of the disease and the impact of reporting biases.

A list of the RIA abbreviations is provided here:

- DBA- Diamond Blackfan Anaemia
- CDA- Congenital Dyserythropoietic Anaemia
- CSA- Congenital Sideroblastic Anaemia
- HS- Hereditary Spherocytosis
- HPP- Hereditary Pyropoikilocytosis
- HSt- Hereditary Stomatocytosis
- PKD- pyruvate kinase deficiency
- G6PD- G6PD deficiency

As of 31st March 2022, 23 SHTs have registered RIA patients on to the NHR with a total of 508 patients (Table 15). 96 patients were registered with no SHT assigned, which is an issue needing resolution with MDSAS. A further piece of work harmonising the list of SHTs is also required as some of the hospitals listed as SHTs are not officially designated as such, and other SHTs are listed more than once (e.g. Oxford). The distribution of RIA patients across SHTs is high, some of which will represent genuine differences in the distribution of patients across the country, but it does raise the possibility that some of the SHTs have not registered all of their RIA patients on the NHR (Table 16).

Barts Health NHS Trust	24
Birmingham Women's and Children's Hospital NHS FT and Sandwell and West Birmingham Hospitals NHS Trust	58
Guy's and St Thomas' NHS Foundation Trust	6
Imperial College Healthcare NHS Trust	2
King's College Hospital NHS Foundation Trust	2
Leeds Teaching Hospitals NHS Trust	15
Lewisham and Greenwich NHS Trust	1
London Northwest University Healthcare NHS Trust	48
Manchester University NHS Foundation Trust	28
North Middlesex University Hospital NHS Trust	2
Nottingham University Hospitals NHS Trust	28
NULL	96
Oxford Children's Hospital	4
Oxford University Hospitals NHS Foundation Trust	27
Royal Liverpool and Broadgreen University Hospitals NHS Trust and Alder Hey Children's NHS Foundation Trust	15
Sheffield Children's NHS Foundation Trust	6
Sheffield Teaching Hospitals NHS Foundation Trust	12
St Georges Healthcare NHS Foundation Trust	3
The Newcastle Upon Tyne Hospitals NHS Foundation Trust	22
University College London Hospitals NHS Foundation Trust	76
University Hospital Southampton NHS Foundation Trust	5
University Hospitals Bristol & Weston NHS Foundation Trust	16
University Hospitals of Leicester NHS Trust	9
Whittington Health NHS Trust	4
Grand Total	**509**

Table 15 - RIA patients on to the NHR

(Note this includes the congenital neutropenia patient which is why the total is 509. Not 508)

ADA 2	1
Congenital dyseythropoietic anaemia type I	11
Congenital dyseythropoietic anaemia type II	10
Congenital dyseythropoietic anaemia type III	2
Congenital dyseythropoietic anaemia type IV	1
Congenital dyseythropoietic anaemia type other	11
Congenital haemolytic anaemia -possible membranopathy and Gilberts Syndrome	1
Congenital Methaemoglobinnaemia	1
Congential Neutropenia (chromosomal 4q duplication)	1
Diamond Blackfan Anaemia	114
Diamond Blackfan Anaemia	2
G6PD Deficiency	8
Glucose Phosphate Isomerase Deficiency	1
Haemolytic Anaemia	1
Hereditary elliptocytosis	1
Hereditary Spherocytosis	26
Hereditary Spherocytosis	2
Hereditary Stomatocytosis	6
Hexokinase Deficiency with Haemolytic Anaemia	1
Hypoplastic Anaemia	1
Methaemoglobin	7
Presumptive diagnosis of congenital dyserythropoetic anaemia although with normal genetics	1
Pure red cell aplasia	2
Pyrimidine 5' nucleotidase	3
Pyruvate Kinase Deficiency	71
Pyruvate Kinase Deficiency	1
Sideroblastic anaemia	33
South East Asian Ovalocytosis	1
Thiamine-responsive megaloblastic anaemia	1
Transfusion dependent membrane disorders	1
Unexplained anaemia	125
Unstable Haemoglobin	57
Hereditary pyropoikilocytosis	3
Glutathione Synthase Deficiency	1
Grand Total	**509**

Table 16 - Rare Inherited Anaemias (RIA)

(Note this includes the congenital neutropenia patient which is why the total is 509. Not 508)

Distribution of diagnoses of RIAs

RIA diagnoses by SHTs

The largest category of RIAs (Table 16) according to the NHR is in fact patients whose diagnosis has not been ascertained (126 patients), followed by patients with Diamond Blackfan Anaemia (120 patients) and red cell enzyme disorders (86 patients). The next most common category is unstable Hb (57 patients), then red cell membrane disorders (41 patients), CDA (36 patients) and congenital sideroblastic anaemia (33 patients). There were very few patients with congenital Methaemoglobinaemia (8 patients) and one patient with congenital megaloblastic anaemia. A learning point from this initial report is that there is a lack of consistency about how each of these rare anaemias are categorised, and a priority for 2023-2024 will be to harmonise the nomenclature used in the NHR. In addition, some patients were reported with diagnoses that do not fall under the NHR, such as congenital neutropenia. These are not included in the following report but will be followed up so that they can be removed from the registry.

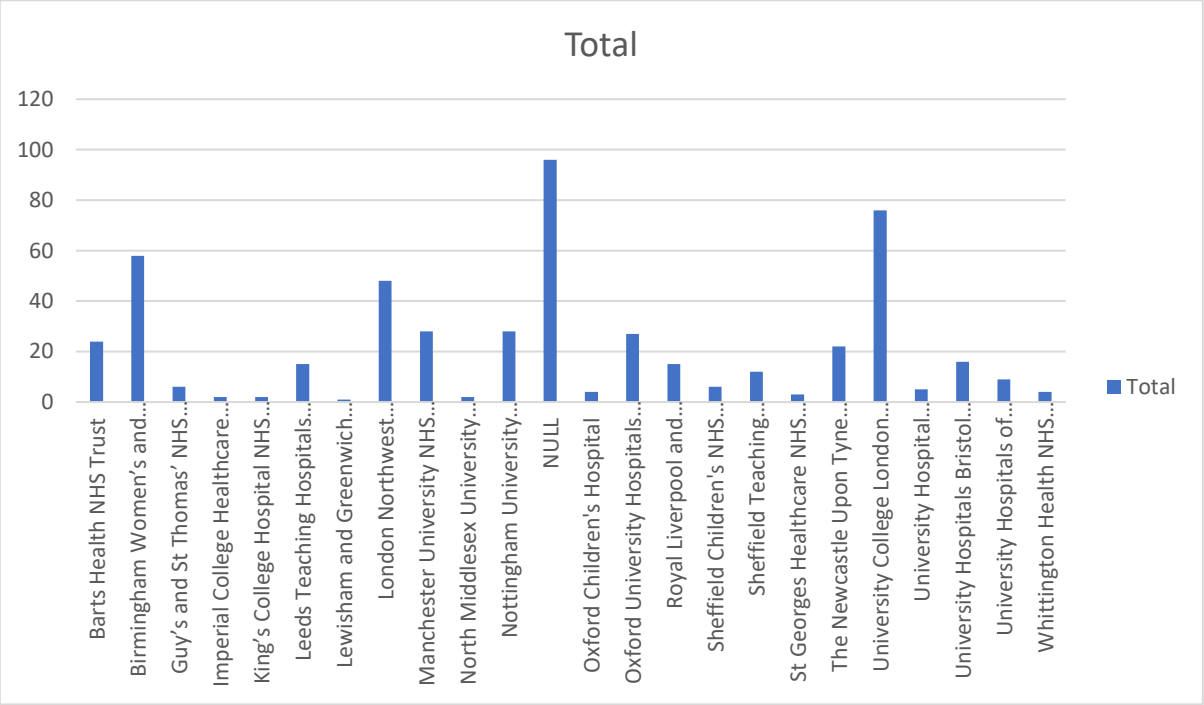


Figure 13 - Rare Inherited Anaemias (RIA) by Trust

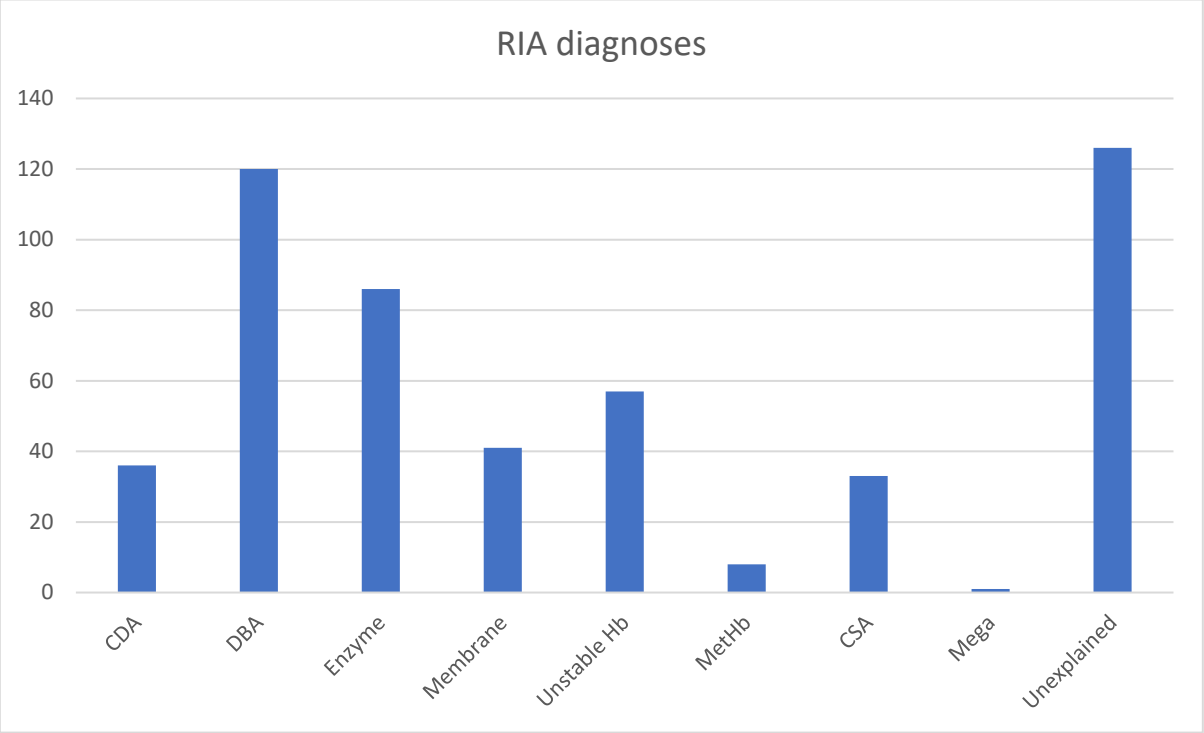


Figure 14 - RIA By Type

Sub-division of diagnoses

Some of the RIAs can be sub-divided into further categories. For example, patients reported with red cell enzyme deficiencies (Figure 15) were made up of 72 PKD, 8 G6PD, 3 P5N, 1 hexokinase deficiency, 1 glucose phosphate isomerase deficiency and 1 glutathione synthase deficiency. Of the DBA patients, a small proportion did not have a formal diagnosis of DBA but just one of 'pure red cell aplasia'. It is not at the moment possible to determine whether patients with RIAs have a genetic diagnosis or whether the diagnosis is just based on phenotype.

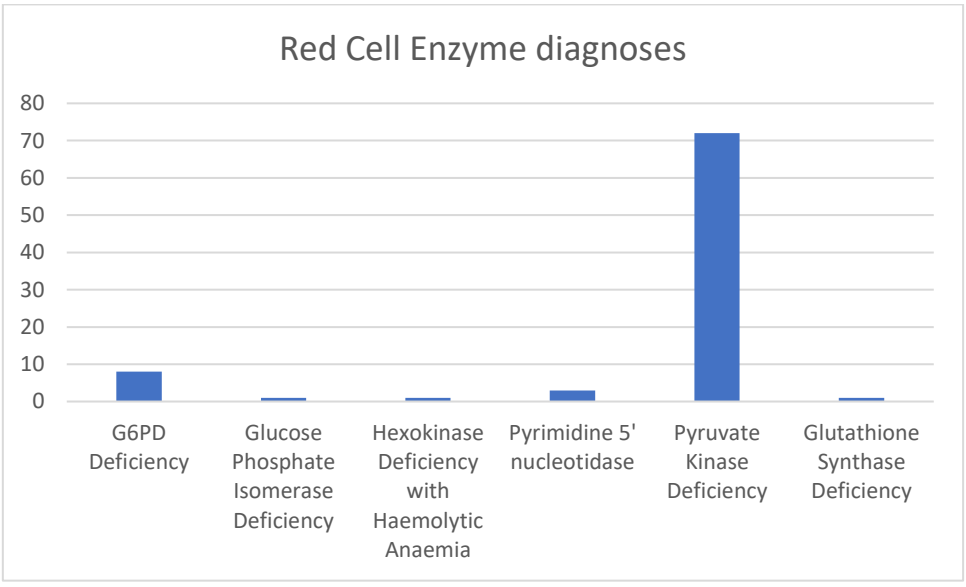


Figure 15 - Red Cell Enzyme Diagnoses

While the commonest cause of red cell membrane disorders, hereditary spherocytosis (HS), is not included in the NHR, HS patients who are transfusion dependent do get included, as do more rare membrane disorders. The current list (Figure 16) includes 28 HS, 6 hereditary stomatocytosis, 3 pyropoikilocytosis, 1 transfusion dependent presumed red cell membrane disorder, and 1 elliptocytosis. It is not clear that all 28

HS patients are transfusion dependent, nor that the hereditary elliptocytosis patient fulfils the criteria for inclusion into the NHR, but this will be taken forward separately.

