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DiSC-ELEVEN: Digital Sickle Cell Disease Data Platform and Wearable Device Implementation

PROTOCOL

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1. Background

1.1 Sickle Cell Disease

Sickle Cell Disease (SCD) comprises a group of red blood cell disorders and is the most common hereditary disease in the world, but rare in many developed countries. In the UK, SCD shows the greatest prevalence in people of African and Caribbean origin, and also affects people from Asian, Middle Eastern and Eastern Mediterranean descent.

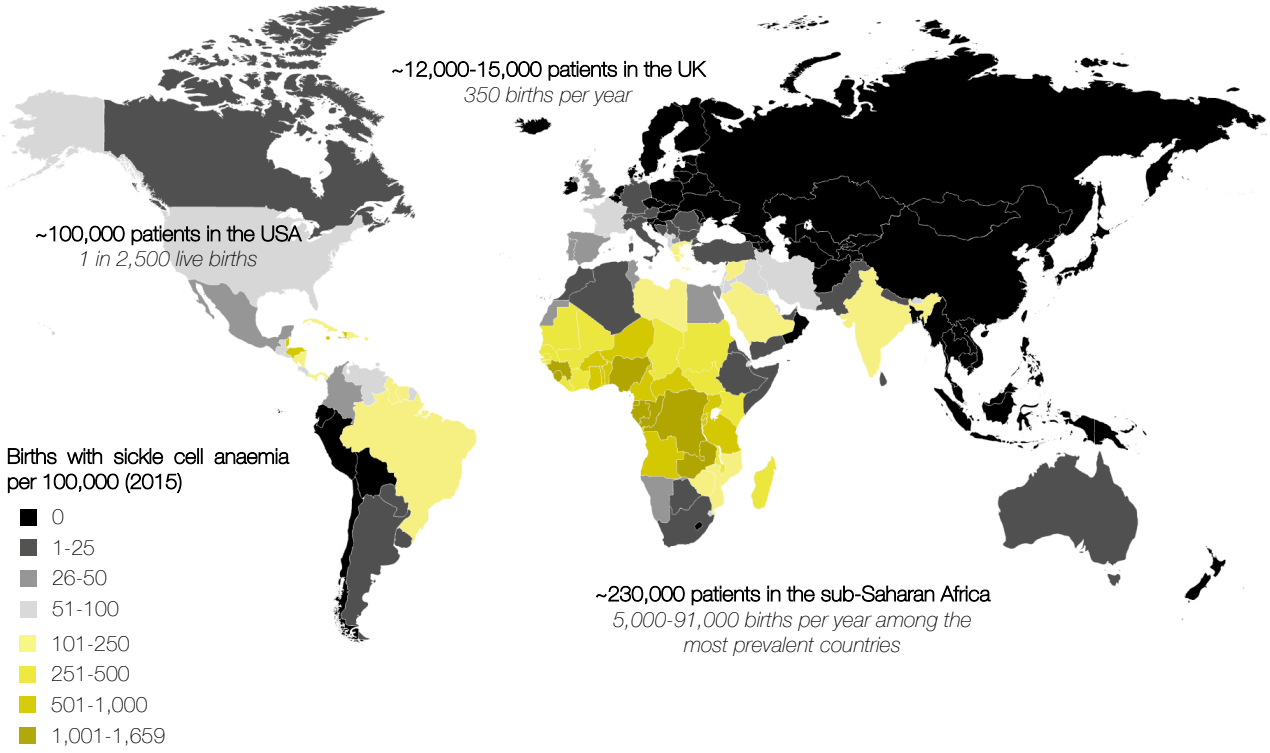
SCD often leads to a chronic, life-long and debilitating illness in affected patients, characterised by morphological abnormalities in red blood cells (RBCs) and their distinctive 'sickle' shape. SCD results from inheritance of the sickle gene (for haemoglobin S) from both parents (haemoblobin SS), or a sickle gene from one parent and from the other parent, another abnormal haemoglobin gene such as, C or beta thalassaemia, that contributes to the clinical effect of the sickle gene.

Due to the role of haemoglobin in oxygen-binding within RBCs, mutations in the beta-globin subunits result in significant distortion and structural change to these cells in low oxygen conditions, which can in turn cause dangerous obstructions within blood vessels, reduced blood flow to vital organs, and a weakened immune system. The hallmark of SCD is severe pain experienced by patients, usually referred to as 'Vaso-Occlusive Crisis' (VOC), and other complications include severe anaemia, susceptibility to infections, splenic sequestration, acute chest syndrome, pulmonary hypertension, chronic organ damage, and stroke.

While it is possible for patients to be asymptomatic carriers of a single sickle cell gene, those who carry two genes can experience mild to more severe forms of the disease, in some cases resulting in a shortened life span and significantly impaired quality of life. With pain and symptoms often beginning during early childhood, SCD has significant impacts on both adult and paediatric patients, many children, particularly in developing countries, dying undiagnosed and untreated due to a lack of newborn screening programmes and inadequate access to healthcare.

1.2 The Global Prevalence and Outcomes of Sickle Cell Disease

While a disease that effects patients across all regions of the globe, with an estimated 250 million genetic carriers and a diagnosed population of approximately 20 million, SCD shows the greatest prevalence across Africa. In particular, of the estimated 300,000 annual SCD births, 75% of these are seen in Sub-Saharan Africa, with West Africa reporting the highest prevalence in the world. While the most heavily affected country of Nigeria reports approximately 91,011 SCD births per year, countries such as the UK report only 350[i].



Kato et al. (2018)

However, in most regions in which SCD is a major public health concern, management of the disease has remained inadequate, with many lacking the necessary national programmes of care, basic treatment facilities, and systematic screening programmes needed to support these patients. Instead, many remain undiagnosed either until a patient presents with severe pain, complications of the disease, or until eventual mortality.

Indeed, while 94% and 98% of affected patients survive to adulthood in the US and UK, respectively, 50-80% of patients across Africa are estimated to die before adulthood[ii], 50% of these before even the age of 5. Much of this results from poor access to treatments within these regions, coupled with the lack of a strong national screening and testing programme for SCD, and is further exacerbated by inadequate health infrastructures, poor nutrition, and infectious co-morbidities. While high-income nations hold <1% of the global disease burden, the same capacities for universal newborn screening and comprehensive care seen within these countries are not present in those of lower income. These morbidity and mortality-reducing interventions largely remain inaccessible, and in turn translate to disparately high mortality rates across many highly effected regions.

