Clinical Commissioning Policy
Treatment of iron overload for transfused and non-transfused patients with chronic inherited anaemias (all ages) (URN 2109) [221004P]

Publication date: October 2022 version number: v1.0

Commissioning position

Summary

DFO/DFX and DFP/DFX combination therapies are recommended to be available as a routine commissioning treatment option for iron overload in transfused and non-transfused patients with chronic inherited anaemias not adequately controlled on monotherapy or DFP/DFO combination within the criteria set out in this document.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Executive summary

This policy is focused on the off-label use of DFO/DFX and DFP/DFX combination therapies as treatment of iron overload for transfused and non-transfused patients with chronic inherited anaemias.

The independent evidence reviews returned evidence for DFO/DFX and DFP/DFX combination therapies, which are presented for a routine commissioning position.

Plain language summary

About chronic inherited anaemias

Inherited anaemia is an umbrella term covering several conditions that affect the red blood cells in the body passed down in families. Red blood cells carry an iron-rich protein (haemoglobin) that binds to oxygen and delivers it around the body. Anaemia occurs when someone does not have enough red blood cells or when their red blood cells do not function properly (NHS Blood and Transplant, 2016). The most common inherited anaemias are sickle cell disease (SCD) and thalassaemia, as well as a number of rare inherited forms of anaemia.

Blood transfusion is a common treatment for these inherited anaemias. It involves giving a patient one or more units of red blood cells donated by a voluntary donor. Each unit contains

approximately 200mg of iron, a key component of red blood cells, and can result in it building up in the body (Auerbach, 2021).

About iron overload

Iron overload can be the result of blood transfusion therapy in chronic inherited anaemias. The human body has no mechanism for removal of the iron and therefore patients who are regularly transfused will develop iron overload.

Patients with non-transfusion dependent thalassaemia (NTDT) and other rare anaemias may develop iron overload in the absence of blood transfusion from increased dietary iron absorption from the gastrointestinal tract due to ineffective erythropoiesis.

Iron overload can cause damage to different organs in the body, resulting in poor growth, failure of puberty, the development of diabetes, liver, and heart complications. Therapies can be used to remove iron from the body (chelation therapy) via the urine and stools. These are either given orally or by injection (parenterally).

Prior to initiating chelation treatment, iron levels are measured using scans of the heart and liver. Patients on iron chelation therapy should be monitored to ensure they are taking the treatment correctly and to check for side effects of treatment.

Before chelation therapy, a regularly transfused patient would develop serious life-threatening complications and ultimately die as a direct consequence of iron overload.

About current treatment

There are currently four licensed iron chelation drug treatment regimens which are routinely commissioned for the treatment of iron overload in patients with chronic inherited anaemias.

1.Desferrioxamine[1] (DFO) monotherapy (parenteral)

2.Deferiprone (DFP) monotherapy (oral)

3.Deferasirox (DFX) monotherapy (oral)

4.DFP/DFO combination therapy (oral + parenteral)

The selection of iron chelation therapy should be guided by the site and severity of iron overload, previous reaction to treatment and patient choice.

Currently most patients receive either DFX alone or a combination of DFP and DFO.

About the new treatment

The policy proposes the off-label use of two combination therapies: DFO/DFX and DFP/DFX in addition to the existing regimens.

What we have decided

NHS England has carefully reviewed the evidence to treat iron overload for transfused and non-transfused patients with chronic inherited anaemias with either DFO/DFX or DFP/DFX combination therapy. We have concluded that there is enough evidence to make these off-label treatment combinations available at this time

Links and updates to other policies

This document updates the Clinical Commissioning Policy 16070/P: Treatment of iron overload for transfused and non-transfused patients with chronic inherited anaemias.

[1] Also known as deferoxamine.

Committee discussion

See the committee papers (link) for full details of the evidence.

The condition

Iron overload causes serious complications in the endocrine system, the liver and the heart. Endocrine complications begin at a young age with irreversible damage to the pituitary gland resulting in growth retardation and failure of pubertal development. In adolescents and adults, endocrine damage results in gonadal failure, insulin-dependent diabetes, hypopituitarism, hypothyroidism, and hypoparathyroidism. Iron overload also results in liver fibrosis, cirrhosis and cancer, cardiac failure and dysrhythmias and death. Heart disease is the commonest cause of death due to iron overload.

Blood transfusion therapy results in accumulation of iron in the body. Patients with NTDT and other rare anaemias may develop iron overload in the absence of blood transfusion simply from increased iron absorption from the gastrointestinal tract.

Before the advent of chelation therapy, these patients would develop serious life-threatening complications and ultimately die as a direct consequence of iron overload. Iron chelation therapy removes the iron gained from the blood transfusion or increased gastrointestinal iron absorption.