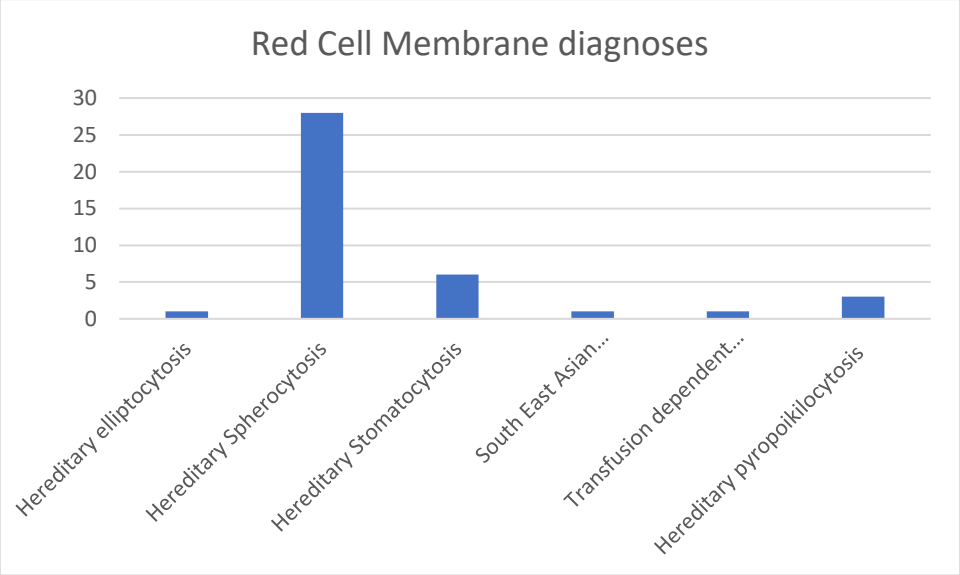


Figure 16 - Red Cell Membrane diagnoses

For patients with CDAs (Figure 17), there were 11 reported with CDA-1, 10 with CDA-2, 2 with CDA-3, one with CDA-4 and 11 with unclassified CDAs.

These numbers are far below the expected number for some of these conditions. For example, patient support groups such as the Diamond Blackfan Anaemia charity DBA UK are aware of ~150-200 DBA patients in the UK. Likewise, CAN (congenital anaemia network) report ~30-40 known UK patients with CDA. As such, the current numbers entered in the NHR is likely to be a significant under-reporting of these RIAs.

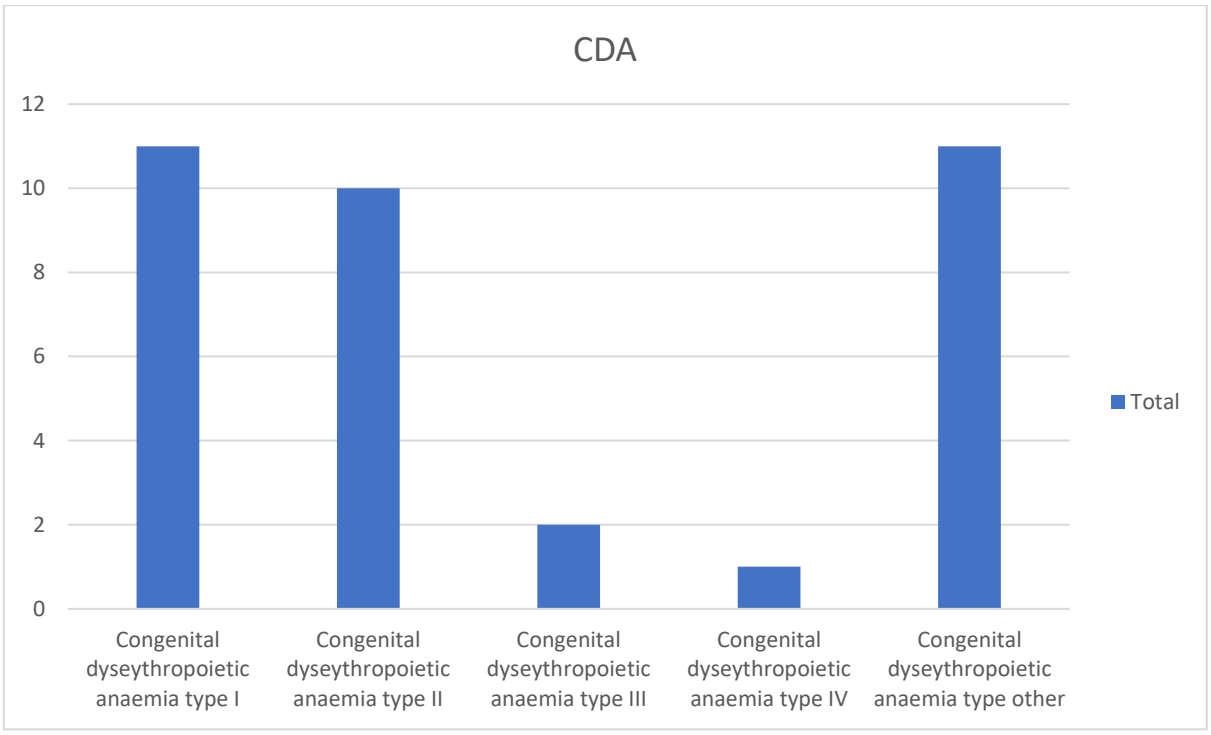


Figure 17 - Patients by CDA Type

Age distribution for all RIAs

The age distribution is highlighted in Figure 18. Interestingly, the age distribution does not quite replicate that in the general population. As might be expected, there are fewer people over the age of 70, likely due to the combination of lack of diagnoses in some of the older patients, and a reduced life expectancy in most of the RIAs. In addition, the spike in younger patients (under age 5) is also not surprising as the improvements in genetic diagnosis in the last 5 years has led to more accurate diagnostic rates in the younger age group.

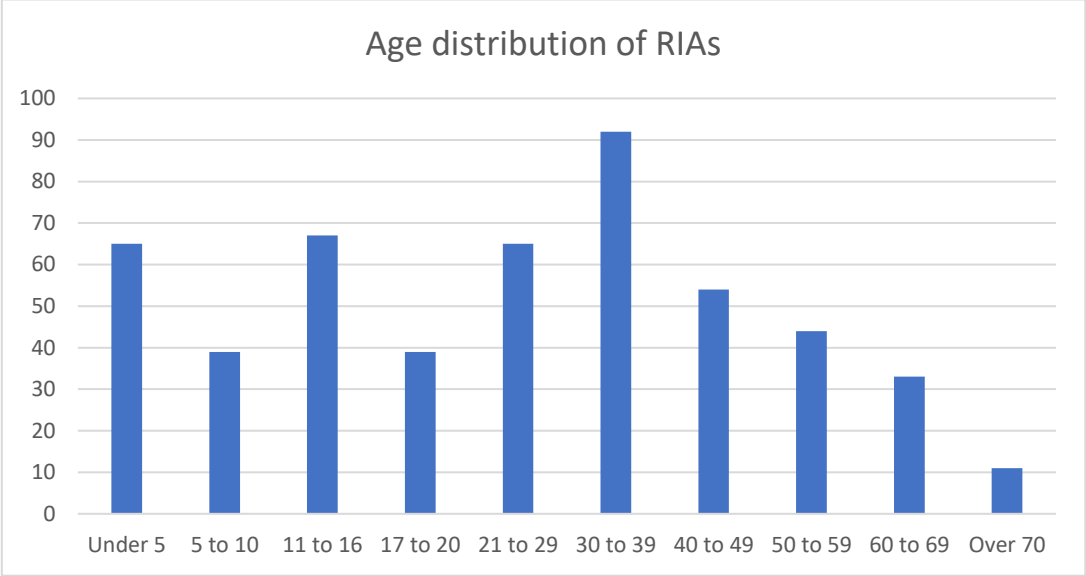


Figure 18 - Age distribution of RIAs

Ethnic distribution for all RIAs

Ethnicity is recorded for all patients with a RIA (Figure 19). The UK 2011 Census data states that the ethnicity of the general population is White 87.2%, Asian/British Asian 4.2%, Black 3%, Mixed 2%, Other 3.7%. Whereas sickle cell disease and thalassaemia do have a significant bias for African and Asian populations respectively, this is less marked for RIAs, which do not tend to cluster in particular ethnic groups.

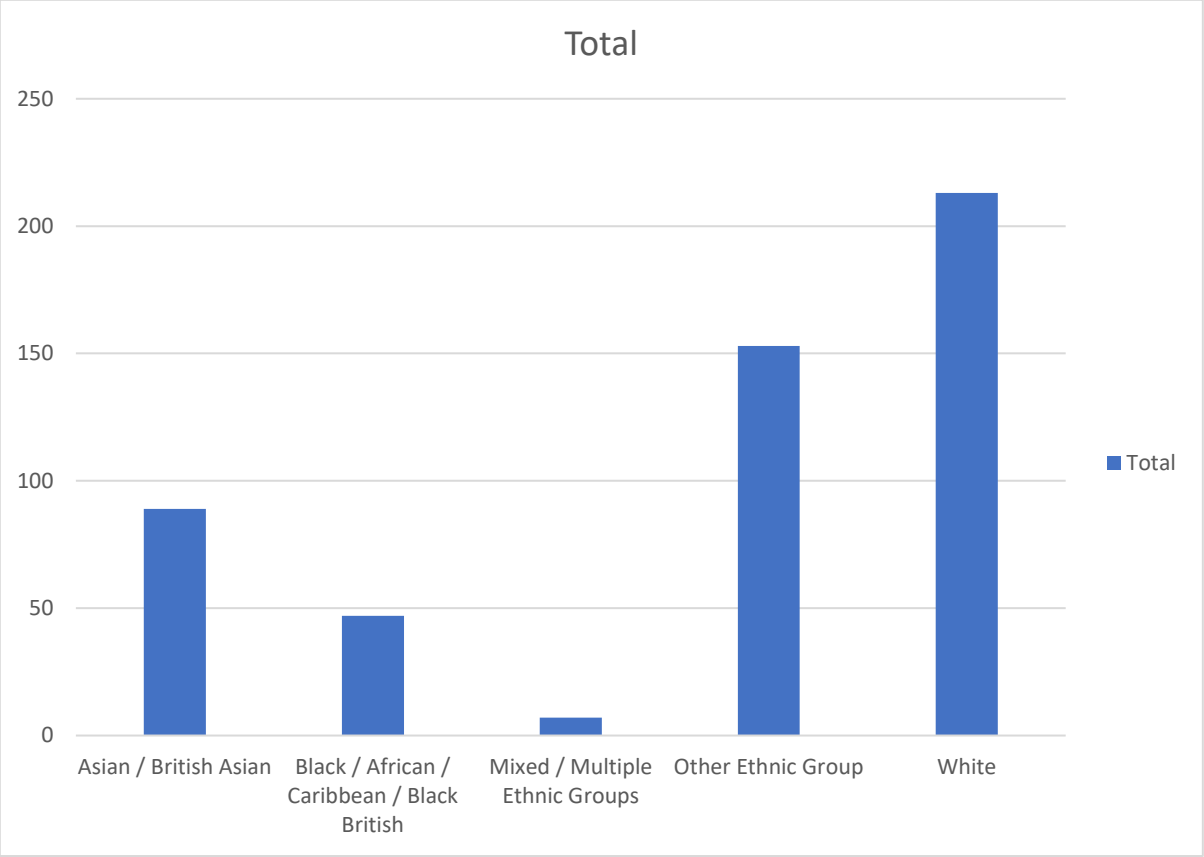


Figure 19 - Ethnicity by RIA

Number of RIA patients regularly transfused and having iron MRI monitoring

Some patients with RIAs will require lifelong transfusions. As expected, the most patients on regular transfusions are DBA patients, the PK Deficiency and sideroblastic anaemia. 75 of the RIA patients are transfusion dependent and 62 have received ad-hoc transfusions. 121 RIA patients have Ferriscan and/or T2* MRIs. Because RIA patients can have non-transfusional iron overload, not all patients having MRI monitoring will be those on regular transfusions, however all regularly transfused patients should be having MRI monitoring. Figure 20 explores the relationship between patients' diagnoses, their transfusion state and whether they have MRI monitoring, but the data is incomplete.

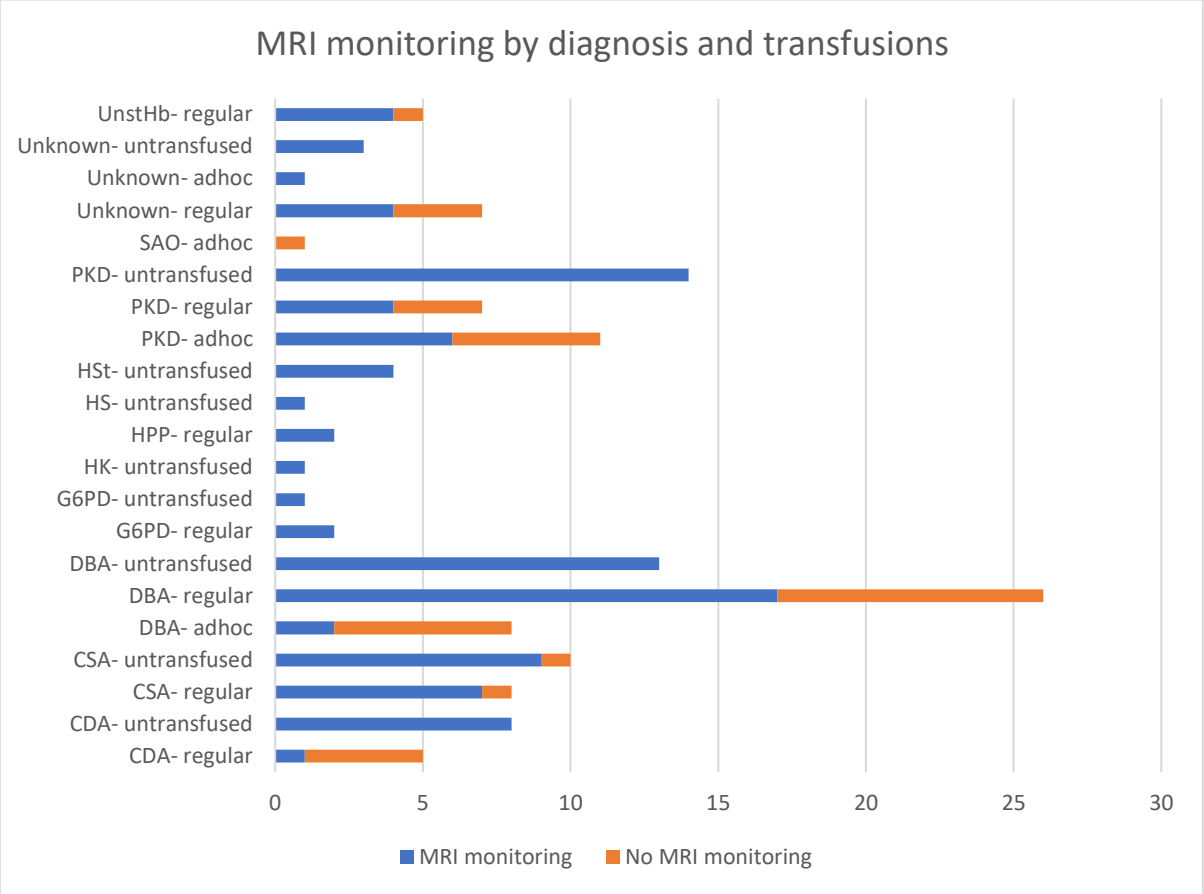


Figure 20 - MRI monitoring by diagnosis and transfusions

Number of patients receiving chelation

84 RIA patients are receiving regular chelation. Of these (Figure 21), 62 take deferasirox only, 14 desferrioxamine only and 4 deferiprone only. The remainder are on combination therapy.