1.3 Access to Treatment

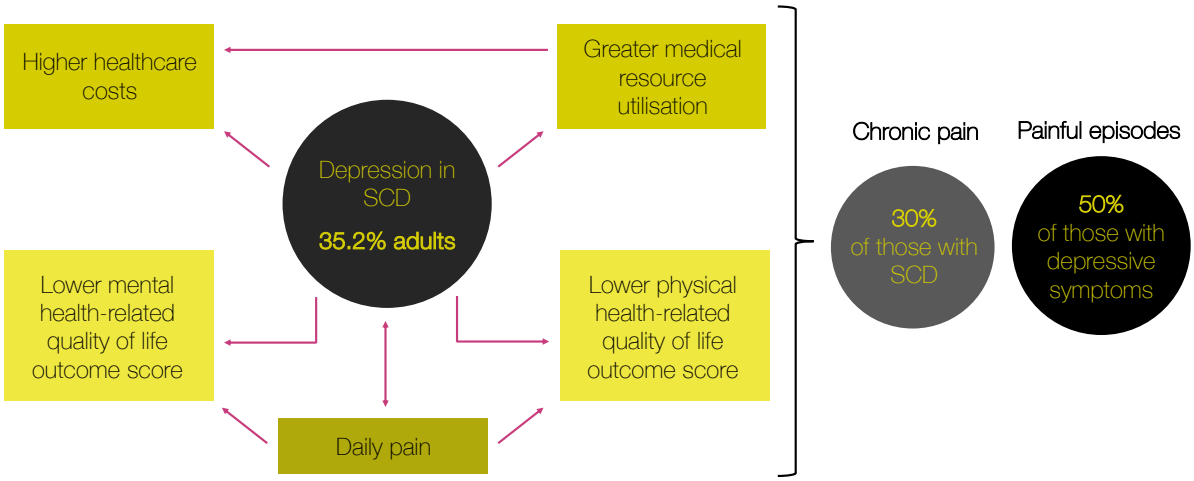
Although access to SCD treatments are often better in developed countries such as the UK and USA, the available options, resources and degree of focus on SCD still falls significantly behind many other diseases. Approximately 12,000-15,000 patients are estimated to live with SCD in the UK, yet despite the relatively vast financial and healthcare-based resources available within the country, a number of patients continue to face limited treatment options, struggle with access to key treatment centres, and do not receive adequate support in managing their disease.

In the UK, 60% of patients with a reported haemoglobinopathy reside in Greater London, despite the area holding only 15% of the overall population. Accordingly, the majority of NHS England's 24 designated Specialist Haemoglobinopathies Teams and biggest Sickle Cell Centres are based within London, Barts Health, Guy's & St Thomas', and King's College Hospital NHS Trusts comprising the 3 largest of these[iii]. However, it is important to note that the disease is not solely contained within London or other regions that form the locations for the remaining large treatment centres, this often leaving patients in the difficult position of travelling great distances on a frequent basis to receive treatment. Moreover, even within these large centres, the lack of specialised units for the treatment of patients or issues around availability within day units for those seeking urgent intervention can leave patients seeking help for pain management and advice around concerns regarding changes in their health unable to receive care they need, or forced to attend A&E.

No patient wishes to attend A&E, but may be left in a situation where they are signposted from day units without any certainty that it is truly an A&E situation, solely due to a lack of capacity. For clinicians specialising in SCD, ED is certainly not the preferred route for handling issues such as pain management, as these are not specialised units and face large patient volumes as standard, with staff often unfamiliar with the disease and substantial delays for patients in receiving the treatment they need. Previous studies have shown the benefits of providing ambulatory care and avoiding admission to A&E in improving patient outcomes, providing those who need it with the treatment they need to get their pain under control and return home quickly and safely, therefore highlighting a significant need for processes which ensure patients are able to receive the appropriate care in the correct environment.

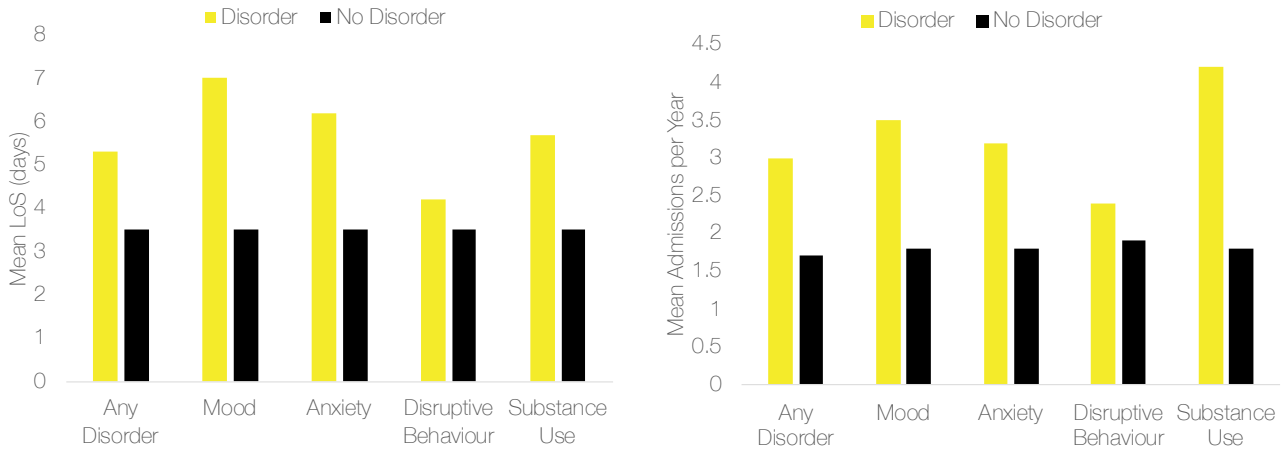
1.4 Impact on Psychological Wellbeing

Beyond the severe impacts of the disease on a patient's physical health, the effects of SCD often surpass the clinical and have a significant yet overlooked long-term bearing on psychological wellbeing, education, and employment. The need for ongoing hospital visits and pain management in the face of SCD crises leave many patients with difficulty in attending work or education, with damaging impacts on their psychological wellbeing and achieving their full educational or vocational potential. Around 35% of adults living with SCD are reported to also experience depression, this creating a feedback loop linked to further exacerbation of physical health issues that can even result in longer term problems, such as medication dependence.



