# CLINICAL PRIORITIES ADVISORY GROUP
# 18 07 2022

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| **Agenda Item No** | 2.3 |
| **National Programme** | Blood and Infection |
| **Clinical Reference Group** | Haemoglobinopathies |
| **URN** | 2109 |

| **Title** |
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| Treatment of iron overload for transfused and non-transfused patients with chronic inherited anaemias (all ages) |

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| **Actions Requested** | 1. Support the adoption of the policy proposition |
| | 2. Recommend the relative priority |

**Proposition**

For routine commissioning

This clinical commissioning policy proposition recommends the extension of the published Clinical Commissioning Policy '*Treatment of iron overload for transfused and non-transfused patients with chronic inherited anaemias*' to include an additional two treatment regimens.

The following iron chelating regimes are currently commissioned:

- Desferrioxamine (DFO) monotherapy
- Deferiprone (DFP) monotherapy
- Deferasirox (DFX) monotherapy
- DFO/DFP combination

The proposition is to include the following iron-chelation combination therapies:

- DFP (oral) / DFX (oral)
- DFO (injectable) / DFX (oral)

(To note: DFP (oral) / DFX (oral) combination will be addressed in a separate CPAG SR)

Iron is a key component of haemoglobin, which is present in red blood cells. The body has no mechanism to remove excess iron and so blood transfusion therapy can result in iron overload. Iron overload can also be non-transfusion related e.g. it can be caused from iron supplementation. Iron overload causes serious

complications particularly in the liver, heart and endocrine system. Heart disease is the commonest cause of death due to iron overload. 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, severity and location of iron burden, and lifestyle issues.

The clinical policy proposition was developed through conducting an externally conducted evidence review and by a Policy Working Group (PWG) consisting of haematology experts, a public health specialist and a specialist commissioner for NHS England. This policy proposition is for use in people with chronic inherited anaemias who are at risk of iron overload due to their need for repeated transfusions. The treatment may also be required for patients with non-transfusion dependent iron overload that occurs due to increased gastrointestinal iron absorption.

These two proposed combination therapies will offer alternative treatment options for patients who are unable to achieve negative iron balance despite adherence to optimal doses of monotherapy or those who are unable to tolerate the currently commissioned iron chelation therapies outlined in aforementioned existing policy.

| **Clinical Panel recommendation** |
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| The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy. |

| **The committee is asked to receive the following assurance:** | |
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| 1. | The Head of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report. |
| 2. | The Head of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports. |
| 3. | The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposition. |
| 4. | The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed. |

| **The following documents are included (others available on request):** | |
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| 1. | Clinical Policy Proposition |
| 2. | Engagement Report |
| 3. | Evidence Summary |

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| 4. | Clinical Panel Report |
| 5. | Equality and Health Inequalities Impact Assessment |

## In the Population what is the clinical effectiveness and safety of the Intervention compared with Comparator?

| Outcome | Evidence statement |
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| **Clinical effectiveness** | |
| **Critical outcomes** | |
| **Quality of life**<br><br>**Certainty of evidence:**<br>Not applicable | This outcome is important to patients as it provides a holistic evaluation and indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Quality of life can inform the patient centred shared decision making and health policy. Quality of life questionnaires include but are not limited to the EQ-5D & SF 36 which can provide information regarding improvement in symptoms.<br><br>**No evidence was identified for this outcome.** |
| **Progression of iron overload**<br><br>**Certainty of evidence:**<br>Moderate to very low | Preventing complications of disease and its progression is important to patients as it has the potential to maintain engagement in activities of daily living and prevent increasing dependence on others. Progression, or lack of progression, of iron deposition in tissues can provide critical information on treatment effectiveness. Iron burden in the liver reflects total body iron and iron in the heart is associated with increased mortality. Changes in iron stores can be determined sooner than overall survival outcome measures and therefore a useful survival outcome for trials with shorter follow-up periods. Examples of measures include liver iron stores as measured by R2MRI or T2* cardiac or liver iron assessment, or persistently raised ferritin in those unable to undergo an MRI assessment.<br><br>In total, six studies (two RCTs, one retrospective cohort study and three prospective case series) provided evidence relating to progression of iron overload in patients with chronic inherited anaemias who develop iron overload who are treated with DFO/DFX. The two RCTs compared treatment with DFO/DFX with treatment with DFX only. The retrospective cohort study included five treatment groups: DFO/DFX, DFO, deferiprone (DFP), DFX, and DFP/DFO. The outcomes were serum ferritin, myocardial T2*, hepatic T2*, myocardial iron concentration and liver iron concentration.<br><br>*Serum ferritin*<br><br>At 24 months: |