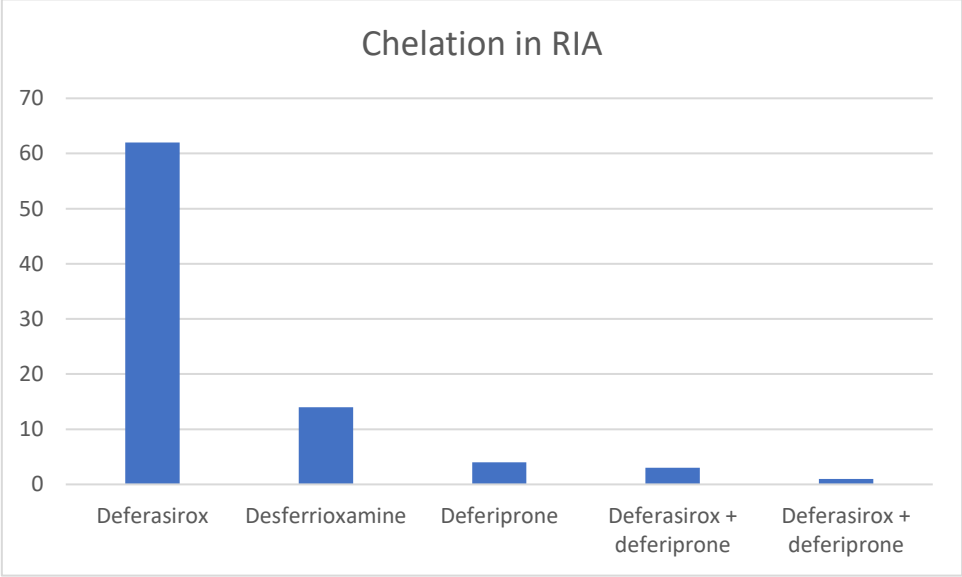


Figure 21 - Chelation in RIA

Number of patients having had splenectomy by RIA diagnosis

A small proportion of RIA patients (6%; 31/508) have had a splenectomy. The largest group of patients is those with a diagnosis of PKD (20), followed by unstable Hb (4), with one or 2 patients with other diagnoses (Figure 22).

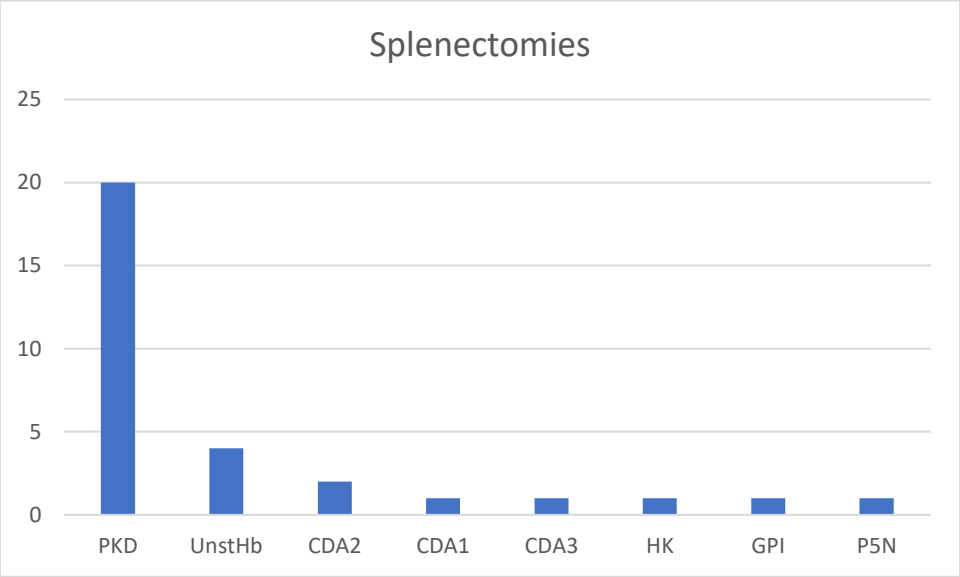


Figure 22 - Splenectomies by Type

Data quality and future directions

There are concerns about the completeness and the quality of some of the data for the RIA patients currently entered in the NHR. As noted above, the number of patients reported for each of the rare anaemias is far lower than that predicted by fairly well-established estimates of incidence for these conditions. Of additional concern is the lack of standardisation in how each of the rare anaemias is classified, and the large number of "undiagnosed" RIAs. One of the priorities for improvement of the NHR for the next financial year will be to harmonise the way in which each of the RIAs is described, as well as clarify which patients have received a genetic diagnosis, which have been tested by the current NHSE standard-of-care genomic test (R92 panel), and which have not been tested using this assay. In addition, some of the fields currently required for the annual review are not designed specifically for RIAs but are more appropriate for either SCD or thalassaemia. It will therefore be important for the next financial year that these fields are modified so that the most relevant information is collated for each of the RIA diagnoses. While it is clear that the current data is incomplete, this is the first report of a national compulsory registry for all of these conditions, and as such provides a wonderful initial picture of the distribution and severity of disease for people living with RIAs in England.

Chapter 7: Psychological Support

Author: Kofi Anie

Background

Psychological issues for individuals living with sickle cell disease, thalassaemia, and rare inherited anaemias and their families may result from the impact of these conditions on their daily lives, and public attitudes to those affected. There is considerable variability in the ability of individuals to cope with their condition. Individuals experience different levels of health, and such variations can lead to differences in psychological wellbeing. Some individuals cope relatively well, attend school or work, and are active physically and socially. Their efforts should be recognised and encouraged where necessary. Others have difficulties in coping, leading more limited and secluded lives. Nonetheless, this may not necessarily be a consequence of severe disease, and the reasons for these should be sought and addressed. Quality of life in individuals may therefore be more impaired than that of the general population, and with severe disease; this may deteriorate as people grow into adulthood.

Peer Review Quality Standards associated with Health Services for People with Haemoglobin Disorders stipulate that all individuals should have access to specialist psychology services. Recommended psychology staffing is one whole time equivalent for 300 patients.

Outcomes

The majority of completed annual reviews for psychology were for females with sickle cell disease (Table 17). This is consistent with the total number of individuals registered on the NHR. Specialist psychological support was received by a similar proportion of individuals as compared with their primary diagnosis.

Children and adolescents with sickle cell disease, thalassaemia and rare inherited anaemias aged 11 to 16 years received most of the psychological support (Figure 23, Figure 25, Figure 27).

On the other hand, for both female and male adults with sickle cell disease, psychological interventions received was highest from 30 to 39 years of age, although this was only marginally more than was received in females with sickle cell disease aged 21 to 29 years and 40 to 49 years, and males with sickle cell disease aged 17 to 20 years and 21 to 29 years (Figure 24). By contrast adult females with thalassaemia aged 30 to 39 years distinctly received a larger share of psychological support than any other age group (Figure 26). In the case of males with thalassaemia, those aged 30 to 39 years and 40 to 49 years received more psychological help (Figure 26). Furthermore, adults with rare inherited anaemias were similar in their requirements with females aged 30 to 39 years and 40 to 49 years and males aged 30 to 39 years receiving most of the psychology input (Figure 28).

Summary

Older children and adolescents with sickle cell disease, thalassaemia and rare inherited anaemias may require increased psychological support for several reasons. First, as children with these chronic illnesses grow older, they become more aware of their condition and its impact on their daily life. This increased awareness can lead to emotional and psychological difficulties as they tackle the reality of their illness. Second, this age group is often during adolescence, a period marked by significant physical, emotional, and social changes. Adolescents may face additional challenges related to their condition, such as body image concerns, peer pressure, and the desire for independence. Adolescents are encouraged to take on more responsibility for managing their disease, including medication adherence, monitoring their symptoms, and recognising when to seek medical attention. This added responsibility can be overwhelming and stressful, leading to increased psychological needs. Adolescents may also face difficulties in school due to frequent absences, pain episodes, and fatigue. They may encounter social challenges, such as stigma or bullying related to their condition, which can negatively impact their self-esteem and mental health. Adolescents may need support in navigating their peer relationships, as their condition can sometimes make them feel different from their peers. Psychosocial support can help them build social skills and resilience in dealing with peer-related issues. Furthermore, as adolescents approach adulthood, they need to transition from paediatric to adult healthcare. This transition can be a challenging and anxiety-provoking process, and psychological support can help ease the transition and promote continuity of care. Third, sickle cell disease in particular is often associated with episodes of pain (vaso-occlusive crises). Individuals may struggle with the physical and emotional toll of these painful crises, and they may need support in developing effective pain management strategies and coping mechanisms. Fourth, children and adolescents with these conditions are at an increased risk of developing anxiety and depression. Psychological support can be crucial in identifying and addressing these mental health concerns.

Sickle cell disease, thalassaemia and rare inherited anaemias are lifelong conditions that require continuous management, including regular blood transfusions and iron chelation therapy for a significant number of individuals. By the age of 50 years, many individuals have often been managing their condition for decades. The ongoing nature of their treatment can be emotionally demanding, leading to feelings of frustration and exhaustion. Over time, individuals with these conditions may experience various health complications including organ damage. These complications can result a diminished quality of life, leading to increased psychological distress. As young adults, they may face unique challenges related to family planning, relationships, and career choices. Concerns about passing on the condition to their children, navigating intimate relationships, and managing work-life balance can all contribute to increased stress and anxiety. Growing older comes with the effects of aging, such as comorbidities, which can exacerbate the challenges adults face. Coping with these age-related changes can be emotionally challenging. Furthermore, dealing with uncertainty about future health outcomes can lead to worry and stress, making it essential for psychological interventions to build resilience and adaptive coping strategies. In addition, support systems may change over time, and individuals may benefit from connecting with peers who are experiencing similar challenges. Some individuals may have experienced the loss of loved ones who also had their condition or may have friends in the community who have passed away. Psychological support can provide a platform for them to share experiences and coping strategies for loss and grief that can be emotionally challenging.

In conclusion, the emotional and psychological needs of children, adolescents, and adults with sickle cell disease, thalassaemia and rare anaemias are complex and multifaceted. Providing them with appropriate psychological interventions at all stage of their lives can significantly improve their quality of life and help them better manage their condition as they transition from childhood into older adulthood.

Gender	Primary Diagnosis	Completed Annual Reviews for Psychology	Specialist Psychology Support Received
Female	Another Rare Inherited Anaemia	1%	1%
	Sickle Cell	58%	60%
	Thalassaemia	4%	4%
Female Total		62%	64%
Male	Another Rare Inherited Anaemia	1%	0%
	Sickle Cell	34%	34%
	Thalassaemia	3%	2%
Male Total		38%	36%
Grand Total		**100%**	**100%**

Table 17 - Psychology Reviews by Gender

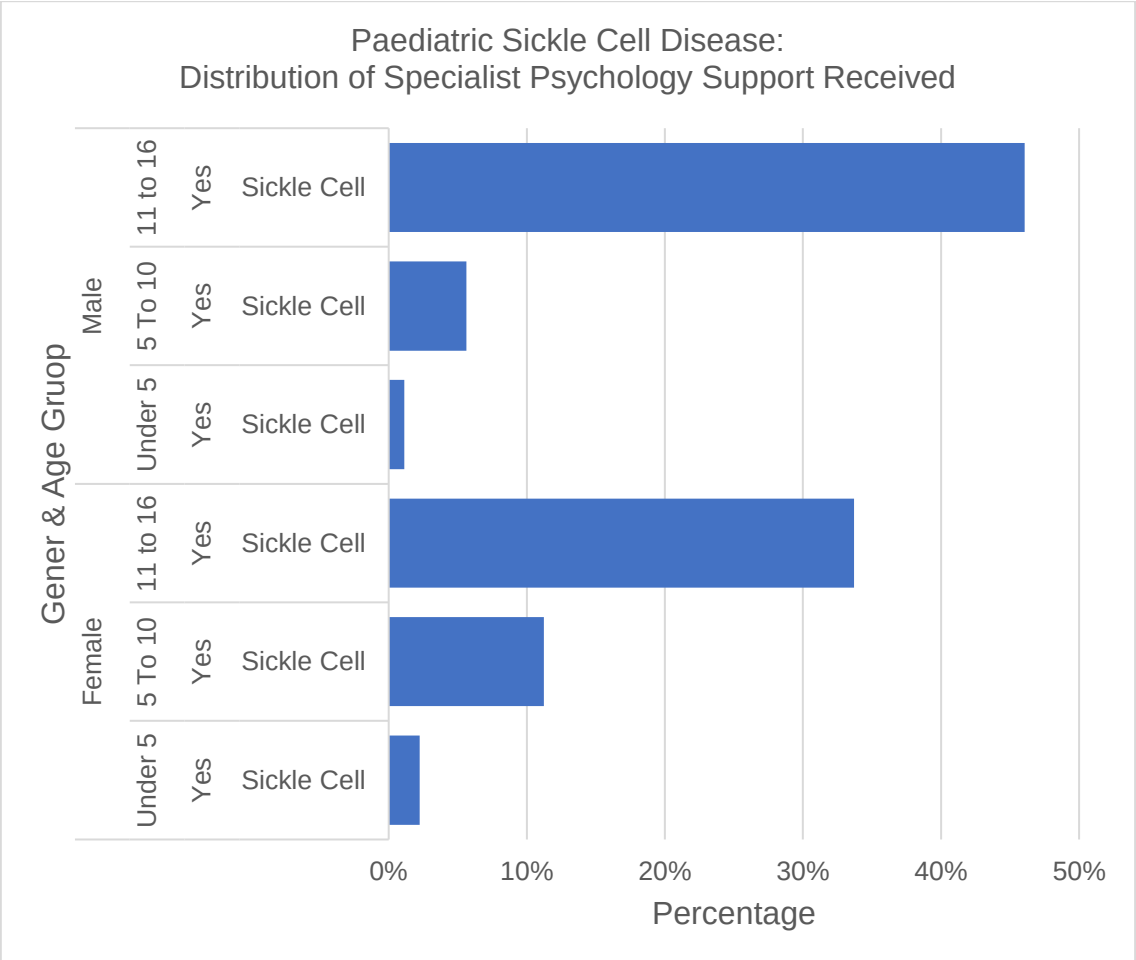


Figure 23 - Paediatric SCD - Distribution of Specialist Psychology Support Received