Moreover, this impact on psychological wellbeing is not confined to adults alone, many children with SCD also facing similar ongoing emotional issues. However, this is not always addressed by clinicians, and research presented by the American Society of Haematology found that, within their study cohort, only 83% of haematologists were reported to have asked questions around the child's mental health during clinic visits at baseline[iv]. In countries and regions where healthcare infrastructure and access to crucial treatments are not as strong, it can only be expected that the availability of psychological support, both for adults and children, as well as their families or carers, will be lower even than this. With further studies highlighting the impact of mental health on increasing the mean lengths of stay and admission rates among paediatric SCD patients[v], ongoing efforts to support patients and their loved ones in managing their condition is therefore an important area of focus.

Impact of mental health on admission rates and Length of Stay in paediatric patients with vaso-occlusive pain events



Myrvik et al. (2013)

2. Study Rationale

SCD poses a profound impact on the health-related quality of life and life expectancy of affected patients, as well as their family, friends, and carers. With around 350 births in the UK every year[vi] and a global SCD prevalence expected to grow by around 30% by 2050, there is a vital need to ensure that patients are able to receive efficacious treatment and disease management, and that the supporting knowledge central to delivering this is available.

Ensuring that the quality of life, patient experience, and treatment options available to those living with SCD forms the focal point of this work. A critical part of this will revolve around the collation and real-time monitoring of data from multiple clinical sources, both from more traditional databases such as EMR, as well as expansion to include wearable data collection, ensuring patients and clinicians have access to this information in an easily visualisable way within a unified data platform. Through this, the aim of this research is to improve the collection, analysis and comprehension of SCD natural history and acute and chronic complications in terms of pain and symptoms, and to provide deeper understanding and management of the impacts and patient outcomes of the disease, outside of limited interactions with hospitals or clinics.

2.1 Data Limitations in Understanding Sickle Cell Disease's Natural History & Intervention Best Practice

There are significant challenges in fully understanding the natural history of SCD or the events surrounding a VOC, given the rare nature of the disorder and limited patient contacts within a healthcare setting. SCD is often considered an "invisible disease", and patients are not always given the full understanding of their condition needed to effectively manage it in day-to-day life. Furthermore, much of the burden in monitoring symptoms and disease progression falls upon patients themselves, mood or pain diaries forming a substantial source of information for clinicians. Previous studies incorporating mobile health tools in supporting patients with SCD have highlighted the issue of adherence in self-monitoring and managing symptoms in such a way, reporting a mean compliance rate over the 28-day study period of 75.0%, peaking at 85.7% in week 1 and dropping to 57.9% in week 4[vii]. These studies used mobile devices requiring the patient to log in and enter information every day over a short time period. The resulting information gathered therefore captures only short periods of time, with a low proportion of patient coverage, and emphasises the need for systems through which data can be collected from patients during their everyday life, in the long-term, and without pushing responsibility onto the shoulders of patients.

With this limited data, patient care and quality of life can suffer in turn, as the full picture is not available upon which to base swift and effective treatment. Use of hospital data alone, particularly in the case of SCD where coding does not always cover the outcomes of interest for clinicians, is therefore limited by questions of the quality and accuracy of the data which are vital to clinical decision making. Clinicians are often left with the question of what is really happening to their patients between hospital visits, day-to-day, and while many have their own suspicions around what causes a crisis, there remains a great deal of variability and complexity between patients. Indeed, clinicians and studies are currently limited to brief snapshots of what is happening to patients through interactions with hospitals, through blood tests, and through clinic visits. Frequently, only the most severely affected patients make regular contact with their health services, meaning it may be that approximately only 10% are seen, with real-time data capture of patient experiences during everyday life missed completely. With many studies and trials similarly compounded by narrow inclusion criteria and a homogeneous group of participants, study groups can often be limited to a representation of only a small proportion of the targeted population, from which understanding and decision making for the patient population as a whole must be extrapolated[viii]. This is a particular concern in the case of paediatric patients, best practice for whom is often based upon the findings of studies in adult patients, despite previous programmes demonstrating that, of 253 studies specifically conducted to repeat pharmaceutical trials in paediatric patients, only 50% of these actually resulted in a new indication for the paediatric setting as it had within the adult setting[ix].

A significant part of addressing these issues will involve creating as in-depth but far-reaching a profile of each patient as possible across all age groups, bringing together several sources in order to create a better understanding of the disease, to support patients both directly and through their clinicians. Data sources such as hospital databases, HES, unstructured information including medical and GP notes – digitised into a form from which analytics can be conducted – as well as genetic information through organisations such as 23andMe, form an important part of building an initial understanding of SCD's natural history, providing a historic overview of patient outcomes and disease progression. However, such sources are again faced with the issue of limitation in terms of

the frequency at which patients attend settings whereby this form of data is recorded, these often providing only snapshots at the most severe points of the disease or pain cycle. Therefore, following creation of a full specification of the most crucial metrics, informed by both patients themselves and specialist clinicians, the aim of this work will be to further integrate live data points from patients through the use of wearable technology, with ongoing monitoring of measures such as heart rate, blood O_2 saturation, blood pressure, physical activity, and diet.

Improving the supporting foundation of knowledge around SCD's natural history is an important step in understanding why particular subsets of patients face the outcomes that they do, and therefore what interventions would be best suited to preventing patients from reaching these severe disease states. For example, with issues such as opioid dependency in patients facing chronic pain and frequent spells in hospital, it is not necessarily a question of disease severity, often coming with surrounding concerns regarding social, psychological, and environmental factors. Previous case studies have highlighted the issues around addiction vs. pseudoaddiction and the impact of factors such as "dysfunctional family backgrounds" in cases of addiction without an identifiable cause of chronic pain, and the resulting need for alternate forms of treatment for such patients[x]. While studies have identified potential causal factors in regard to the psychosocial backgrounds of these patients and the association with addiction, the complete role of this in each patient's perception of pain or ability to cope with pain therapy remain unknown, and require further investigation. With the resulting impact on healthcare resources, an estimated 70% of clinician time spent on treating these patients, as well as the severe impact on patient quality of life, developing a stronger knowledge base and analysing the underlying data in order to pinpoint the factors that contribute to this outcome by identifying common metrics associated with this outcome will help clinicians in taking the steps and providing the support needed to these patients.