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| | • One prospective case series (Aydinok et al 2015) reported a mean (range) serum ferritin of 5551 (1163-11317) ng/ml at baseline (n=60) and 2491 (108-11508) ng/ml at 24 months (n=34) in patients taking DFO/DFX (lower value is better). No statistical comparison was reported. (VERY LOW)<br><br>At 12 months:<br>• One RCT (Eghbali et al 2019) reported a *statistically significant* between-group difference in mean serum ferritin at 12 months between groups taking DFO/DFX and DFX only, in favour of DFO/DFX (p=0.001) (MODERATE). They reported a mean ± SD serum ferritin at baseline and 12 months of 1446 ± 987 µg/l and 737 ± 459 µg/l in patients taking DFO/DFX (n=28), a *statistically significant improvement* (p<0.01), and 1390 ± 816 µg/l and 1085 ± 919 µg/l in patients taking DFX only (n=27) (*not statistically significant*, p=0.06).<br>• One RCT (Molavi et al 2014) reported mean ± SD serum ferritin at baseline and 12 months of 4004.8 ± 1717.14 µg/l and 3529.04 ± 1540.36 µg/l in patients taking DFO/DFX (n=46), and 4094.4 ± 4552.84 µg/l and 3441.2 ± 1910.0 µg/l in patients taking DFX only (n=48). There was *no statistically significant difference* between groups at 1 year (p value for between-group difference at 12 months =0.807). No statistical comparisons were reported comparing the groups at baseline, or comparing 12 months with baseline. (LOW)<br>• One retrospective cohort study (Bordbar et al 2019) reported the mean difference in serum ferritin between baseline and 1 year follow-up for patients taking five different chelation therapy regimes. There was *no statistically significant difference* between the groups in the mean difference in serum ferritin at 1 year (p value for between-groups difference =0.353). The mean (95% CI) difference was 559.27 (-235.6 to 1354.14) for patients taking DFO/DFX (n=41) (p=0.163), 18.86 (-321.05 to 358.77) for patients taking DFO (n=44) (p=0.911), -147.36 (-341.93 to 47.2) for patients taking DFP (n=12) (p=0.122), -5.57 (-214.35 to 203.2) for patients taking DFX (n=71) (p=0.958) and 38.85 (-313.26 to 390.97) for patients taking DFP/DFO (n=88) (p=0.827). *None of the changes were statistically significant* compared to baseline. (VERY LOW)<br>• One prospective case series (Arandi et al 2015) (n=32) reported mean ± SD serum ferritin at baseline of 4031 ± 1955 ng/ml (range 2100–8000) and at 12 months of 2416 ± 1653 ng/ml (range 370–6400) in patients taking DFO/DFX, a *statistically significant improvement* (p<0·001). (VERY LOW) |