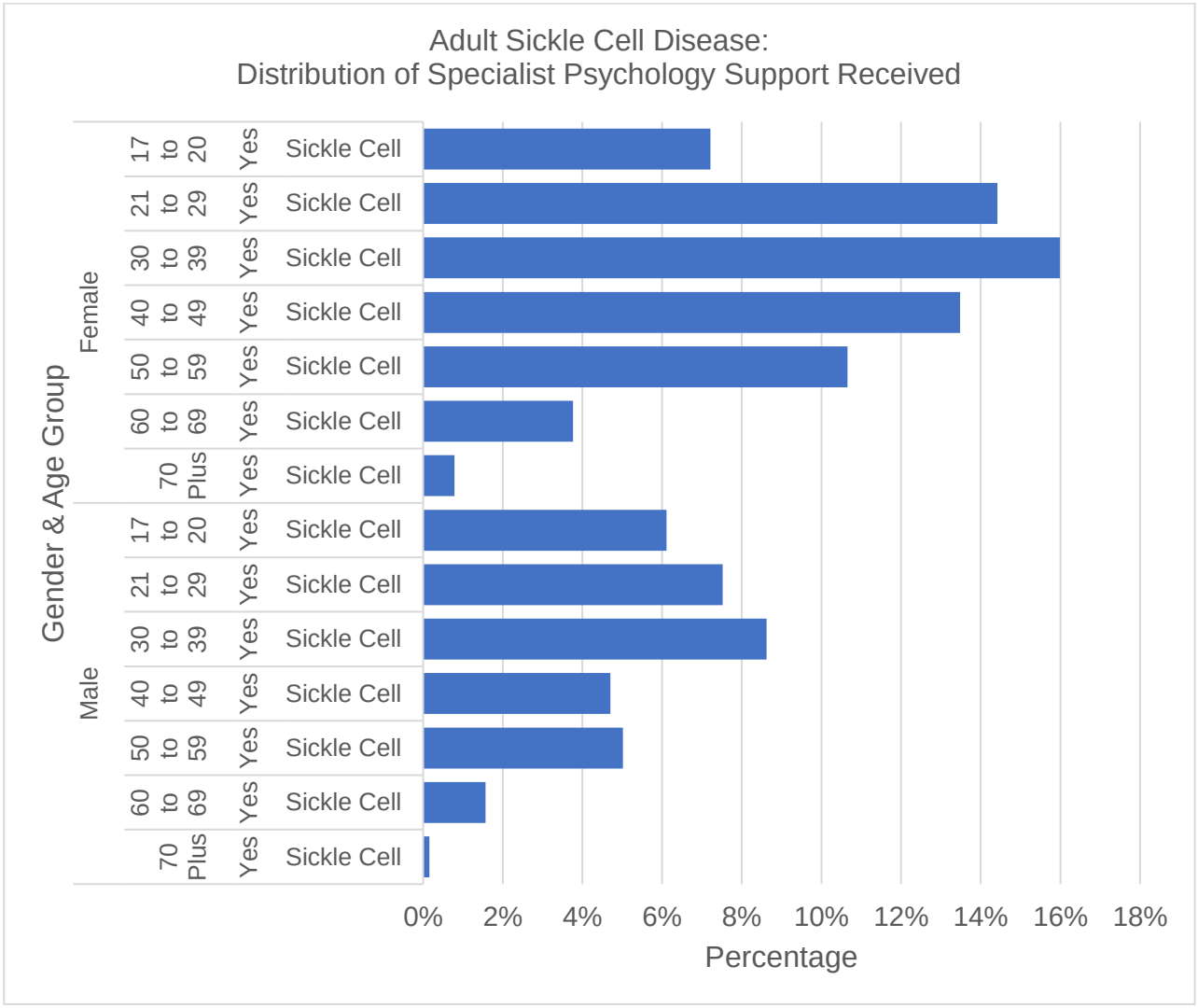


Figure 24 - Adult SCD: Distribution of Specialist Psychology Support Received

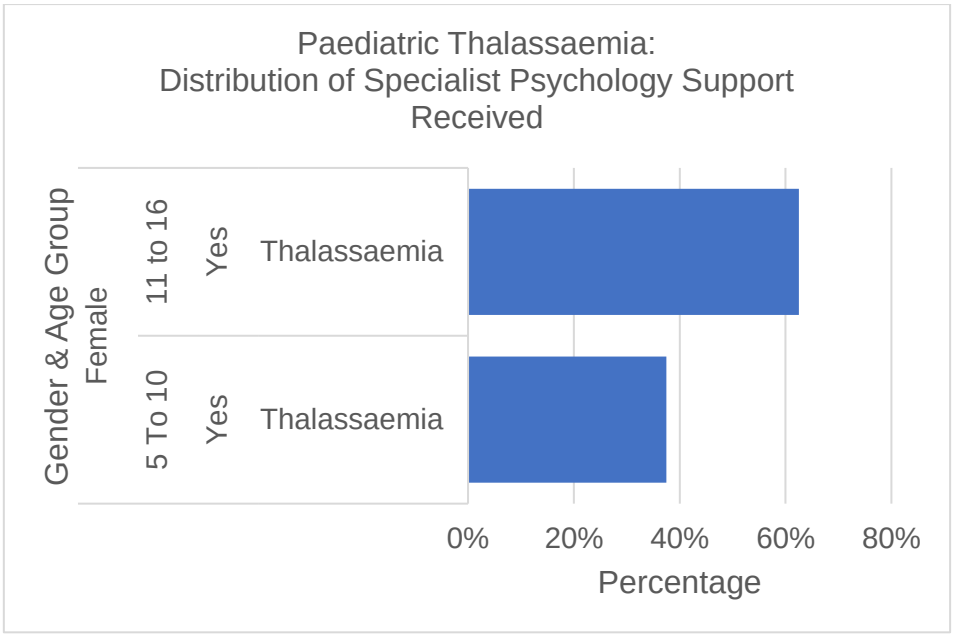


Figure 25 - Paediatric Thalassaemia: Distribution of Specialist Psychology Support Received

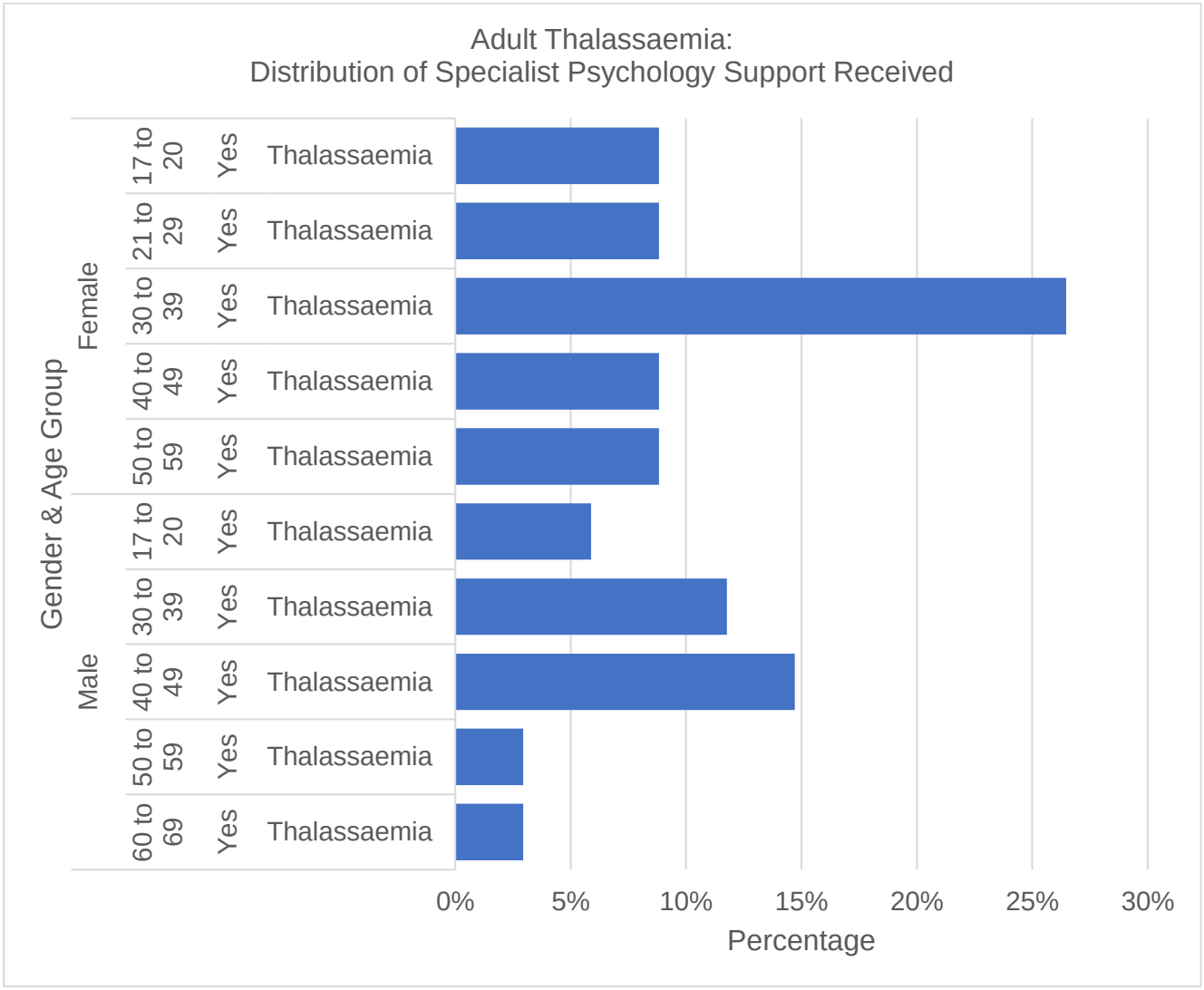


Figure 26 - Adults Thalassaemia: Distribution of Specialist Psychology Support Received

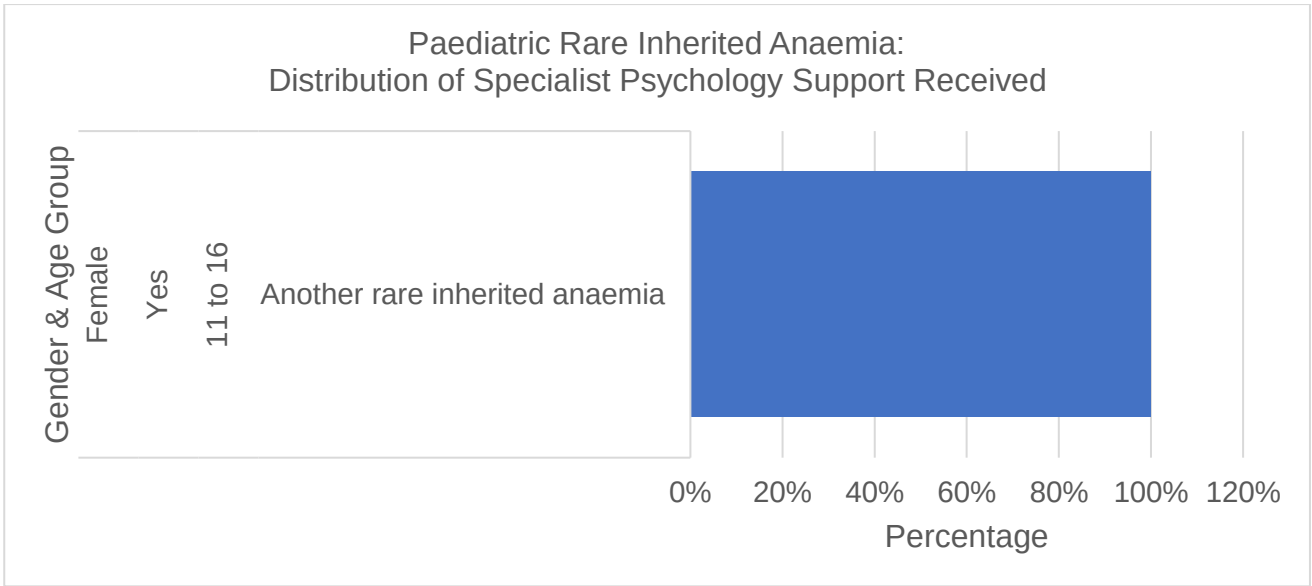


Figure 27 - Paediatric Rare Inherited Anaemia: Distribution of Specialist Psychology Support Received

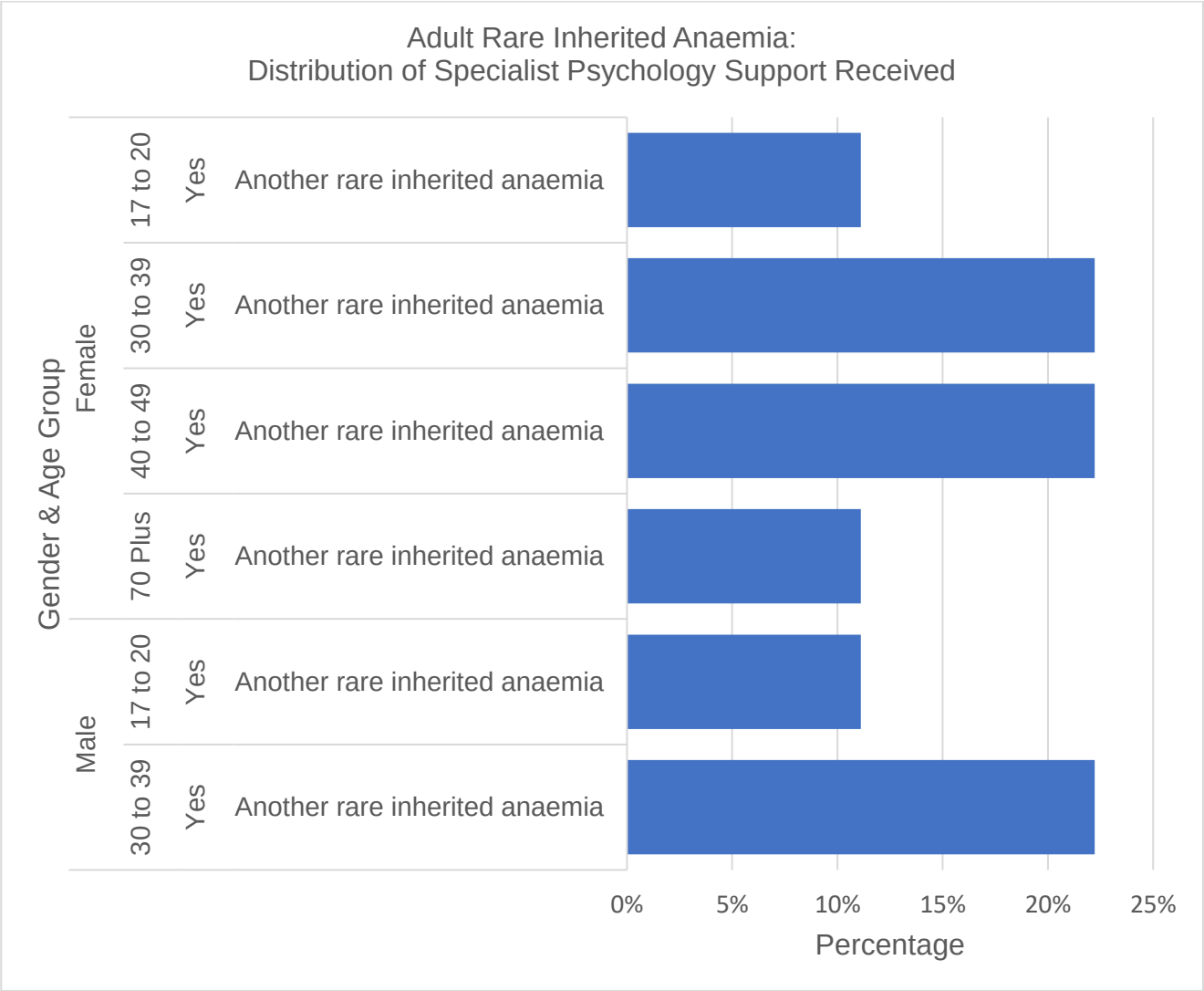


Figure 28 - Adult Rare Inherited Anaemia: Distribution of Specialist Psychology Support Received

Chapter 8: Novel Treatments in Sickle Cell

Author: Kate Gardner

Introduction

Until 2021, apart from regular transfusions, the only disease modifying therapy available to manage sickle cell was hydroxycarbamide. Two new treatments were recently made available to patients with sickle cell: crizanlizumab, a monoclonal antibody against p-selection (anti-vaso-occlusion agent), and voxelotor, a sickle-haemoglobin polymerisation inhibitor (anti-sickling agent). Each new therapy was only available to a specific group of patients for which there were nationally agreed eligibility criteria. As well as these novel therapies, 2020 also saw the approval of sibling bone marrow transplant (haematopoietic stem cell transplant) for adults. Bone marrow transplant was already available to children with SCD.