Similarly, patients living with SCD are faced with an increasing risk of chronic complications and organ damage (e.g. renal failure, pulmonary hypertension) as they age, and the need to understand the currently uncertain cause underlying the progression to these states in certain patients will be essential in detecting, predicting and preventing these complications in the future. Long term studies following large cohorts of patients through ongoing and in-depth data collection are currently severely lacking, clinicians as a result unable to definitively identify those patients at risk of advancing to these severe disease states or establish which interventions would provide the best outcomes for these patients, based on their demographics, genetics, comorbidities and disease progression thus far. Although a number of studies have investigated the associated metrics linked to renal failure within their SCD patient cohorts, previous work having identified male gender, proteinuria, cardiovascular diseases, and transfusions as potential risk factors in acute renal failure, these findings are based solely upon databases comprised of inpatient services, inpatient admissions, outpatient services, and prescription drug claims[xi]. While certainly an important part of establishing the potential causes or triggers of renal failure, such data again looks only at the patient profile at their most severe points in their pathway, and subsequently miss the complex network of additional factors which may cause the gradual progression to renal failure over the years.

These frequently flagged issues in providing the best standards of care to their patients demonstrate the importance of a better understanding of the specific metrics involved, correlating the factors that have historically shown a strong likelihood of progression to a severe disease state, and matching patients with others of a similar profile in terms of areas such as age, gender, comorbidities and genotype who may be at a more advanced stage of their disease, in order to

see which treatment options have offered the best outcomes. Closer monitoring of patients beyond this on a day-to-day basis provides the ability to change treatment pathways or provide interventions in a preventative manner, identifying potential adverse events or outcomes before the point of no return. The aim of this study is therefore to build a digital patient profile which will help to support the study of SCD's natural history, produce risk stratifications, predict long-term impacts, and create a correlation matrix of metrics signalling, for example, a potential crisis or the early stages of progression to renal failure, flagging issues earlier in the cycle for faster interventions, or even raising the alarm before a crisis is triggered. Patients will have full visibility of their data and the resulting insights to manage their own care more effectively and pre-emptively, with support from clinicians through earlier detection of adverse events.

2.2 The Patient Experience

Beyond the monitoring of physical health and biological metrics, the issue of patient experiences for those living with sickle cell, particularly in more severe cases requiring support to manage VOC and periods of extreme pain, is critical to improving quality of life and outcomes. Difficulties surrounding access to care at the point of requirement is one faced by many patients, even within some of the UK's largest SCD treating trusts. Despite clinical advice typically supporting treatment outside of A&E where medically possible, due to the lack of specialist care available within these units, unnecessary referral of patients to ED is not uncommon.

While exacerbated by the current COVID-19 pandemic and the associated new requirements for testing and health questionnaires prior to admission, poor access to the day units providing more specialised SCD care is one that has existed since long before the outbreak first began. Historically, too many patients have struggled to secure the treatment they need in receiving pain management at these day units. Patients are frequently advised to either seek treatment through A&E or to try again the following day, ignoring the crux of the issue for these patients – "But I am in pain now".

This is in some cases accompanied by a lack of information or advice around their specific issues, patients instead directed to A&E without having first been given the opportunity to discuss their symptoms and options with a clinician. Patients with SCD tend only to seek such assistance in situations where they truly need it, and the resulting feeling of dismissal by the very systems designed to deliver their specialist care poses significant issues, not only around the physical prolonging of their pain, but also through the accompanying psychological stress and potential risk of infection associated with exposure in an A&E environment.

As such, an additional component to this work and the patient platform will incorporate not only their clinical data, psychological wellbeing and deep insights around their ongoing health status, but will also provide a gateway through which to manage their care. Indeed, crisis pain and patient needs cannot be expected to conform to working hours or trust capacities, and so the project further looks to incorporate a booking portal and remote specialist service within the platform, through which patients can access advice and care as and when they need it, even out of hours. This project therefore works to address the key concerns and challenges faced by patients every day, building upon these known issues with deeper insight as to what may help, directly from the patient viewpoint, and developing the means with which to do so within a single, patient-friendly platform, improving the day-to-day patient experience for those living with SCD.

2.3 Sickle Cell Disease Treatment Options

A significant part of improving the quality of life for all patients with SCD is the development of new therapeutics beyond the limited options currently available, no new treatment options having emerged for 30 years prior to the announcement of FDA approval for L-glutamine in 2017[xii]. While a number of new drugs are currently undergoing clinical trials, these are hampered by the checkpoints, patient cohorts and sources available in gathering a full view of outcomes, efficacy and safety.

Indeed, much of the difficulty in developing new therapeutic options arise from a lack of in-depth and long-term outcome information, requiring a strong foundation of real-world data to demonstrate the effectiveness of each treatment. Studies are therefore limited to brief snapshots of what is happening to patients through interactions with hospitals, blood tests, clinic visits, and self-recorded pain diaries, with smaller patient numbers covering a potentially homogeneous subgroup of patients, non-representative of the entire SCD patient cohort[viii] and over shorter term projects.

As such, with a number of new treatments now in the pipeline, an additional aim of this work is to provide the evidence base needed to support these essential new medications in gaining approval and licensing, in order to guarantee patients are offered a wider range of more effective and safer treatment options. Collation and feeding of the crucial real-time data collected through wearable devices on a daily basis into studies around new pathways or treatments will therefore further benefit patient care, through the greater depth of understanding of real-world outcomes it provides to biopharmaceutical companies in measuring the safety and efficacy of treatment options.