A patient who has iron overload will start chelation therapy with one agent but then may require various chelation regimens in their lifetime dependent on tolerability, complications with the drugs, lifestyle issues and severity of iron burden.

Current treatments

Chelating medications come in two forms, oral and parenteral, which can be self-administered. The following iron chelating regimes are licensed and currently commissioned:

1.DFO

2.DFP

3.DFX

4.DFP/DFO combination

Currently most patients receive DFX or a combination of DFP and DFO. Fewer patients receive DFO or DFP monotherapy. The selection of iron chelation therapy should be determined by the site and severity of iron overload and history of compliance, prior toxicity and patient choice. Patients on iron chelation therapy should be monitored for concordance and side effects of treatment.

Oversight of iron chelation therapy is the responsibility of specialist haemoglobinopathy teams (SHT); oversight encompasses decisions about starting, monitoring, changing and stopping therapy. MRI is used for monitoring of cardiac and liver iron.

The provision of therapy is either through the SHT or local haemoglobinopathy team (LHT) as part of network arrangements.

However, chelation drug dispensing and prescription can and should occur at the centre where the patient is normally transfused.

Proposed treatments

The term ‘combination therapy’ has been used for the various ways in which any chelators can be combined. The proposed combination therapies would be considered as second line and used for patients:

- who fail to achieve negative iron balance despite adherence to optimal doses of monotherapy or DFP/DFO combination
- who develop dose limiting toxicities

- where compliance with monotherapy at the required frequency is inadequate.

Rarely, it may be considered first line, for example in patients:

- at risk of drug side effects due to comorbidities
- with a pattern or degree of iron overload which is more likely to respond to combination therapy.

Combination DFO/DFX is likely to allow a reduction in DFO dosing and attendant costs. Although it is a more expensive combination than DFP and DFO, it allows flexibility for patients who cannot tolerate DFP or optimum doses of DFO. This will lead to longer term health costs savings in terms of medication costs as well as reduction of complications from iron overload.

Combination DFP/DFX offers a treatment that is purely oral. This combination can allow for reduced doses of the individual chelators to be used. The drug combination has particular value in those patients with cardiac iron loading and can improve compliance in those who are unable to adhere to parenteral chelation.

Patients and carers are involved in decisions around chelation regimens to optimise adherence. This will include information about treatment schedule options, side effects and goals of the regimes proposed and confirming patients / carers understand the options discussed.

Making these off-label treatment regimens available to clinicians would give increased flexibility to optimise a patient's iron chelation, reducing toxicity and improving tolerability. This can reduce the risk of later complications and the associated healthcare attendance costs.

Epidemiology and needs assessment

The treatment is indicated for patients diagnosed with an inherited anaemia who develop iron overload. The most common presentations are in those with SCD and thalassemia.

The inherited genetic changes leading to SCD and thalassaemia are associated with an individual's ethnic origin. The prevalence of these disorders in any locality will be affected by the proportion of the population that are genetically linked to susceptible populations.

In England, in total 11,456 people with SCD are registered on the National Haemoglobinopathy Register (NHR) as of March 2021. On average, 1 in 2,400 babies born in England will have the disease. It is more common in people whose family origins are African, African Caribbean, Asian or Mediterranean. It is rare in people of North European origin. Data from the NHR shows that approximately 9% of patients with SCD are on long term transfusion programs and about 40% of those transfused are currently receiving iron chelation. It is recognised that this data may be incomplete and underestimate the numbers on transfusion and on iron chelation.

Thalassaemia is more prevalent amongst Southern European, Middle Eastern and South East Asian populations. There are 1598 people with thalassaemia registered on the NHR and 20 to 30 children born with thalassaemia per year in England. According to the NHR, approximately half of thalassaemia patients are on lifelong transfusions and around 60% are reported to receive iron chelation, the difference being a proportion of patients with NTDT who can still develop complications due to iron overload.

It is anticipated that the improved life expectancy of patients with thalassaemia and SCD will result in increasing prevalence of the conditions in the UK, and correspondingly the need for iron chelation, will continue to increase.

There are also an unknown number of patients with rare inherited forms of anaemia, who may require transfusion and/or chelation (estimated fewer than 500). These diseases are not population specific and are encountered across the breadth of the UK. Clinical management closely resembles that of patients with SCD and thalassaemia. Whilst data from the NHR is incomplete, clinical consensus has estimated around 20-30% of patients on iron chelation would be suitable for combination therapy.

Evidence summary

An independent evidence review was conducted for the use of DFO/DFX and DFP/DFX combination therapies as treatment of iron overload for transfused and non-transfused patients with chronic inherited anaemias.

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of these treatments for the indication.