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| | At 6 months:<br>• One RCT (Molavi et al 2014) reported mean ± SD serum ferritin at baseline and 6 months of 4004.8 ± 1717.14 µg/l and 4073.9 ± 2060.44 µg/l in patients taking DFO/DFX (n=46), and 4094.4 ± 4552.84 µg/l and 4425.8 ± 2045.77 µg/l in patients taking DFX only (n=48). There were *no statistically significant differences* between groups at 6 months (p value for between-group difference at 6 months =0.105). No statistical comparisons were reported comparing the groups at baseline, or comparing 6 months with baseline. (LOW)<br>• One prospective case series (Keikhaei et al 2011) (n not stated) reported a mean (range) serum ferritin at baseline of 3590 ng/ml (1200-7200) and at 6 months of 2563 ng/ml (750-5800) in patients taking DFO/DFX, a *statistically significant improvement* (p<0.005). (VERY LOW)<br><br>*Myocardial T2**<br><br>At 24 months:<br>• One prospective case series (Aydinok et al 2015) reported a geometric mean (Gmean)[1] myocardial T2* (mT2*) of 7.2ms at baseline (n=60) and 9.5ms at 24 months (n=36) (higher value is better) in patients taking DFO/DFX. No p value was reported. The ratio of Gmeans (95% CI) at month 24 vs baseline was 1.30 (1.17 to 1.44) (30% improvement). (VERY LOW)<br><br>At 12 months:<br>• One RCT (Eghbali et al 2019) reported a *statistically significant* between-group difference in myocardial T2* at 12 months between groups taking DFO/DFX and those taking DFX only, in favour of DFO/DFX (p=0.01) (MODERATE). They reported a mean ± SD mT2* at baseline and 12 months follow-up of 23.1 ± 7.5 ms and 27.1 ± 7.0 ms in patients taking DFO/DFX (n=28) a *statistically significant improvement* (p<0.05), and 23.3 ± 7.4 ms and 22.1 ± 6.9 ms in patients taking DFX (n=27) (*not statistically significant*, p=0.3).<br>• One prospective case series (Aydinok et al 2015) reported a geometric mean (Gmean) myocardial T2* (mT2*) of 7.2ms at baseline (n=60) and 7.7ms at 12 months (n=52) (higher value is better) in patients taking DFO/DFX. No p value was reported. The ratio of Gmeans (95% CI) at month 12 vs baseline was 1.09 (1.04 to 1.15) (9% improvement). (VERY LOW) |

[1] The authors did not provide any details about how they derived the geometric means.

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| | *Hepatic T2** <br><br> At 12 months: <br> • One RCT (Eghbali et al 2019) reported *no statistically significant* between-group difference in hepatic T2* at 12 months between groups taking DFO/DFX and those taking DFX only (p value for between-group difference at 12 months =0.094) (MODERATE). They reported a mean ± SD hepatic T2* at baseline and 12 months follow-up of 9.8 ± 8.8 ms and 10.2 ± 8.2 ms in patients taking DFO/DFX (n=28), *no statistically significant difference* (p=0.5), and 7.0 ± 5.6 ms and 7.0 ± 5.3 ms in patients taking DFX (n=27), *no statistically significant difference* (p=0.7). <br><br> *Myocardial iron concentration* <br><br> At 24 months: <br> • One prospective case series (Aydinok et al 2015) reported a mean ± SD myocardial iron concentration of 4.2 ± 1.0 mg Fe/g dw at baseline (n=60), 3.9 ± 1.4 mg Fe/g dw at 12 months (n=46) and 3.1 ± 1.4 mg Fe/g dw at 24 months (n=36) in patients taking DFO/DFX (lower value better). No p value was reported. (VERY LOW) <br><br> *Liver iron concentration* <br><br> At 24 months: <br> • One prospective case series (Aydinok et al 2015) reported a mean ± SD hepatic iron concentration of 33.4 ± 14.5mgFe/g dw at baseline (n=60) and 12.8 ± 11.7mg Fe/g dw at 24 months (n=35) in patients taking DFO/DFX (lower value better). No p value was reported. (VERY LOW) <br><br> One RCT provided moderate certainty evidence of a statistically significantly lower (better) serum ferritin at 12 months in the group taking DFO/DFX compared with those taking DFX only. In patients taking DFO/DFX the improvement in serum ferritin compared to baseline was statistically significant, while in those taking DFX only it was not. A second RCT provided low certainty evidence of no statistically significant differences between patients taking DFO/DFX and DFX in serum ferritin at 12 months or at 6 months; ferritin had decreased in both groups but it was not reported if the decrease was statistically significant. One retrospective cohort study provided very low certainty evidence of no statistically significant difference between groups taking DFO/DFX, DFO only, DFP only, DFX only or DFP/DFO combination therapy in the mean difference in serum ferritin at 1 |