2.4 Wearables, Telemonitoring, and Software Generated Classifications in Patient Care

With the growing functionalities and capabilities of publicly available wearables, the potential utilisation of such devices in collecting data for improved monitoring of patient wellbeing and in clinical trials has seen growing interest within the healthcare and biopharmaceutical R&D space over recent years. With multiple types of device available and rapidly maturing sensor capabilities, current smart watches are now able to monitor a range of clinically important metrics, from basic activity levels and heart rate, to blood pressure, blood oxygen saturation, and ECGs[vii].

One of the earliest and most common features seen across wearable devices is activity tracking, widely utilised to improve overall fitness in both healthy individuals and, increasingly, in specifically improving the wellbeing of patients. With the known positives of increased physical activity in reducing the risk of a wide range of diseases, as well as in improving clinical outcomes, emotional wellbeing, and quality of life, a growing number of studies have begun to focus on the particular benefits of increased exercise in specific diseases.

As such, activity trackers and wearable technology provide an important means of conducting such studies, recent work by Delrieu et al. (2020) in the context of metastatic breast cancer demonstrating both a high adherence rate, 96%, over the 6-month intervention period and significant improvements to patient wellness. While self-reported global quality of life remained stable among participating patients, specific metrics such as appetite loss and fatigue saw notable decreases, with overall measures of physical fitness including 6-minute walking distance tests and BMI showing significant improvements[xiii]. Similarly to many early trials, the degree of statistical significance in these study outputs may have been limited by smaller patient cohort sizes and limited study periods. Nonetheless, it provides an encouraging proof-of concept as to the utilisation of

activity trackers in supporting patient wellness, both physically and psychologically, and the potential for empowering patients through self-management of their disease. As both a means of improving overall wellbeing, microvasculature health[xiv], and as an important indicator of potential periods of pain or crises and the need for clinical intervention, wearable activity tracking to provide a fuller understanding of the benefits to patients with SCD therefore comprises a vital part of this work.

As with any new developments, concerns regarding the clinical accuracy of such technology, particularly in those designed to provide patients with the trigger needed to seek further medical attention or drive clinical decision making, are paramount. Blood pressure (BP) measurements form a substantial part of the diagnosis and monitoring of cardiovascular conditions, also playing a role in SCD disease management due to the impact of relative hypertension on increased stroke, pulmonary hypertension and renal dysfunction risk, as well as forming an important indicator of stress and its role as a marker or even trigger of VOC.

Already, previous work has demonstrated the comparability of software-generated BP status classifications with physician assessments, reporting 87.9% agreement in untreated patients and 91.9% agreement in treated patients through the utilisation of a specialised algorithm, providing accurate self-interpretation of home BP results under considerations for both recommended normal thresholds and patient specific characteristics[xv]. With improvement of this degree of agreement to 95.4% following further correction and development of the algorithm, this study highlighted a powerful potential for the use of technology in empowering patients to better manage and drive their own care through clinically accurate software-generated classifications, as well as in prompting further and pre-emptive interventions through automatic alerts to those patients identified to exhibit high BP readings – these patients potentially at risk of cardiovascular complications and requiring further intervention.

The move towards incorporating remote monitoring systems into patient care has already been seen within other disease areas, one such study by authors Zan et al. (2015) exploring the feasibility of mobile technology and portable digital devices in improving clinical outcomes for patients suffering with congestive heart failure. In the context of the ongoing COVID-19 pandemic, such technology provides an important potential route to ensure patients with SCD can still receive monitoring and the necessary support during lockdown and shielding. Much as is the case for SCD and other chronic conditions, and with the frequency of cardiac complications in patients with more severe forms of SCD, the role of intensive remote monitoring and expansion of this to self-management in heart failure is an important one; reducing the rate of readmissions, supporting better outcomes, and empowering patients in regards to their own care outside of the hospital setting.

Indeed, within this trial over a 90-day study period, 20 patients were provided with a Bluetooth weighing scale, self-inflating blood pressure cuff, and an iPad Mini tablet, in order to measure and self-track relevant metrics. The resulting benefit to patient satisfaction was clear – 95% reporting a feeling of greater connection to their health care teams alongside improved confidence in performing care plan activities, and 90% feeling better prepared to initiate discussions about their health with their doctor[xvi]. With more than half of patients demonstrating an 80% greater degree of weekly and overall participation in the programme, this demonstrates a promising outlook for remote and self-monitoring of chronic diseases by patients themselves, an improvement of particular importance within the treatment of patients with SCD who can often feel disconnected from their treatment plans and brushed off by the very units intended to care for them.

However, this study also highlights the potential for improved adherence through greater utilisation of automated tracking, much of the technology within used requiring significant levels of patient input. While trends in improved outcomes such as quality of life and average length of hospital stay were noted, these were not found to be statistically significant, likely due to the relatively short duration of the programme and the smaller patient sample size[xiii]. As such, this emphasises the need for further trialling of this form of technology in wider patient cohorts, and over sustained periods of time.

Despite the widely demonstrated promise for the usage of wearable devices in healthcare and clinical studies, these come with the caveat that researchers are often unable to manage the vast quantities of data collected on an ongoing, automated, 24/7 basis as patients continue through their everyday routines. Data infrastructures, as well as procedures for data processing, analysis and interpretation may not be equipped for such magnitudes of information, and have yet to be standardised within the industry[vii]. As such, an additional component of this research works to explore the feasibility and means by which to collect and combine vast quantities and sources of data, including the live data points extracted from wearable devices as patients go about their daily lives. Our aim is therefore to demonstrate the benefits to patients of incorporating wearables and a supporting data platform into the standard disease management pathways for SCD, generating insight as to long-term patient adherence and clinical outcome improvements within an ongoing longitudinal study, beyond the shorter-term trials typically seen.

3. Objectives

The goal of this research is to ensure better quality patient care and experience, through both the advancement of standards and speeds of interventions through closer tracking of key metrics and predictive technology integration, as well as to reduce the burden on patients through the incorporation of automated monitoring of the relevant vitals. By feeding this into a unified digital platform, the goal is to provide the knowledge needed for clinicians and researchers to shape their resulting treatment pathways and boost each patient's understanding of their disease, without the need to manually input data themselves.