As part of the crizanlizumab licensing agreement, data has to be added to the NHR. There is no such requirement for voxelotor or bone marrow transplant.

The NHR has evolved dramatically over the last year which means there are some data omissions and data quality issues which impact on the interpretation of data on novel treatments. These problems are compounded for new therapies because these NHR pages have only become available during the last year. See section 10 for a list of data issues regarding interpretation of the results.

Crizanlizumab

Background

Crizanlizumab was made available through a managed access agreement (MAA) from early 2022. Part of the agreement mandated documentation of its use on the NHR. These data are reported to NICE. Eligibility criteria for use within the managed access agreement (MAA) are listed in Table 18:

Patient has a confirmed diagnosis of sickle cell disease (SCD), any genotype.
Patient is aged 16 and over
Patient has had 2 or more confirmed vaso-occlusive crises in the previous 12 months, defined as an acute painful episode that requires pain relief medication to manage at home or in hospital.
Application for treatment is made by a Specialised Haemoglobinopathy Team (SHT) having been discussed and approved by the Haemoglobinopathy Coordinating Centres (HCCs) MDT prior to initiation of treatment.

Table 18 - UK Eligibility criteria for crizanlizumab in sickle cell

The terms of the MAA were agreed based on the assumption that:

- All people with SCD would have been offered or had hydroxycarbamide and it has not adequately reduced vaso-occlusive crises, or is inappropriate, before being considered for crizanlizumab AND
- People are unlikely to have crizanlizumab alongside regular blood transfusions to prevent recurrent VOCs.

The NHR crizanlizumab dataset has been developed over the past 12 months, specifically:

(1) crizanlizumab has been added to the medication page.
(2) a separate and new NHR crizanlizumab page has been created.

Given that the NHR pages for crizanlizumab have evolved during 2022, data interpretation should be cautious.

The administrative process for treating a patient with crizanlizumab under the MAA is:

1 patient identified as interested and eligible in clinic
2 patient being agreed at HCC multidisciplinary meeting for crizanlizumab
3 patient having blueteq referral completed
4 patient starting crizanlizumab in day unit
5 patient being recorded on the NHR

There is attrition along this pathway, for both patient and doctor reasons.

Patient Eligibility

Eligibility for crizanlizumab listed in Table 18 includes a criterion for at least two sickle acute pain episodes in the previous 12 months, however these could have been managed in hospital or at home. The only suggestive NHR data is emergency department hospital presentation data collected in clinic as part of the haemoglobinopathy "annual review".

Of 15481 patients with sickle cell, 10887 are over 16 (our data has been grouped into 0-16, 17+).

Of 10887 patients who are over 16, 5678 (52.5%) have had an annual review in the previous year, and only 5411 (49.7%) have had "resource utilisation" data completed as part of annual review. The patients with annual review data completed may not necessarily be representative of the wider sickle cohort: it may be skewed towards patients who have better clinic attendance.

Of 5411 over-16 patients who have available "resource utilisation" data, there was a median 0 emergency presentations for all sickle patients (range 0-167, interquartile range 0-1). 1487 of 5411 over-16 patients (27.5%) have had at least one emergency presentation, and 770 (14.2%) at least two. The distribution of emergency presentations is displayed in Figure 29:

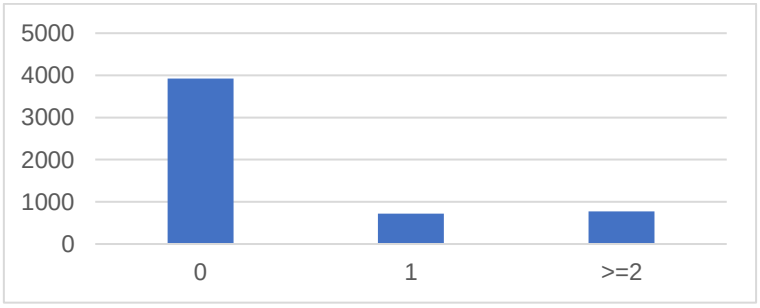


Figure 29 - Distribution of emergency presentations based on NHR data for patients over 16

Of the 770 with at least 2 admissions, 93 patients are on a transfusion programme (and therefore ineligible for crizanlizumab). This translates to 677/5411 (12.5%) of over-16 patients meeting crizanlizumab eligibility criteria (having had at least two emergency presentations but not being on a transfusion programme). Crucially, though, this figure does *not* include (1) pain episodes patients managed at home and therefore could *underestimate* crizanlizumab eligibility (2) other exclusion criteria e.g. poor renal function, and so could *overestimate* crizanlizumab eligibility rates.

Overall crizanlizumab uptake

To calculate numbers, both the "medication" and "crizanlizumab page" datasets were reviewed. In summary:

- 107 patients have had crizanlizumab added to the crizanlizumab page.
- 113 patients have had crizanlizumab added to the medication page.

In total, 123 of 15492 unique individuals with SCD (0.8%) are recorded in some way as starting crizanlizumab on NHR (and 104 of 9993 individuals with HbSS (1.0%)).

Sickle genotype

There are multiple subtypes of sickle cell, with (broadly) different severities and therefore different needs for disease modifying therapy. There are also different frequencies of different subtypes in different ethnic groups. Data on crizanlizumab uptake in different sickle genotypes is displayed in Table 19 and Figure 30. Considering only the HbSS and HbSC patients, there was no statistical difference in crizanlizumab uptake ($p=0.155$ in X^2 testing) although this may be related to small numbers in the crizanlizumab group, especially in the HbSC subgroup.

	NHR wide	Crizanlizumab	p-value
HbSS	9993	104 (1.0%)	0.155
HbSC	4318	14 (0.3%	
HbS beta + thalassaemia	627	3 (0.5%)	
HbS Beta 0 thalassaemia	298	1 (0.3%)	
HbS D Punjab	41	1 (2.4%)	
HbS HPFH	141	0 (0%)	
HbS Lepore	7	0 (0%)	
HbS O Arab	7	0 (0%)	
HbS: variant	23	0 (0%)	
HbSE	37	0 (0%)	
Total	**15492**	**123 (0.8%)**	

Table 19 - Crizanlizumab uptake by sickle genotype

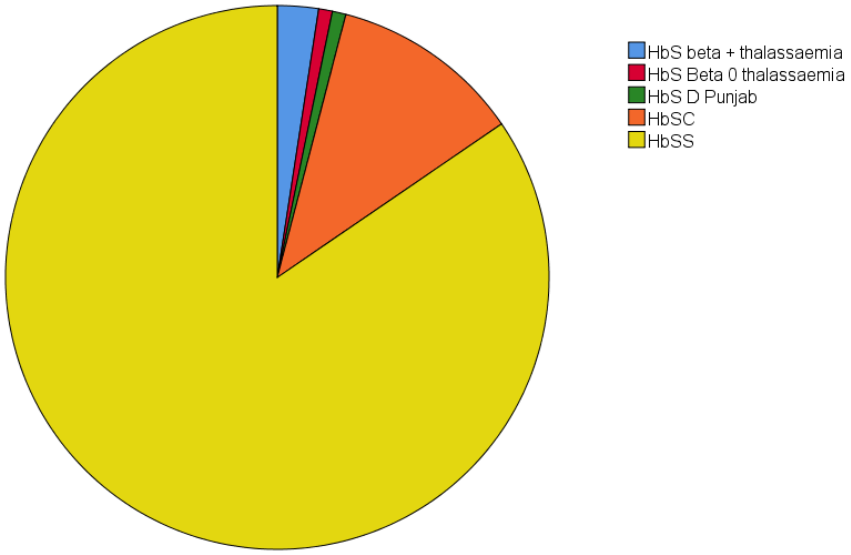


Figure 30 - Distribution of sickle genotypes in crizanlizumab patients

Sex

65 “females” (0.79%), 58 “males” (0.80%) and 0 “other” have been recorded as taking crizanlizumab on the NHR. There was no statistical difference between uptake of crizanlizumab in males and females (p=0.68 in X^2 testing). Data is displayed in Figure 30**Error! Reference source not found.** and Figure 31.

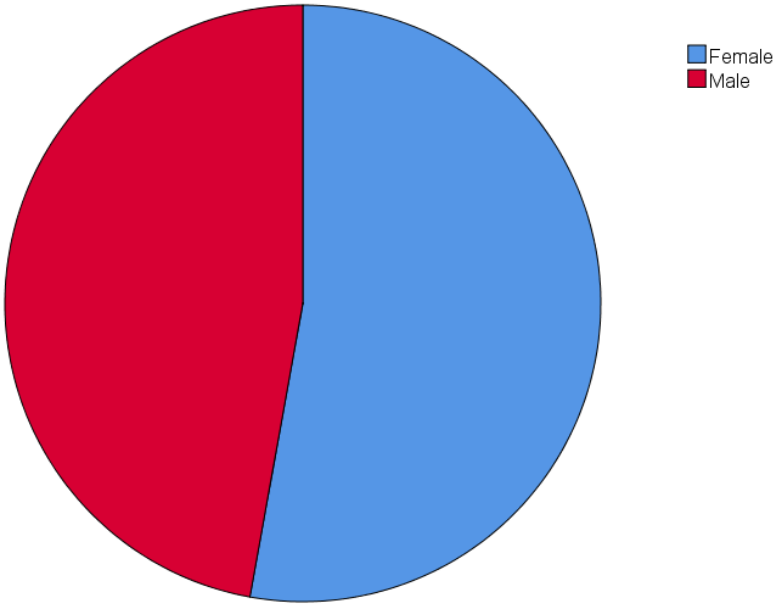


Figure 31 - Distribution of sex in crizanlizumab patients

	NHR wide	Crizanlizumab	p-value
Female	8215	65 (0.79%)	0.68
Male	7272	58 (0.80%)	
Other	5	0 (0%)	
Total	15492	123 (0.8%)	

Table 20 - Crizanlizumab uptake by sex

Age

Crizanlizumab is only available to patients with sickle cell aged 16 and older. We only have age group data for this analysis in the following age bands: <=16, 17-18, 29-29, 30-49, 50+. It is therefore difficult to disentangle the differences for 16 year olds (often under paediatricians) from 17-18 year olds (could be under paediatricians or adult haematologists) and those 19+ (generally under adult haematologists).

Data is displayed in Table 21 and Figure 32.

For those aged 17+ years, there were no significant difference in the take up of crizanlizumab between different age groups (p=0.746 X^2 testing).

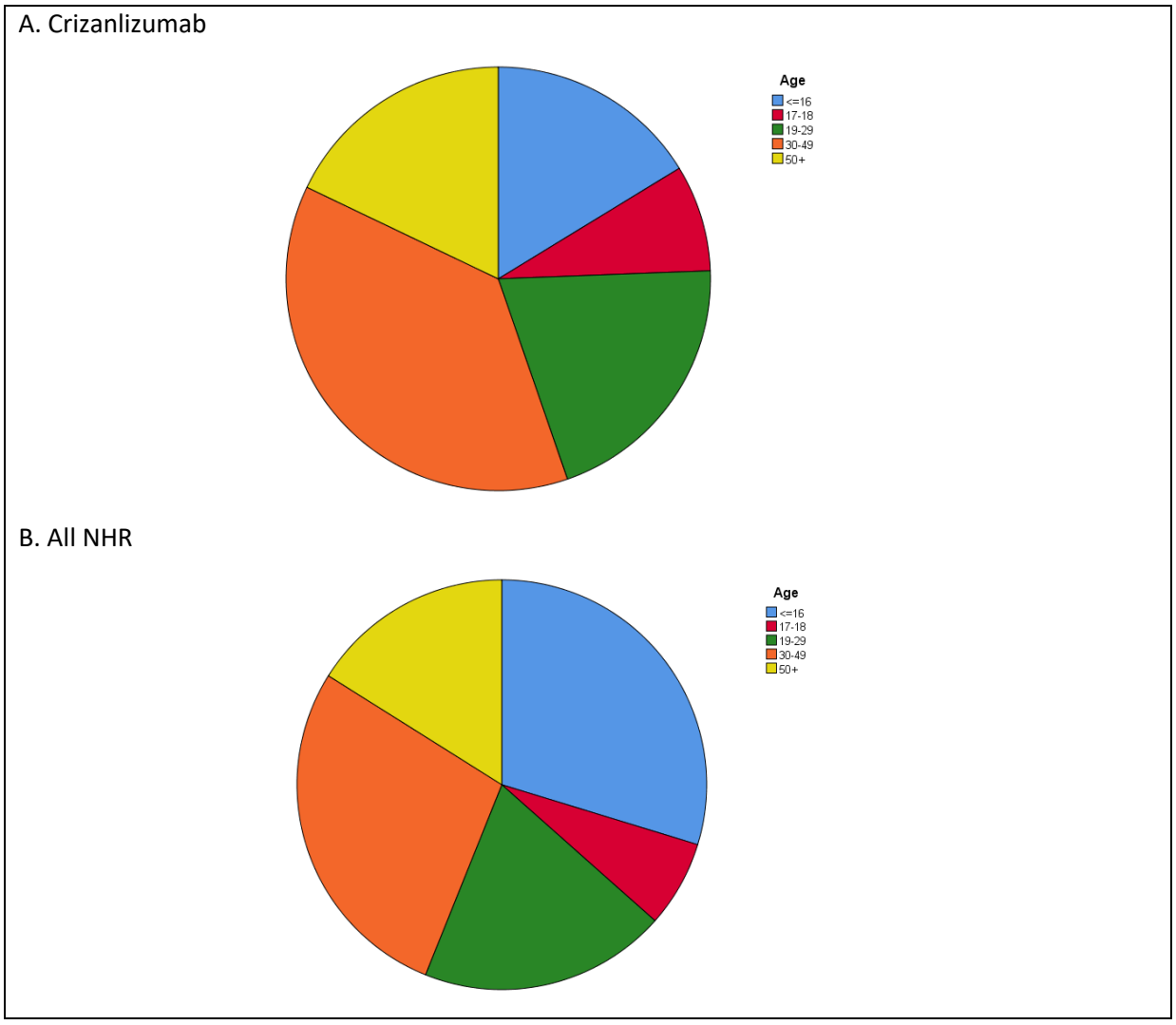


Figure 32 - Distribution of sickle genotypes in crizanlizumab (A) and all-NHR (B) patients

	Crizanlizumab	NHR-wide	p-value
<=16	20 (0.4%)	4605	p=0.746
17-18	10 (0.9%)	1058	
19-29	25 (0.8%)	3025	
30-49	46 (1.1%)	4314	
50+	22 (0.9%)	2490	
Total	**123**	**15492**	

Table 21 - Crizanlizumab uptake by age

8.2.3.4 Ethnicity

Data by broad ethnic group is displayed in Table 22 and Figure 33.