The evidence reviews which inform this commissioning position can be accessed here:

NHSE Evidence Review_2109a_DFO_DFX for iron overload in anaemias_FINAL_Sep 2021.pdf

NHSE Evidence Review_2109b_DFP_DFX for iron overload in anaemias_Sep_2021 with adults added.pdf

Implementation Criteria

Inclusion criteria

To be eligible for DFO/DFX or DFP/DFX combination therapy, patients (all ages) should have the following:

- transfusional iron overload in patients with inherited haemoglobinopathies or rare anaemias who either are on or have previously been transfused either regularly or intermittently

OR

- patients with non-transfusion dependant inherited anaemia who have iron overload as documented by baseline scan or an MRI (liver iron of above 5 mg/g/dw as measured by R2 MRI or T2* liver iron assessment less than 5 ms at initiation of chelation or persistently raised ferritin (e.g. usually >500 ug/l) if the patient is unable to undergo an MRI assessment;

AND

- not adequately controlled on monotherapy or DFP/DFO combination (due to compliance, toxicity, site of iron overload).

Exclusion criteria

Patients who meet the following criteria are not eligible for treatment with either DFO/DFX or DFP/DFX combination therapy:

- patients with transfusional iron loading due to other conditions such as aplastic anaemia, myelodysplasia, and haematological malignancies
- patients with iron overload for other reasons such as hereditary haemochromatosis or iatrogenic iron overload.

Starting criteria

- patients must be children or adults with transfusion dependent thalassaemia or SCD or rare anaemias who are receiving regular blood transfusions

OR

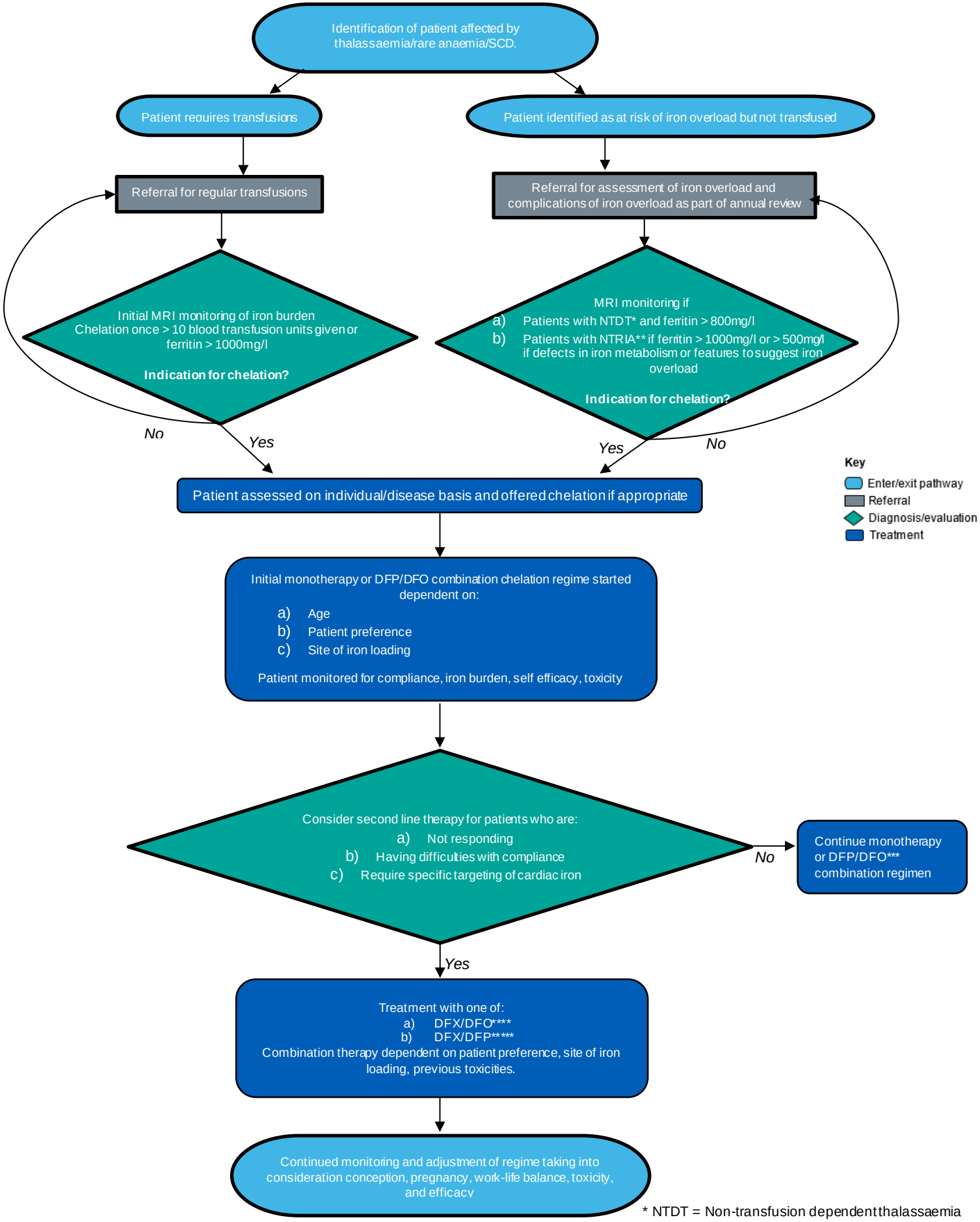
- in non-transfused thalassaemia or rare anaemias with iron overload, chelation may be started when liver iron level is ≥5mg/g dw as measured by baseline scan or Ferriscan or T2* liver iron assessment less than 5ms or persistently raised ferritin (e.g. usually >500ug/l) if the patient is unable to undergo an MRI assessment. If a patient starts a transfusion regime their chelation should be similar to that of a regularly transfused patient.