The main objective of this project is to establish a digital patient profile to identify and monitor for the key risk factors or triggers around SCD pathologies, such as VOC and organ damage, as well as the best treatment options for these patients. Furthermore, the resulting unified platform will help to collate the necessary information needed to empower patients in managing their own care, and access specialist clinician advice as and when they need it.

3.1 Primary Aim

The primary aim is to study the continuous pattern of vital parameters, collected over a long duration, within a sample cohort of consenting patients with SCD in order to determine how these relate to acute and chronic illnesses, as well as healthcare utilisation.

This will be through the creation of a unified data platform – comprising historical patient data, a full genetic background, and real-time patient data – through the incorporation of a wearable device into patient disease management.

Through this, the intended outcome will be improved quality and duration of life in patients.

3.2 Secondary Aim

A secondary aim is to further develop the features and usability of the data platform and wearable device through a patient lens, in an ancillary study with patient focus groups around 3 key research areas: SCD's impact on psychological wellbeing, the usefulness of wearables in day-to-day patient life, and concerns around consenting to data sharing.

4. Project Design

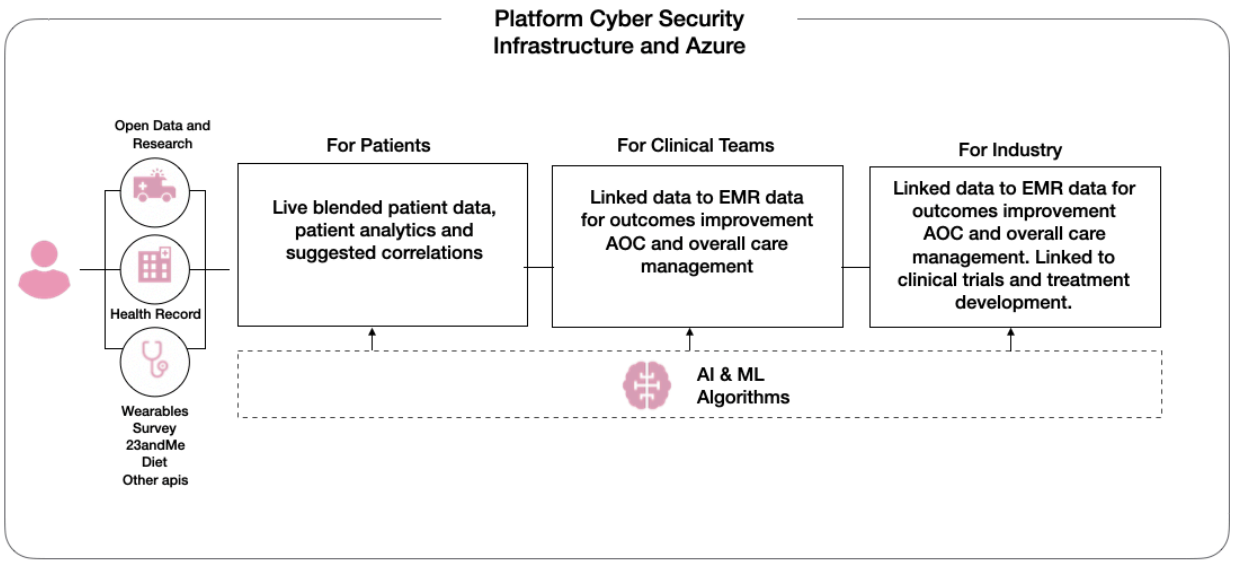
The project will be a combination of focus groups and data collection. This will be an ongoing, data-driven project, revolving around the collation of episodic and live data points including admission, diagnostic, pathology, radiology, primary care, pharmacy, physiotherapy, Hospital Episode Statistics (HES), Open Data, clinical data points, and the incorporation of live wearable device data. Cultivation of the most relevant data points in the context of SCD has been ongoing with the support of expert clinicians in the field, and will be further developed through the input of patients themselves during a series of patient focus groups, in order to establish what the most important factors are to SCD care through a patient-lens. Wearable devices will be provided to patients who do not already own one, in support of the unified digital data platform, within a pilot study with consenting patients who choose to register following these patient focus groups, as well as those who have enrolled through the Sickle Cell Society and from patient cohorts at treatment centres such as London North West University Healthcare NHS Trust and Barts Health NHS Trust. The project's development will further be supported through the inclusion of a number of focus groups between specialist doctors and nurses, as well as healthcare managers, public health officials and commissioners.

4.1 Sample Size

There is an estimated 12,500-15,000 people living with SCD in the UK[xvii]. Our patient sample size is based upon an estimated minimum proportion of the total population of patients with SCD we aim to enrol onto the digital platform and wearables pilot study, assuming not all patients will be reached by the initial programme launch through the Sickle Cell Society and partnering trusts, and that of those who are, not all will provide consent or be interested in participating. As such, our starting goal is to recruit 2% of the total UK SCD patient population, at 300 patients.

4.2 Data Sources, Access and Flow

From the starting point of sources including hospital Electronic Medical Records (EMRs), open data, and Hospital Episode Statistics (HES), the data platform will integrate written medical and primary care records from GPs, structured and unstructured EMIS/TPP records, as well as genetic information through external organisations such as 23andMe, following full patient consent. With additional wearables collected data (Section 4.3), these sources will be combined within a specialised SCD unified data platform to allow the application of a set of advanced algorithms, providing granular analysis of key patient metrics.



4.3 Wearable & App Data Points

Following specification of the most crucial metrics, live data points will be integrated into the unified data platform directly from patients through the use of wearables and ongoing monitoring of factors, or through optional manual input of additional information, such as a pain scale of mood, through the platform's mobile app by patients. These include:

Metric	Rationale
Heart Rate	A fast heart rate is linked to anaemia and low blood O_2, stress, and panic attacks.
Blood O_2 Saturation	Low arterial blood oxygen saturation is common in SCD, and Obstructive Sleep Apnoea is also highly prevalent in patients with SCD.
Body Temperature	Raised or decreased temperatures are linked to crises, with low body temperatures known to trigger vasoconstriction. High temperatures can also be an indication of infection and in turn trigger crises.
Blood Pressure	Blood pressure is known to be lower in SC anaemia, with relative hypertension linked to an increased risk of stroke, pulmonary hypertension, renal dysfunction & death. This can also be used as an important indicator of stress.
ECG Abnormalities	ECG abnormalities are common in SCD & early identification / intervention can help to prevent serious cardiac events, e.g. Myocardial Infarction during VOC.
Sleep Cycles	Disrupted sleep cycles / patterns are linked to increased pain and periods of crisis.
Fitness & Activity	Low activity levels may be an indicator of the onset of a crisis, and certain exercises are linked to relieving pain.
Nutrition / Diet / Medications taken	Can be an important indicator of emotional wellbeing & pain levels, with disrupted eating patterns or loss of appetite potentially indicating periods of chronic pain or VOC.
Pain and Symptoms	Provides a direct monitor of patient wellbeing and will support correlation of metrics with symptoms of SCD pathologies.