81.8% of sickle patients on the NHR are of "African/African-Caribbean/Black-British" ethnicity, and 81.3% of sickle patients on crizanlizumab have "African/African-Caribbean/Black-British" ethnicity.

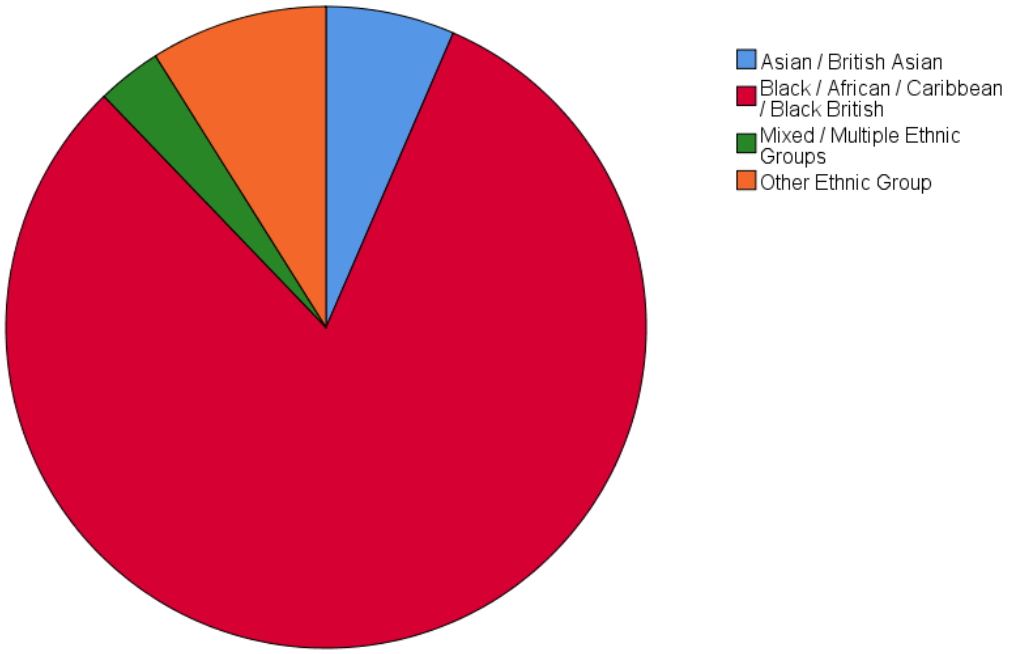


Figure 33 - Distribution of ethnicity in crizanlizumab patients

	NHR-wide	Crizanlizumab
Asian / British Asian	230	8 (3.5%)
Black / African / Caribbean / Black British	12666	100 (0.8%)
Mixed / Multiple Ethnic Groups	438	4 (0.9%)
Other Ethnic Group	2076	11 (0.5%)
White	82	0 (0%)
Total	**15492**	**123**

Table 22 - Crizanlizumab uptake by ethnicity

8.2.3.5 Treating Centre

Patient numbers in the 10 sickle HCC regions vary enormously, from 223 patients in the "South West of England" region, to 3481 patients in "South East London and the South East" region.

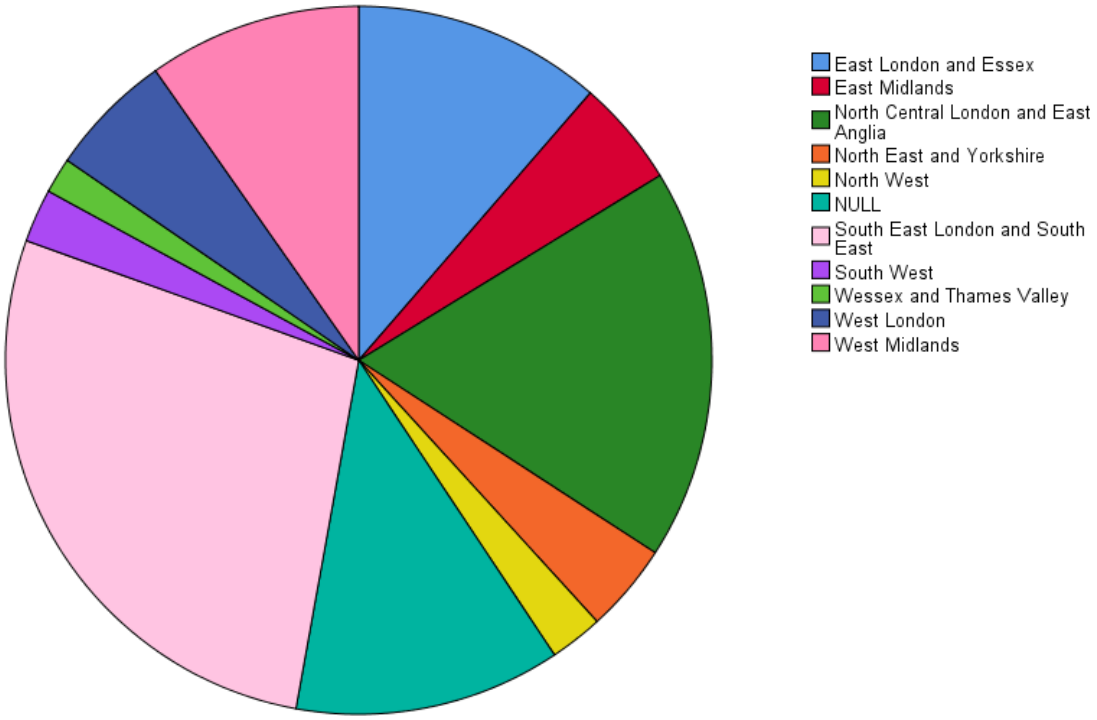
Interpretation of HCC data needs to be cautious: there are some pitfalls in the allocation of patients to a HCC: 1950 patients with sickle cell are *not* allocated a HCC, and 23 patients were allocated a *thalassaemia HCC* (rather than a sickle HCC).

Relative uptake varied between HCCs from 0.4% to 1.3%. Absolute uptake varied between HCCs from 2 to 34 patients. However, there was no statistical difference between take-up in different HCCs (X^2 p=0.322), probably due to small numbers.

	NHR-wide	Crizanlizumab
East London and Essex	2083	14 (0.7%)
East Midlands	667	6 (0.9%)
North Central London and East Anglia	1973	22 (1.1%)
North East and Yorkshire	784	5 (0.6%)
North West	731	3 (0.4%)
NULL	1950	15 (0.8%)
South East London and South East	3481	34 (1.0%)
South West	223	3 (1.3%)
Wessex and Thames Valley	562	2 (0.4%)
West London	1663	7 (0.4%)
West Midlands	1352	12 (0.9%)
Total	**15469**	**123 (0.8%)**

Table 23 - Crizanlizumab uptake by HCC

A. Crizanlizumab



B. All NHR

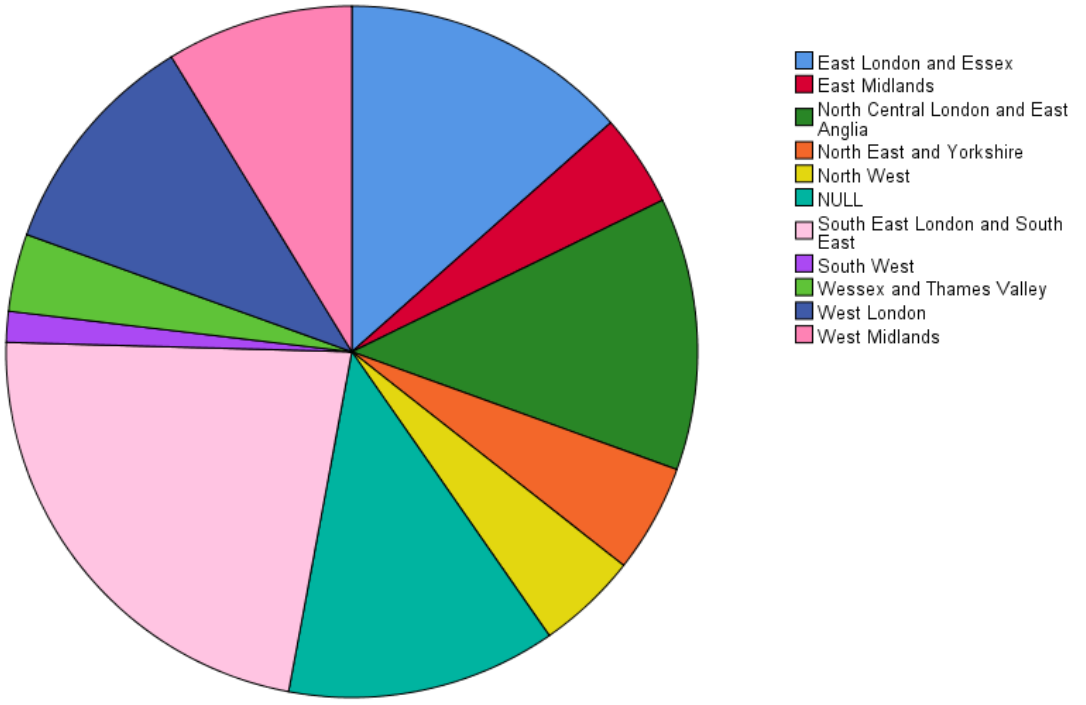


Figure 34 - Distribution of treating centres (HCCs) in (A) crizanlizumab and all-NHR (B) patients

Disease modifying therapies

Hydroxycarbamide

Hydroxycarbamide has been used as a disease modifying therapy in sickle cell for about 30 years, with the eligibility criteria widening as time has passed and long-term data has shown its efficacy and low side effect profile. The most recent UK guidelines on hydroxycarbamide in SCD (Qureshi et al BJH 2018) suggest it be discussed and offered to all children/parents/ adults with HbSS/Sβ^0 thalassaemia, with certain groups encouraged more strongly, including those with HbSS/Sβ^0 who have 3 or more sickle cell-associated moderate to severe pain crisis in a 12-month period, or who have sickle cell pain that interferes with daily activities and quality of life, or have a history of severe and/or recurrent ACS. In those with non-HbSS disease, Hydroxycarbamide is recommended for those who have recurrent acute pain, acute chest syndrome or episodes of hospitalisation.

The terms of the crizanlizumab MAA were agreed based on the assumption that patients would have been offered hydroxycarbamide but that it has not adequately reduced acute pain episodes, else hydroxycarbamide was deemed inappropriate before being considered for crizanlizumab.

Hydroxycarbamide data is stored in two places on the NHR:

- in the annual review when other questions are asked about access to hydroxycarbamide,
- in the medication section.

There are lots of data omissions in both these sections, and discrepancies between the two sections, which limits interpretation, but for the purposes of this analysis we have assumed that a patient is on hydroxycarbamide if either were completed as the patient being on hydroxycarbamide. Table 24 shows the patients taking both hydroxyurea and crizanlizumab.

	Hydroxycarbamide Use
Yes	62 (50.4%)
No	22 (17.9%)
No annual review data	35 (28.5%)
Unknown	4 (3.3%)
Total	123 (100%)

Table 24 - Hydroxycarbamide use in crizanlizumab patients

This means, in the 84 cases where known, 62/84 (73.8%) of patients on crizanlizumab are documented as on hydroxycarbamide.

Transfusions

The terms of the crizanlizumab managed access agreement were based on the assumption that patients were unlikely to have crizanlizumab alongside regular blood transfusions. On the NHR, there are lots of data omissions on transfusion status: we only have data on transfusions for 40 crizanlizumab patients. Currently, no patients are documented as being on both crizanlizumab and regular blood transfusions.

	Number
No	40 (32.5%)
No data	77 (62.6%)
Unknown	6 (4.9%)
Total	123 (100%)

Table 25 - Crizanlizumab Transfusions

Voxelotor

One patient is documented as on crizanlizumab and voxelotor. In the national protocol, dual therapy with both these therapies was to be agreed only in exceptional circumstances.

Resource utilisation

The section on eligibility for crizanlizumab describes resource utilisation data capture in the haemoglobinopathy review and documented on EPR. Interpreting the resource utilisation data for the crizanlizumab cohort requires some considerations because of how the data is collected:

- It relates to resource utilisation in the *previous* financial year. This could include either 2020-2021 or 2021-2022 and therefore doesn't necessarily represent the 12 months immediately prior to a patient starting on crizanlizumab (there could either be a gap between data entry of resource utilisation data and crizanlizumab data, else there could be an overlap with crizanlizumab starting). Since most patients do not have a start date for crizanlizumab recorded we cannot use this information to determine whether the resource utilisation data precedes initiation of therapy. However, we would expect in most cases that this to be, on average, data in the year roughly preceding start crizanlizumab.
- As previously discussed, this is hospital resource utilisation data, not patient-reported pain outcomes unlike the crizanlizumab eligibility criteria (which includes any pain events, including those managed at home).

For the crizanlizumab patient cohort, 88 of 123 patients had valid resource utilisation data including number of emergency presentations, number of emergency hospital admissions and number of bed days recorded for the previous financial year, reviewed below.