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| | year. There was no statistically significant difference in serum ferritin at 12 months compared with baseline in any of the groups. In patients taking DFO/DFX, two prospective case series provided very low certainty evidence of a statistically significant improvement in serum ferritin at 12 months and at 6 months respectively compared with baseline.<br><br>One RCT provided moderate certainty evidence of a statistically significantly higher (better) myocardial (m) T2* in the group taking DFO/DFX compared with DFX only. In patients taking DFO/DFX the improvement in mT2* at 12 months compared to baseline was statistically significant, while in those taking DFX only it was not. The same RCT provided moderate certainty evidence of no statistically significant difference between the groups in liver T2* at 12 months. There was no statistically significant difference in liver T2* at 12 months compared with baseline in either group. In patients taking DFO/DFX, one prospective case series provided very low certainty evidence of an improvement in the Gmean mT2* at 12 months and 24 months compared with baseline, but no p values were reported. The same prospective case series found very low certainty evidence of a reduction (improvement) in myocardial iron concentration and liver iron concentration at 24 months compared with baseline, but no p values were reported. |
| **Disease response**<br><br>**Certainty of evidence:**<br>Very low | Disease response includes but is not limited to improvement in cardiac function, endocrine function (including pituitary, pancreatic, reproductive and bone health), reduction of hepatic iron stores or other validated measures of organ function. This outcome is important to patients because it can reflect the benefits the treatment may have for a patient. This can be important to control the symptomatic burden of the disease and/or reflect subgroups who may configure additional response benefits, allowing the treatment protocol to be individualised.<br><br>In total, three studies (one retrospective cohort study and two prospective case series) provided evidence relating to disease response in patients with chronic inherited anaemias who develop iron overload who are treated with DFO/DFX. The retrospective cohort study included five treatment groups: DFO/DFX, DFO, deferiprone (DFP), DFX, and DFP/DFO and the case series included only patients receiving DFO/DFX. The outcomes were echocardiography findings and bone mineral density.<br><br>***Echocardiography findings***<br><br>**At 24 months**:<br>• One prospective case series (Aydinok et al 2015) reported a mean left ventricular ejection fraction (LVEF) |

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| | of 66.5% at baseline (n=60) and 67.9% at 24 months (n=36) (no p value reported) in patients taking DFO/DFX. The authors commented that both these values were within the normal range. **(VERY LOW)**<br><br>**At 12 months**:<br>• One prospective case series (Arandi et al 2015) (n=32) reported a mean ± SD LVEF of 55 ± 5% at baseline and 61 ± 4% at 12 months (p<0·001), a mean ± SD left ventricular diastolic dimension of 4.5 ± 0.5cm at baseline and 4 ± 0.3cm at 12 months (p<0.001), and a mean ± SD left ventricular systolic dimension of 3.2 ± 0.3cm at baseline and 2.5 ± 0.2cm at 12 months (p<0.001) in patients taking DFO/DFX. All three represented a *statistically significant improvement*. **(VERY LOW)**<br><br>*Bone mineral density*<br><br>**At 12 months**:<br>• One retrospective cohort study (Bordbar et al 2019) reported the mean lumbar spine bone mineral density (BMD) and BMD Z-score at baseline and 1 year follow-up for patients taking five different chelation therapy regimes (DFO/DFX n=41, DFO n=44, DFP n=12, DFX n=71, DFP/DFO n=88). There was *no statistically significant difference* between the groups in the mean difference in lumbar spine BMD at 1 year (p value for between-groups difference =0.642). Lumbar spine BMD increased (improved) in all groups; the increase was *statistically significant* in patients taking DFO/DFX (p=0.025) and DFX only (p=0.001). Mean lumbar spine BMD Z-score at baseline was less than -2 in all groups (range -2.86 to -3.34) [2]. The authors reported a statistically significant difference in lumbar spine BMD Z-score between groups pre-treatment (p=0.037) but no significant difference post-treatment (p=0.067). There was *no statistically significant difference* between the groups in the mean difference in lumbar spine BMD Z-score at 1 year (p value for between-groups difference =0.170). Lumbar spine BMD Z-score increased (improved) in all groups; in DFO/DFX the change was *statistically significant* (p=0.015). **(VERY LOW)**<br><br>• One retrospective cohort study (Bordbar et al 2019) reported the mean femoral neck BMD and BMD Z-score at baseline and 1 year follow-up for patients taking five different chelation therapy regimes (DFO/DFX n=41, DFO |

[2] BMD Z-score compares BMD to the average for age and gender. A Z-score below -2 is defined as below the expected range.