4.4 Focus Groups

Part of this project will involve hosting a number of focus groups and collating the key learnings from these over a 12-month period. The purpose of these focus group studies revolves around incorporating the patient voice directly into the development of the unified SCD data platform and the introduction of a digital data platform and wearable device into care management. The goal of this is to assess how patients feel in the context of a 3-pronged programme: psychological wellbeing, wearables, and consent for data sharing over the SCD data platform. By gaining a deep level of insight around the specific needs of the patient, the aim is to fully incorporate the patient voice into future developments, ensuring all features are aligned to what will benefit patients day-to-day. An overview of the 3 research questions is given in the table below:

Focus / Objective	Key Questions
Psychological Wellbeing To identify the psychological support needs of SCD patients and their families / carers.	Impact of SCD on psychological wellbeing and the support patients are currently receiving • How does SCD affect your daily living and quality of life? • How does SCD effect you emotionally? • What are your thoughts / feelings about SCD, and how do you cope with these? • What emotional support have you received, and what would be useful? • How could wearables be used to help monitor and manage your emotional wellbeing?
Devices/Wearables To find out the likelihood of wearables adoption by SCD patients and the key features that would benefit patient care management.	Wearables, devices and capturing data • Do you currently use any wearables? If so, what type? • How often do you use it or any accompanying apps? • During a crisis, what are the key things you would want to monitor / track? • Are there any triggers or warning signs of an oncoming crisis that you have become aware of over the years? • What are the key features you would want to see in your wearable device? • Would you consider using anything requiring manual input during a crisis or solely automated monitoring?
Data platform & consent To identify the key concerns around health data collection for SCD patients and the factors that would encourage consent.	Data and consent for data collection from GP practices, hospitals, wearables into the platform • What would your main concerns be around this form of data collection? • What would be the key factors in ensuring you feel comfortable with this?

Each focus group session will host discussion between 15-20 patients over a dedicated Zoom call, led by a clinician facilitator, and will be divided by age group:

i. Parents with their effected children

ii. Teenagers / adolescents, 13-18 years of age
iii. Young adults, 19-25 years of age
iv. Adults, 26-39 years of age
v. Older adults, 40-64 years of age
vi. Elderly, 65 years and over

4.5 Procedure

4.5.1 Focus Groups

Patients will be approached and enrolled onto the initial focus group programme with support from the Sickle Cell Society and specialists at London North West University Healthcare NHS Trust and Barts Health NHS Trust. Following the introduction to the purposes and structure of the focus groups, with details provided from which to request additional information, patients will be given adequate time prior to the planned commencement of the focus groups to decide if they wish to participate. All patients will receive the necessary consent forms and full confidentiality and data security will be ensured, with no patient identifiable data collected, shared or transmitted over the internet. Any information recorded, either through manual recording of responses throughout the session, through the pre-focus group survey or through the interactive focus group form (Section 6) will be anonymised and require the input of no identifiable data.

4.5.2 Digital Data Platform and Wearables Pilot

Patients who enrol onto the pilot trial, either as a follow on from the patient focus groups or through recruitment via the Sickle Cell Society, London North West University Healthcare NHS Trust, or Barts Health NHS Trust, will be able to use either their own existing device or will be provided with a comparable market available smartwatch by the study. Data points, as summarised in Section 4.3, will be collected in an automated fashion on an ongoing basis, before transmission to a secure cloud database. This provides a novel approach to the monitoring of SCD that forgoes the need for patients to manually record information themselves and provides the potential for a larger patient cohort through remote monitoring, collecting a greater wealth of more in-depth, real-time and longitudinal data from patients during their daily lives. This supports a higher degree of compliance through decreased intrusion and an improved quality of data through improved objectivity and the elimination of retrospective recall. Furthermore, the utilisation of a wearable device provides the establishing of a baseline identified by 24/7 monitoring of data collection, providing a precise comparison for any patterns and changes over time to inform improved treatment pathways.

Patients will be set up with an electronic account and access to the digital platform through which their personal data can be accessed and visualised, and any additional metrics – such as body weight, dietary intake, emotional wellbeing, and additional medication consumption – can be manually input by the patient themselves as desired.

5. Project Plan

As part of the process of engaging patients prior to the full study and technology pilot trial, the project entails a series of initial pre-study patient focus groups over a 2-month period, in order to gather the relevant insights to ensure the study design, steps and outcomes are curated around a patient-centric outlook. Our intended timetable is as follows:

Project Stage	2 months	3 months	12 months					1 month
1 Pre-Study Focus Groups Engaging patients in study development prior to initiation of the full wearable pilot								
2 Pilot Study Enrolment Patients recruited to participate in the pilot through pre-study focus groups, the Sickle Cell Society & participating trusts								
3 Wearables Pilot Study Trialling of the live wearable and digital platform with patients, data collection, and analysis								
4 Post-Study Focus Groups Sessions with participating patients to gather feedback from the pilot and outline next steps accordingly								

6. Population

Any patient with a diagnosis of SCD, or child under 16 years of age with parental guidance, will be eligible to participate in the digital data platform / wearable pilot and focus group studies.

Patients will be recruited through multiple channels in order to ensure the involvement of as large and heterogeneous a patient cohort as possible. For these initial focus groups and digital data platform / wearable pilot trial, this recruitment will therefore be through the Sickle Cell Society's patient network, as well as patients treated at the hospitals of London North West University Healthcare NHS Trust and Barts Health NHS Trust. Estimates from the National Haemoglobinopathy Registry suggest a potential patient cohort of 1,324 patients at Barts Health NHS Trust, and an additional 418 patients at London North West University Healthcare NHS Trust. It is hoped that a greater number of patients outside of the London region will also be included via the Sickle Cell Society, and that the trial will be expanded to include additional treatment centres with time.