Acute, emergency presentations:

The number of emergency presentations (either to A&E or to a day unit facility) is recorded, whether or not admitted, in the most recent annual review for the previous financial year.

The median number of emergency presentations for the 88 patients with data was 1 (range 0-159, IQR 0-3), see Figure 35.

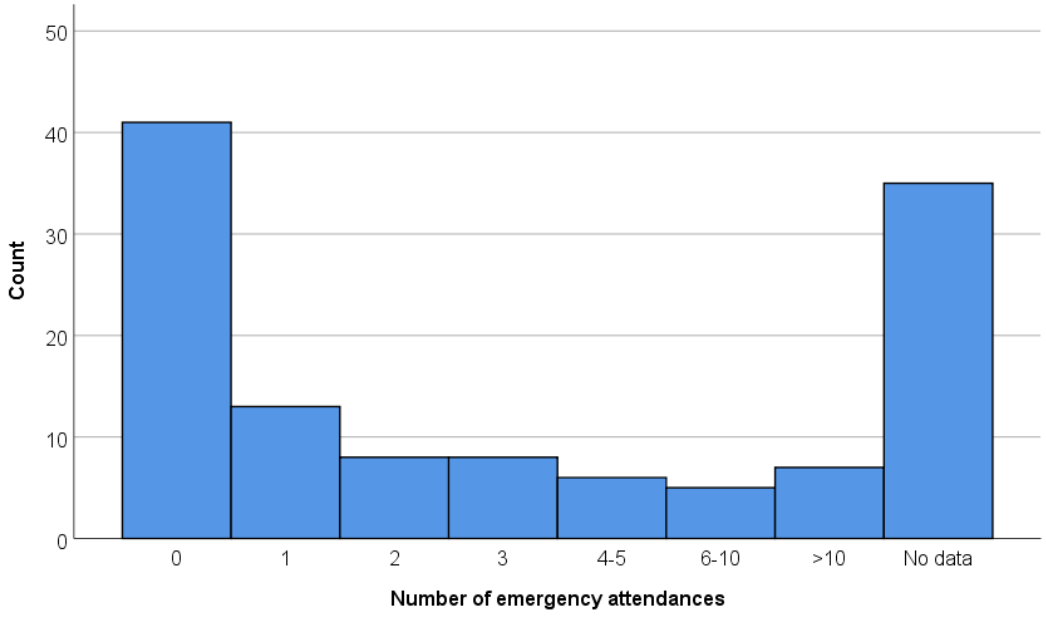


Figure 35 - Number of emergency attendances for the crizanlizumab cohort

Emergency hospital admissions

The median number of hospital admissions for the 88 patients with data was 1 (range 0-100, IQR 0-3), see Figure 36.

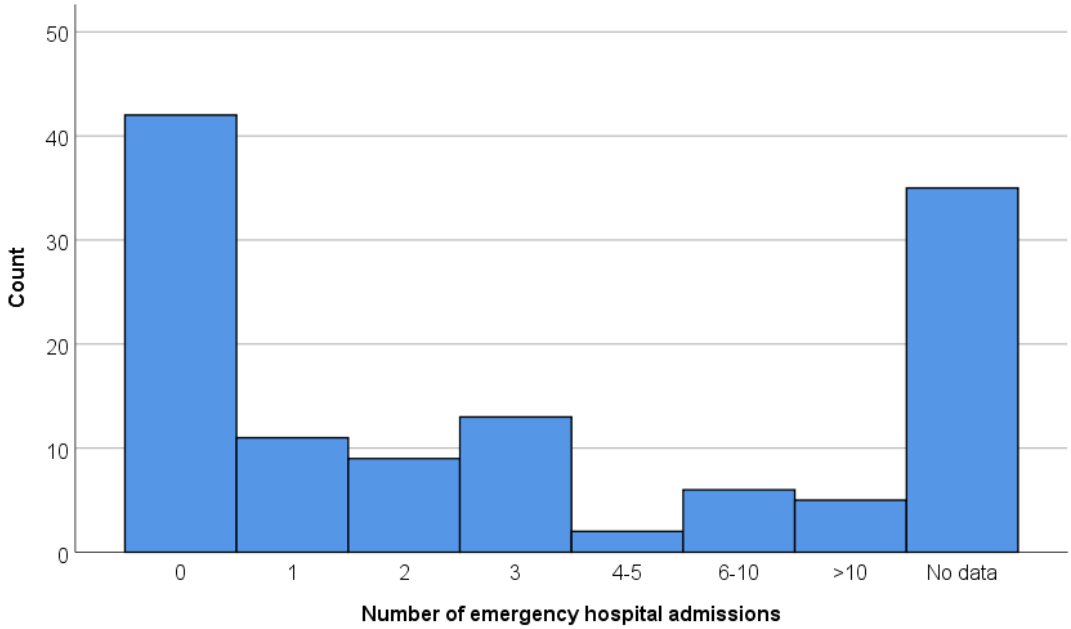


Figure 36 - Number of emergency hospital admissions for the crizanlizumab cohort

Inpatient bed days

The median number of inpatient hospital bed days was 1.5 (range 0-291, IQR 0.9.75), see Figure 37.

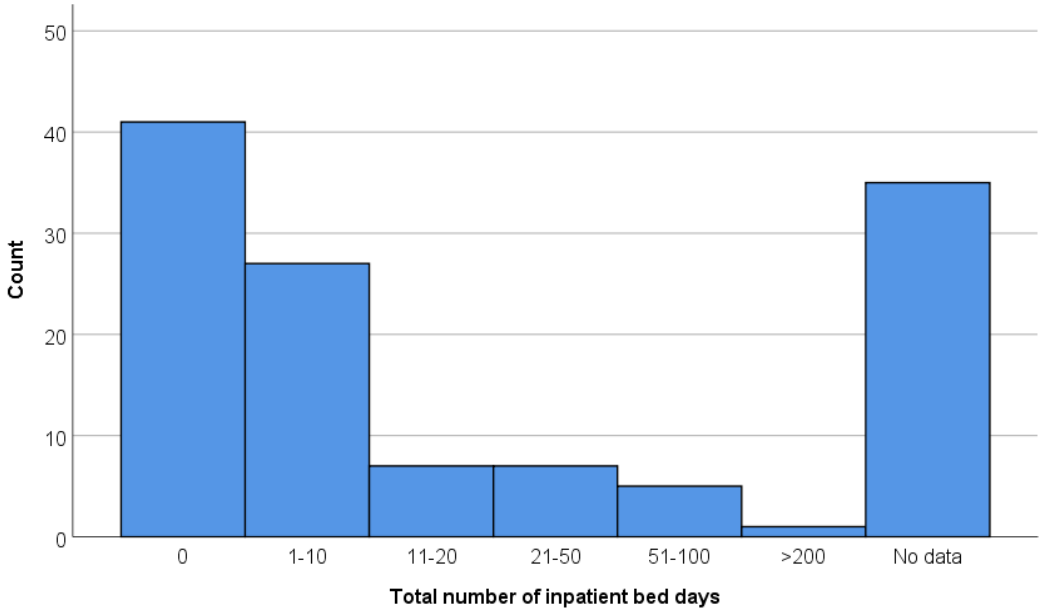


Figure 37 - Number of inpatient bed days for the crizanlizumab cohort

Mortality

No patients have started crizanlizumab and then since been recorded as deceased.

Who has stopped crizanlizumab?

Of 123 patients who have started crizanlizumab *and* in whom we have information on the extra "crizanlizumab" page, 19 (5.4%) have since stopped, with reasons for stopping documented in Table 26.

Reason	N (%)
Increase in pain crises	4 (21%)
Moved house	2 (11%)
No effect	1 (5%)
Non-compliant	1 (5%)
Other	2 (11%)
Not known	9 (47%)

Table 26 - Reasons for discontinuing crizanlizumab documented on NHR

Is being crizanlizumab being offered to patients?

A new feature of the NHR annual review includes a section assessing crizanlizumab availability (in a manner similar to the hydroxycarbamide uptake questions). However, 14583/15492 patients have not had this answered making the data too incomplete to report on usefully.

Voxelotor

Background

Voxelotor was initially available through a commercially funded access scheme from summer 2021, then an NHS Early Access to Medicines Scheme (EAMS) from January 2022 for "the treatment of haemolytic anaemia in adults and paediatric patients 12 years of age and older with sickle cell disease (SCD)". The EAMS scheme closed in September 2022 so since then patients have not been able to start voxelotor. The scheme did *not* mandate NHR documentation, but NHR users can choose voxelotor in the "medication" section. The EAMS eligibility criteria for voxelotor are listed in Table 27:

EAMS eligibility criteria for voxelotor

Inclusion Criteria:

Patients who meet all the following criteria will be eligible for inclusion in this programme:

12 years of age and older. Willing and able to provide written informed consent (age ≥ 16 years) or legal representative consent (age 12 - 15 years), as required per institution and local regulations

2. Documented diagnosis of SCD (all genotypes)

3. Evidence of haemolytic anaemia associated with SCD (Hb < 105 g/L) and one or more of the following

3a: Haemolytic phenotype (i.e., leg ulcers, priapism, pulmonary hypertension) who are untransfusable or very difficult to transfuse due to previous transfusion reactions or significant alloimmunisation or not consenting to regular blood transfusions

3b. Poor response (on maximum tolerated dose) or toxicity to hydroxycarbamide (HC) or not consenting to HC

3c. Symptomatic of anaemia (i.e., hypoxia, fatigue, worsening cardiac function, poor performance status) who cannot be transfused as in 3a

4. If patients taking HC, the dose of HC (mg/kg) must be stable for at least 3 months prior to participation in EAMS

Exclusion Criteria:

Patients who meet any of the following criteria will not be eligible for inclusion in this programme:

1. History of hypersensitivity reaction to voxelotor or excipients

2. Pregnancy or breastfeeding

3. Hepatic dysfunction characterised by alanine aminotransferase > 4 times upper limit of normal

4. Severe renal dysfunction (estimated glomerular filtration rate at the Screening visit; < 30 mL/min/1.73m^2 or on dialysis

5Haemoglobin ≥105 g/l

6. Participated in another clinical trial of an investigational agent (within 30 days of participation in EAMS)

7. Medical, psychological, or behavioural conditions, which, in the opinion of the treating physician, makes patient unsuitable to participate in this programme

8. Significant drug interactions with voxelotor.

9. Active malignancies

10. On transfusion programme only for stroke prevention

Table 27 - EAMS eligibility criteria for voxelotor

eligibility for voxelotor

Unfortunately, since the NHR does not mandate documentation of some of the key eligibility criteria (notably Hb levels, "transfusability", response to hydroxycarbamide, anaemia symptoms), it is not possible to comment on voxelotor eligibility based on NHR data.

Patients initiated on voxelotor

To calculate numbers, the "medication" NHR page was reviewed. 32 of 15492 (0.2%) unique individuals with SCD are documented as starting voxelotor on the NHR. The demographics of these 32 patients are listed below:

Sickle genotype

All patients on voxelotor have HbSS disease (so 0.3% of HbSS patients have started voxelotor).

Sex

17 females and 15 males.

Age

Age distribution is summarised below, with too low numbers to analyse statistically, but a possible trend to increasing use with age.

	NHR-wide	Voxelotor
<=16	4605	2 (0.04%)
17-18	1058	0 (0%)
19-29	3025	8 (0.3%)
30-49	4314	13 (0.3%)
50+	2490	9 (0.4%)
Total	**15492**	**32 (100%)**

Table 28 - Voxelotor Age Distribution

Ethnicity

31 patients were in the broad "Black / African / Caribbean / Black British" ethnic group, and one was of "Mixed / Multiple Ethnic Groups".

Ethnic groups	NHR-wide	Voxelotor
Asian / British Asian	230	0 (0%)
Black / African / Caribbean / Black British	12666	31 (0.2%)
Mixed / Multiple Ethnic Groups	438	1 (0.2%)
Other Ethnic Group	2076	0 (0%)
White	82	0 (0%)
Total	15492	32 (0.2%)

Table 29 - Voxelotor by Ethnic Origin

Treating centre/HCC

TCC/HCC	NHR-wide	Voxelotor
East London and Essex	2083	6 (0.3%)
East Midlands	667	3 (0.4%)
North Central London and East Anglia	1973	6 (0.3%)
North East and Yorkshire	784	0 (0%)
North West	731	0 (0%)
NULL	1950	1 (0.05%)
South East London and South East	3481	11 (0.3%)
South West	223	1 (0.4%)
Wessex and Thames Valley	562	3 (0.5%)
West London	1663	0 (0%)
West Midlands	1352	1 (0.07%)
Total	**15469**	**32 (100%)**

Table 30 - Voxelotor by HCC

Disease modifying therapy

Hydroxycarbamide

19/32 patients are on concomitant hydroxycarbamide (as recorded in *either* the medications or annual review sections). The voxelotor eligibility criteria requires (1) a poor response to hydroxycarbamide (on maximum tolerated dose) or (2) toxicity to hydroxycarbamide or (3) not consenting to hydroxycarbamide.

However, it must be noted that the hydroxycarbamide information may or may not be updated when the voxelotor data was added making cross-checking of these data sources potentially unreliable.

Transfusions

Two patients are recorded as currently on transfusions based on annual review data.

As with other data entry on the NHR on different pages, there may be a discrepancy between the transfusion data being entered (as part of annual review) and the voxelotor data being entered e.g. if a patient stopped a transfusion programme to start voxelotor, the user might have recorded the voxelotor, but not that the transfusions have stopped.

Mortality

One death was recorded in the patients taking voxelotor.

Bone marrow transplant

Background

Bone marrow transplant / haematopoietic stem cell transplant (HSCT) using sibling donors has long been available for children with sickle cell meeting the eligibility criteria. In 2020, sibling HSCT became a funded option for adults with severe sickle cell who met the eligibility criteria in Table 31. There was a delay in starting the adult transplant programme due to the COVID-19 pandemic, but patients are now being transplanted across the country.

1. Eligibility: does patient at least meet ONE of the following criteria:

- Clinically significant neurologic vascular event or deficit lasting > 24 hrs and confirmed radiologically.
- History of >2 acute chest syndrome despite optimum treatment with hydroxycarbamide (HC) or transfusion therapy.
- History of >3 severe pain crises or other acute complications per year despite the institution of supportive care measures (optimum treatment with HC or transfusion therapy). Other acute complications would include acute hepatopathy or splenic sequestration or acute priapism.
- Administration of regular transfusion therapy, either by simple transfusion or exchange transfusion with the aim to prevent severe sickle complications by maintaining a low HbS %.
- Patients assessed as requiring transfusion but with red cell alloantibodies / very rare blood type, rendering it difficult to continue or commence chronic transfusion.
- Patients requiring HC/transfusion for treatment of SCD complications who cannot tolerate either therapy due to significant adverse reactions
- Established and related end organ damage relating to sickle cell disease, including but not limited to progressive sickle neurovasculopathy and hepatopathy.