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| | n=44, DFP n=12, DFX n=71, DFP/DFO n=88). There was *no statistically significant difference* between the groups in the mean difference in femoral neck BMD at 1 year (p value for between-group difference =0.506). The changes in femoral neck BMD at follow-up compared with baseline were *not statistically significant* in any of the groups. Mean femoral neck BMD Z-score at baseline was less than -2 in all groups but one (range -1.96 to -2.52). The authors reported no statistically significant difference in femoral neck BMD Z-score between groups pre-treatment (p=0.250) or post-treatment (p=0.234). There was *no statistically significant difference* between the groups in the mean difference in femoral neck BMD Z-score at 1 year (p value for between-group difference =0.828). Femoral neck BMD Z-score increased (improved) in all groups; in DFO/DFX and DFO only the change was *statistically significant* (p=0.022 in both groups). **(VERY LOW)**<br><br>One retrospective cohort study included patients taking five different iron chelation regimes (DFO/DFX, DFO only, DFP only, DFX only, DFP/DFO). The study provided very low certainty evidence of no statistically significant difference between the treatment groups in the mean difference in lumbar spine BMD or lumbar spine BMD Z-score at 1 year. The study reported a statistically significant improvement in lumbar spine BMD at 12 months compared with baseline in patients taking DFO/DFX and DFX only, and a statistically significant improvement in lumbar spine BMD Z-score at 12 months compared with baseline in patients taking DFO/DFX. The study also provided very low certainty evidence of no statistically significant difference between the groups in the mean difference in femoral neck BMD or femoral neck BMD Z-score at 1 year. There were no statistically significant changes in femoral neck BMD at 12 months compared with baseline in any of the treatment groups, but a statistically significant improvement in femoral neck BMD Z-score at 12 months compared with baseline in patients taking DFO/DFX and DFO only. There were no statistically significant changes in BMD or BMD Z-scores in patients taking DFP or DFP/DFO. Of note, the BMD Z-score was below the expected range for age and gender in all groups at baseline.<br><br>One prospective case series provided very low certainty evidence that left ventricular ejection fraction (LVEF) was within the normal range at baseline and 24 months follow-up in patients taking DFO/DFX. A second prospective case series provided very low certainty evidence that LVEF, left ventricular diastolic dimension and left ventricular systolic dimension all improved statistically significantly at 12 months follow-up compared with baseline in patients taking DFO/DFX. |

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| **Important outcomes** | |
| **Adherence to treatment**<br><br>**Certainty of evidence:**<br>Very low | This is important to patients because it is vital to the function of iron chelating drugs that they are taken regularly as prescribed in order to gain the maximum effect, improve iron burden and prevent the complications of iron overload.<br><br>In total, three studies (three prospective case series) provided evidence relating to adherence to treatment in patients with chronic inherited anaemias who develop iron overload who are treated with DFO/DFX.<br><br>**At 24 months**:<br>• One prospective case series (Aydinok et al 2015) reported that 26 out of 60 (43%) patients recruited had discontinued treatment with DFO/DFX. Most discontinuations (21 out of 60, 35%) occurred within the first 12 months. Reasons included mT2* <5 ms (n=5), an adverse effect (n=5), loss to follow-up (n=6) and consent withdrawal (including relocation) (n=6). **(VERY LOW)**<br><br>**At 12 months**:<br>• One prospective case series (Arandi et al 2015) (n=32) reported 100% treatment compliance with DFO/DFX. Treatment compliance was defined as having consumed DFO 2 days per week and DFX every day, assessed by patient self-report and when patients returned medication cartridges to receive the next doses. (**VERY LOW)**<br><br>**At 6 months**:<br>• One prospective case series (Kheikhaei 2011) (n not stated) reported 95% treatment compliance with DFO/DFX (assessed by pill counts and diary cards). **(VERY LOW)**<br><br>One prospective case series provided very low certainty evidence that 26 out of 60 patients (43%) had discontinued treatment with DFO/DFX at 2 years, of whom 21 out of 60 (35%) had discontinued within the first 12 months. In contrast, two prospective case series provided very low certainty evidence of treatment compliance of 100% at one year and 95% at 6 months respectively. |
| **Psychological outcomes**<br><br>**Certainty of evidence:**<br>Not applicable | These outcomes are important to patients because they can impact their mood, motivation and self-esteem which can have implications for treatment compliance. Positive healthcare outcomes rely upon patients' ability to comply with their rigorous treatment regimes. Delayed puberty due to poor iron control is the most common endocrine complication in thalassaemia. Often this can result in diminished self-esteem and body |