Stopping criteria

Treatment with either DFO/DFX or DFP/DFX combination therapy will be stopped if the following applies:

- where transfusions are stopped and the iron burden has returned to safe levels
- patients with normal iron burden but continuing transfusions will require doses commensurate with iron loading.

Patient pathway



* NTDT = Non-transfusion dependent thalassaemia
** NTRIA = Non-transfused rare inherited anaemia
*** DFP/DFO = Desferrioxamine/Deferiprone
****DFX/DFO = Deferasirox/Desferrioxamine
***** DFX/DFP = Deferasirox/Deferiprone

Governance arrangements

Specialist-Haemoglobinopathy-Teams-Service-Specification.pdf (england.nhs.uk)

Haemoglobinopathy-Coordinating-Centres-Service-Specification.pdf (england.nhs.uk)

Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Mechanism for funding

DFO/DFX and DFP/DFX combination therapies for the treatment of iron overload for transfused and non-transfused patients with chronic inherited anaemias will be commissioned and funded by NHS England under existing arrangements.

Audit requirements

Data will be reviewed through use of prior approval forms and also by the entry of the use of all chelating agents onto the NHR. This data will be updated into the NHR at a minimum at annual reviews.

Data will be fed back to the Haemoglobinopathy Coordinating Centres (HCCs) and onto the SHTs. National review will take place by the National Haemoglobinopathy Panel (NHP) to consider trends.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Definitions

Anaemia	A condition in which there is a deficiency of red cells or reduced haemoglobin concentration in the blood.
Blood transfusion	The process of transferring donated blood (or components of blood i.e. red blood cells) into a patient intravenously (through a vein).
Combination therapy	When more than one chelation drug is used as part of a treatment strategy.
Desferrioxamine (DFO)	Iron chelation medication administered through a needle, inserted under the skin or via a central line such as a port-a-cath or PICC/Hickman line. It is administered through a pump that runs for between 8-24 hours. Patients have to take this treatment for 5 to 7

	days a week as monotherapy or between 2 to 7 days a week as part of a combination therapy regimen.
Deferiprone (DFP)	Oral iron chelation medication taken as tablets or syrup 3 times a day.
Deferasirox (DFX)	Oral iron chelation medication currently administered as a dispersible tablet taken once daily.
Ferritin	This is a blood test used to monitor iron levels.
Iron chelation	Treatment given to patients to remove excess iron. A medicine is used to remove iron from the body – by binding to iron and passing out of the body through the urine or stools.
MRI	A medical imaging technique that uses magnetic fields to generate images of the organs in the body. Used to monitor iron burden in both the liver and the heart to ensure that chelation is given in effective doses and identifies cardiac complications before the patient develops cardiac failure.
Sickle Cell Disease	Patients who have the sickle beta globin mutation. Sickle cell disease is associated with a variety of both acute and chronic complications that can cause serious morbidity and many are on regular transfusion as part of their clinical management.
Thalassaemia	Inherited anaemia due to absence or reduced production of either alpha or beta globin chains of haemoglobin. Patients are either transfusion independent, intermittently transfused or regularly transfused but at a lower intensity.

References

American Society of Haematology. (2021). *Anaemia.* Available: https://www.hematology.org/education/patients/anemia. Last accessed 8th Nov 2021.

Auerbach, M. (2021). *Patient education: Anaemia caused by low iron in adults (Beyond the Basics).* Available: https://www.uptodate.com/contents/anemia-caused-by-low-iron-in-adults-beyond-the-basics. Last accessed 8th Nov 2021.

NHS Blood and Transplant. (2016). *Anaemia.* Available: http://www.dgft.nhs.uk/wp-content/uploads/2018/02/anaemia.pdf. Last accessed 8th Nov 2021.