2. Eligibility: does patient meet ALL of the following criteria:

- Karnofsky score > 60
- Cardiac function: LVEF >45% or shortening fraction >25%.
- Lung Function: FEV1, FVC and DLCO >50%
- Renal function: EDTA GFR > 40 ml/m2/1.73m2
- At least one first-degree relative willing to act as a donor and confirmed as fully matched sibling donor.
- Agrees to refer case to NHP for consideration of allo transplant

Table 31 - Eligibility criteria for bone marrow transplant

Eligibility for bone marrow transplant

Using currently available NHR data, it is not possible to discern patients who meet the inclusion and exclusion criteria for bone marrow transplant. Of note, 563 of patients (3.6%) are documented as being on a transfusion programme (according to the annual review record) which is one inclusion criterion.

There is currently no place to store information about a patient having had a haematopoietic stem cell transplant (HSCT, also known as a bone marrow transplant), nor further clinical data about the transplant e.g. date, outcome, donor source, complications.

However, a new question has been added recently to the NHR annual review page: "Was referred for HSCT or Gene Therapy?", see Table 32:

Referred	Number
No	1406 (9.1%)
Yes	20 (0.1%)
Unknown	651 (4.2%)
NULL	13415 (86.6%)
Total	**15492 (100%)**

Table 32 - Has the patient been referred for HSCT or gene therapy?

Given the significant data omissions (only 9.2% have had this completed), it is unclear how to interpret this data, but, of the 1426 individuals where there is a definite No or Yes answer, 20 patients (1.4%) have been referred for haematopoietic stem cell transplant.

Data Considerations

There are specific NHR data issues which limit interpretation of the data in this chapter including:

- Missing data (e.g. recording starting and stopping crizanlizumab but also with basic demographic information). Challenges with recording data - especially outside of the annual review (which includes starting crizanlizumab/voxelotor).
- Evolving NHR data collection / pages over the last year - especially for crizanlizumab.
- Note that the resource health utilisation data we collect in the NHR in the annual review, is not the same as the eligibility criteria (2+ pain crisis per year, *irrespective of whether presented acutely to hospital*).
- Data cut given by MDSAS: 3 March 2023. We have given all data accrued so far but future reports will probably be best to consider fixed financial years, once annual reviews have been completed.
- Crizanlizumab can be recorded in two places on NHR (medications and the separate crizanlizumab page) which results in discrepancies and missing data.

Chapter 9: Research in the NHR

Author: Kate Gardner

Research to benefit current and future patients is an important objective of the NHR. Our focus is that all research should be patient-centred and for patient benefit. We have patient representatives who sit on our Data group to guide our practice.

Data collected on the NHR could be used in a variety of ways.

Ensuring Current Treatment Standards

Anonymised information is used routinely by all hospitals to help ensure that current treatment standards are being met. (For example, how many patients who could have hydroxycarbamide are offered the chance to have it). This is called audit. Only by comparing results across the country can we be sure that we are offering the best care we can, and learn what is not being done well and what needs to improve. This is an important way that hospitals can improve care and is done routinely for all types of illnesses across the NHS.

Anonymised information could also be used by the NHS to help plan resources (do we need more nurses in that town?).

Generalised Information Queries

Generalised anonymised information might be used in research projects (this is a kind of research) perhaps as a comparison to other general information available within the NHS - for example, how many patients with sickle cell eye problems are there in the NHS in England? This sort of information does not require specific consent from each patient but does need to be scrutinised by the data committee to ensure that the data being released is appropriate.

Specific Research programmes

Information could be used for specific research programmes. This sort of information requires consent from the patients involved. We have not had any projects looking at this sort of data yet, but any requests for data like this would have to be approved by our committee including the patient representatives before researchers were even allowed to approach patients for consent.

Analysing use of Medications and Blood

Information about medications or blood use could be used by the NHS, drug companies or the blood transfusion service to help understand where blood or medicines are being used and how to make sure that we are getting best use of these resources. Information on certain drugs is already collected this way by the NHS, to make sure that we can get the best value for money and make sure that everyone who should be able to have a drug has the opportunity to access it.

How to make a request for data:

If you have a research project or other project and would like to use information from the NHR, there is an application process.

1) You should have a fully worked up project proposal.
2) Go to the National Haemoglobinopathy Register home page (https://nhr.mdsas.com/). There are several icons available. The NHR data field list icon should allow you to see what information might be available. For example, we collect information about haemoglobinopathy diagnosis, but not about whether other family members are affected, so if you wanted that information you could not get it from the NHR.
3) The Data Request Process icon will take you to the data request forms and also an email address for further information. We will scrutinise all requests to determine whether we can release the information and whether specific consent is required. In general, patient consent is not required for audit (i.e. checking if what you are currently doing meets standards) but is required for research (i.e. discovering new information). The data committee meets once a month and if the request is approved the data should be released within 3 months of request.

Data requests - 2021/2022

1) How many patients with sickle cell disease in the NHR have retinopathy? (released without explicit consent as fully anonymised).
2) How many deaths occurred in patients with sickle cell disease in the NHR during the COVID pandemic? (released without explicit consent as fully anonymised - and obviously we cannot ask for consent from patients who have died).

Chapter 10: Data quality considerations

Authors: Kate Gardner

Background to data quality

This is the first report of the compulsory NHR, and as such provides an initial picture of the demographics, geography and severity of disease for people living with inherited anaemias in England. However, data challenges, both known and unknown, have been exposed in the writing of this report. Some of these are issues related to the evolving registry over the year and which will likely settle, while others reflect wider concerns about data completeness and data quality.

Data interpretation must therefore be made recognising these data concerns, which reduces the certainty of the conclusions and highlights areas for improvement. Some of the data challenges have been highlighted in the individual chapters where there are specific issues, but here we will collate generic data challenges and identify work to be done.

The current system for data entry is managed in regions by a HCC data manager (a non-clinical administrator), but there is currently no formal method for data monitoring / data assurance. By investing in enough time for the data entry and data assurance, data quality in the NHR would be more dependable.

Data challenges

- Data completeness: no assessment to see if all cases present (e.g. non-NHR estimations of UK RIA prevalence suggest NHR RIA numbers are very low),
- Basic demographics - missing: diagnosis / sex. Can these be mandatory fields?
- Duplication (triplication/quadruplication/…) of cases on NHR. This is allowed because it is not mandatory to have a legitimate NHS number (which is a necessary rule for those who don't have an NHS number/those who don't want records uploaded). For new cases added, can further checks be made if names are very similar (one digit out) or same DOB to an existing record? Need to review existing duplicates - can these be identified centrally to prompt local clinician to review?
- Allocation of patients to a HCC is a major issue and interferes with governance and management of patients by region. It also impairs data analysis as does not allow comparisons between HCCs: 1950 patients with sickle cell are *not* allocated a HCC, and 23 patients were erroneously allocated a *thalassaemia* rather than a sickle HCC. One cause of this is a patient living in two places (e.g. university students) and therefore being under two HCCs - solution might require cross-HCC harmonisation.
- Comprehensive clinical information is not entered for many centres e.g. full medical history, transfusion history, red cell antibodies, medications including chelation.
- Some evidence that incorrect diagnosis has been added for patients with RIAs (i.e. incongruent diagnosis with clinical history and medications).
- In the case of rare inherited anaemias, the number of patients on the NHR is far lower than that predicted by fairly well-established estimates of incidence for these conditions. Need to harmonise how to categorise/diagnose each RIA.
- Annual review is focused on sickle cell rather than thalassaemia or RIA so many fields not relevant in non sickle conditions.
- There are errors in resource utilisation numbers on the annual review page (four have negative admissions e.g. "-4" admissions). Can this be solved with a query on data entry i.e. number check to make sure an integer 0 or greater? Could data queries be added to other variables?

- Timing of data entry might differ between centres: centres will have different process for entering data - some might enter it in real time and other centres do it in batches e.g. focusing on data entry at end of the financial year (along with completing the annual reviews). For future annual report analysis, it might be better to have a 1 April data cut each year to align with the existing annual process.
- There are examples of data discrepancies in data which is collected on different pages and resulting in conflicting data:
    - Hydroxycarbamide appears in *medications* and *AR data*. This could reflect timing differences in terms of data entry (the patient has recently started/stopped and only one page was updated) else could be data errors.
    - Crizanlizumab use appears on *Crizanlizumab page* and in *medications*.
    - Can these issues be resolved by asking user to update other page once one page updated?
    - There might need to be some nuance to this as patients may stop one treatment and start another (e.g. start transfusions and stop hydroxycarbamide): so the user might need to be asked to update all treatments if one is started or stopped.
- Currently there is no place to record that a patient has had a HSCT / store further information about it (e.g. date, conditioning, complications, outcome, chimerism). This is crucial for lots of future data analysis in order to censor data from time of transplant.
- In the sickle cell cohort, 81.8% of sickle patients on the NHR are of "African/African-Caribbean/Black-British" ethnicity - this seems low. Is there any way to check this?
- There are challenges with recording data - especially outside of the annual review. This specifically includes adverse events, death and novel therapies which are recorded separately on the chart. These events may be less well recorded than an annual review as they will be done in an ad hoc manner, possibly in batches in some HCCs.
- There has been evolving NHR pages over the last year that the annual review is reporting on, including the new crizanlizumab pages, and new data fields in the annual review. This makes it particularly difficult to interpret these datasets.

Work to be Done

Correct existing data issues

- Basic demographics - centrally identify missing demographic data and get local clinicians to allocate: diagnosis / sex.
- Identify duplication (triplication/quadruplication/…) of cases. Can these be identified centrally to prompt local clinician(s) to review?
- There is an existing work stream to allocate *all* patients to a HCC.
- Admissions: negative numbers. Identify and inform local clinician of errors.
- Consider having a specified data cut each year after the start of next financial year (e.g. June) to align with the existing annual process.
- Correct data discrepancies where the same data is collected on different pages:
    - Identify where there are discrepancies and inform local providers:
    - Hydroxycarbamide use (appears in *medications* and *AR data)*.
    - Crizanlizumab use (*Crizanlizumab page* and in *medications)*.
- When new pages and data fields are entered, will need to be explicit in future annual reports about developments to enable cautious data interpretation.

Future Developments

- Have more checks when new patients are registered to ensure they are not a duplication. Can further checks be made if names are very similar (e.g. one letter out) or they have the same DOB as an existing record?
- Have basic numeric checks where they can be made e.g. integer, not <0, in appropriate range (e.g. height and weight).
- Provide resource to enable comprehensive clinical data collection e.g. full medical history, transfusion history, red cell antibodies, medications including chelation.
- Consider separate annual review proforma for thalassaemia and RIA.
- Where the same/similar data is collected on different pages, ensure when one page is updated that the user is directed to change the other page.
    - If Hydroxycarbamide is changed in *medications* or *AR data*, then then other page is updated.
    - If Crizanlizumab is updated on the *Crizanlizumab page* or in *medications*, then then other page is updated.
    - When one treatment is started or stopped, then the user is prompted to consider other treatments changes.
- Add data fields to record that a patient has had a HSCT / store further information about it (e.g. date, conditioning, complications, outcome, chimerism).
- Add HSCT details (e.g. date, conditioning, complications, outcome, chimerism).
- Consider bulk data uploads / exports as a means to improve data quality. This could synchronise with / error check against locally held data, whilst reducing the burden of manual re-keying data.

Appendices

Data Collection Form

Instrumentation, facilities & reporting		Submission date:	
HCC:		Completed by:	
HCC TCD Regional Lead:			
HOSPITAL (please use separate sheet for each hospital)			
1	Local policy for infection control	Date reviewed:	
2	TCD Instrumentation service record	Date performed:	
3	Electrical check	Date performed:	
4	TCD system QA	Date performed:	
5	TCD MODE	Imaging ☐ Non-imaging ☐ Both ☐	
6	Patient information sheet available	Tick one	Y ☐ N☐
7	TCD standard operating protocol used	National ☐ Local ☐ None☐	
8	STOP classification	Please provide thresholds (cm/s) used:	
		Normal	
		Conditional	
		Abnormal	
		Please tick vessels included:	
		MCA ☐	
		ACA ☐	
		PCA ☐	
		TICA ☐	
		OTHER ☐	
9	Reporting sheet template used	National ☐ Local ☐ None ☐	
10	Surveillance intervals (months)	Normal	
		Conditional	
		Abnormal	

Please return this form to *soundrie.padayachee@gstt.nhs.uk* on behalf of the National Haemoglobinopathy Panel.

TCD Practitioners & Surveillance Programme		Reporting period:
HCC:		Completed by:
HCC Lead:		
HCC TCD Regional Lead:		
Hospitals supported in HCC:		
1	Number of TCD practitioners in HCC	N =
2	Number performing < 20 scans /year	N =
3	Number of practitioners on Forum register	N =
4	TCD Instrumentation *(tick one box)*	☐ Imaging ☐ Non-imaging ☐ Both
5	Total on surveillance *(exclude transfusion)*	N =
6	STOP normal	N =
7	STOP conditional	N =
8	STOP abnormal	N =
9	STOP non-diagnostic	N =
10	STOP asymmetry	N =
11	STOP low velocity	N =
12	STOP inadequate	N =
13	Surveillance compliance (%)	
14	Lost to follow-up (DNA, moved)	N =
13	No. on transfusion / hydroxcarbamide	N =

TCD Screening for Children with Sickle Cell Disease: NHR TCD data entry

NAME:	SCAN DATE:
NHS NUMBER:	HCC:
DOB:	HOSPITAL:
GENDER:	CONSULTANT:
GENOTYPE: SS ☐ βthal ☐ SC ☐	TCD PRACTITIONER:

TREATMENTS:	Hydroxyurea ☐ Transfusion ☐ Hydroxyurea & Transfusion ☒ Not known ☒

TCD VELOCITY DATA AND STOP CLASSIFICATION				
	RIGHT		LEFT	
	TAMMV	Depth	TAMMV	Depth
MCA				
ACA				
PCA				
TICA				
BIFURCATION				
BASILAR				
eICA (PSV)				

SCAN QUALITY	GOOD ☐ AVERAGE ☐ POOR ☐
UNOBTAINABLE REASON:	PATIENT COMPLIANCE ☐ ATTENUATION ☐
MCA TRACEABILITY ☐ (Entire MCA traceable by spectral Doppler or colour flow)	

STOP	ABNORMAL ☐ LOW VELOCITY ☐ INADEQUATE ☐ DNA ☐ CONDITIONAL ☐ ASYMMETRY ☐ UNOBTAINABLE ☐ NONE ☐ NORMAL ☐

FOLLOW-UP DUE:	

Shaded areas optional