6.1 Inclusion Criteria

I. Patients aged 5-15 years of age, with consent from and attendance / guidance by parent or guardian
II. Patients aged 16 years and over
III. Able and willing to sign written Informed Consent
IV. Interest in participating in the study
V. Known history / diagnosis of Sickle Cell Disease

6.2 Exclusion Criteria

I. Incapacity to provide informed written consent
II. Known allergic reaction to any materials in wearable device

7. Pre-Focus Group Surveys and Focus Group Interactive Forms

Patients who enrol to participate within the focus groups will be sent a pre-focus group survey through which to record basic background information around their interest in technology as part of their care, to be self-administered by each patient and with multiple choice questions including:

1. *Do you own a wearable device, e.g. a smart watch? If so, which device do you currently own?*
2. *If owned, how often do you use a wearable device?*
3. *What are your biggest hesitations around wearable technology?*
4. *Which wearable device would you be most interested in using?*
5. *What features would you most wish for your wearable to have?*
6. *Would you be more inclined to use a wearable if it included healthcare features?*
7. *Would you want to link your wearable to a smartphone app?*

During the focus group sessions themselves, patients will be asked to participate in an interactive survey that follows the structure of the session and is guided by the group facilitator, outlined in Section 4.4. All answers remain anonymised and non-identifiable, intended solely to understand experiences and feelings around SCD and the impact of technology from a patient-perspective among the group as a whole. Both the pre-focus group survey and interactive focus group forms will be hosted on Typeform, which provides the platform for a patient friendly survey under full GDPR (General Data Protection Regulation) compliance.

7.1 Patient Numbering

A patient number uniquely identifies each patient in the study; this is a combination of their treatment centre number and participant number. Upon signing the informed consent form, the patient will be assigned a patient number by a health professional at their centre, which they have to enter when they log into the focus group interactive forms.

7.2 Patient Withdrawal

Patients may voluntarily withdraw from the study at any time, as protected by GDPR, or be dropped from it at the discretion of the responsible clinician (investigator) at the NHS Trust. Patients may be withdrawn from the study if any of the following occur:

Patient or parent withdrew consent

Lost to follow-up

Death

Administrative problems

For patients who are lost to follow-up, the investigator will show ‘due diligence’ by documenting steps taken to contact the patient, such as dates of telephone calls, and mailings.

8. Statistical Analyses

An initial high-level investigation using descriptive analysis will be conducted across all variables in order to identify key trends and insights, from which further correlations and statistical significance will be tested. This will predominantly be performed using IBM SPSS Statistics 24 and Microsoft Excel, collected data analysed for outliers through Boxplot and Q-Q Plots, for normal distribution using Shapiro-Wilks testing, and for homogeneity of variance using Levene's testing. Due to the exploratory nature of the study, hierarchical stepwise regression of the outlined data points (Section 4.2 & 4.3) will be conducted, and any outliers detected through assumption testing will not be immediately excluded from analyses, instead further investigated to identify any clinically significant causes. For data that do not violate these assumptions, either independent t-tests (for experiments with two experimental groups) or one-way ANOVA (for experimental groups of 3 or more) will be performed, with Bonferroni post-hoc testing. Those that do violate these assumptions will undergo non-parametric Kruskal-Wallis testing. Each analysis will be based upon demographic variables, such as age and gender, correlated against genetic and clinical variables including hospital admissions, comorbidities, genotype, phenotype, and wearables collected data (Section 4.3). Those with p-values below 0.05 will be considered as statistically significant and undergo further study.

An additional focus for the study regards data collected over extended periods of time and the progression of the disease state over this period, therefore requiring the inclusion of two independent variables. For such data, this will require Mauchly's test for sphericity in addition to Shapiro-Wilks testing for normal distribution. These data will then be tested for statistical significance using a two-way repeated measures ANOVA with a Bonferroni adjustment. Each step of the analytical output will be reported alongside changes in variance and F change, and collinearity of the independent variables will be investigated within the regression model.

This statistical analysis will in part feed into and be supported by the data platform's advanced AI and ML algorithms. However, the primary purpose of the AI technology will revolve around the predictive element of this study, highlighting potential outcomes and suggestions for optimal treatment pathways based upon the statistical analysis conducted, and key trends or associations identified.

9. Administrative Procedures

9.1 Ethical Compliance

The project protocol will be reviewed and approved by an NHS Research Ethics Committee. The proposed patient information sheet and informed consent form will be in accordance with the guidelines from the NHS National Research Ethics Service.

As per the European Union's GDPR, data generated by any wearable device, regardless of its approval as a medical device, will require full consent from each patient with clearly defined purposes for use, consent for which can be withdrawn by patients at any time.

9.2 Research and Development

The London North West University Healthcare NHS Trust and Barts Health NHS Trust's Research and Development Departments will also register the study protocol in accordance with their research governance guidelines.

9.3 Involvement of Service Users

Service users would be an integral part of the project. They would be involved in the project set up, preparation of materials, and project meetings. Service users would be identified through the Sickle Cell Society, London North West University Healthcare NHS Trust and Barts Health NHS Trust, as well as other NHS treatment centres as the study expands, in accordance with the guidelines of Involve (invo.org.uk).

9.4 Data Security

Data security will be ensured through the implementation of strict IT security controls, in-line with those of peers and adopting best practices in areas such as encryption, data anonymisation or pseudonymisation, and identity and access management. This is based on up-to-date appraisals of their security gaps in personal data. Remote access into the trust environment will occur with explicit authorisation from named leads within the trust's business intelligence team via VPN/Citrix/TeamViewer or other remote connectivity. Data from NHS trusts and from the pilot study wearable devices will be collected and stored within a highly secure cloud foundation managed by Microsoft, the infrastructure and cyber security provided by Azure's multi-layered, built-in security controls and unique threat intelligence to identify and protect this data against any risks.

9.5 Funding

The project will be patient funded and sponsored by Mr Orlando Agrippa.

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