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| | confidence as the secondary conditions causes illnesses that can deform, debilitate and disable them. Lack of concordance can be a ubiquitous threat to not only patients' physical health but compound their psychosocial well-being.<br><br>**No evidence was identified for this outcome.** |
| **Mortality**<br><br>**Certainty of evidence:**<br>Not applicable | Mortality is usually the gold standard for assessing survival benefit of drug treatments. This outcome is important to patients because it considers whether the treatment reduces mortality although it does not reflect morbidity or patient experience.<br><br>**No evidence was identified for this outcome.** |
| **Activities of daily living (ADL)**<br><br>**Certainty of evidence:**<br>Not applicable | ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home and recreational settings. They encompass patients' individual rehabilitation goals and facilitate inclusion and participation.<br><br>**No evidence was identified for this outcome.** |
| **Safety** | |
| **Adverse events (AEs)**<br><br>**Certainty of evidence:**<br><br>Moderate to very low | Adverse events are important to patients because they will impact on their treatment choices, adherence, recovery and could have long term sequelae if they are irreversible. It reflects the tolerability and adverse effects of the treatment. From a service delivery perspective, it reflects the additional demands placed on the health system to manage the adverse consequences of the treatment. [Serious adverse events include agranulocytosis, renal impairment, heart failure, and severe gastrointestinal side effects (e.g. perforated gastric ulcer). Common adverse effects include gastrointestinal disturbances (such as dyspepsia, gastrointestinal pain, nausea, vomiting, diarrhoea, and constipation), somatic complaints, physical symptoms, high emotionality and low sociability, skin reaction at the injection site and joint pain.]<br><br>In total, five studies (two RCTs and three prospective case series) provided evidence relating to adverse events in patients with chronic inherited anaemias who develop iron overload who are treated with DFO/DFX.<br><br>***Adverse events***<br><br>**At 24 months**:<br>• One prospective case series (Aydinok et al 2015) reported that out of 60 patients recruited taking DFO/DFX, 54 (90%) had any AE. Of these 5 (8.3%) had discontinued treatment as a result of AEs, 2 (3.3%) had |

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| | abdominal pain, and 1 (1.7%) had each of arthritis, DRESS and pruritis. In 29 (48.3%) patients, AEs had led to dose adjustment or interruption; these comprised UPCR increase in 6 (10.0%), abdominal pain in 5 (8.3%), diarrhoea in 5 (8.3%), pyrexia in 4 (6.7%), nausea in 3 (5.0%), influenza in 3 (5.0%) and blood creatinine increase in 3 (5.0%). They also reported mean ± SD ALT of 82.6 U/l ± 59.1 at baseline and 42.2 U/l ± 43.4 at 12 months in n=34 patients (no p value reported) (lower value better). **(VERY LOW)**<br><br>**At 12 months**:<br>• One RCT (Eghbali et al 2019) reported an incidence of mild gastrointestinal symptoms in 11 (39%) patients taking DFO/DFX (n=28) and 11 (40%) patients taking DFX only (n=27). They reported an incidence of transient skin rashes in 4 (14%) patients taking DFO/DFX and 5 (18%) patients taking DFX only. No comparison between the groups was reported. They also reported that both ALT and AST increased from baseline in both DFO/DFX (n=28) and DFX (n=27) groups, but *statistically significantly* more in the DFX group ($p<0.05$ for both ALT and AST) (no details provided). The same RCT also reported that bilirubin was *significantly higher* at follow-up in the DFO/DFX group (n=28) than the DFX group (n=27) ($p<0.05$) (no details provided). They also reported *no significant increase* in creatinine in either the DFO/DFX (n=28) or DFX (n=27) group (no details provided), and that BUN increased from baseline in both groups, but within the normal range (no details provided). **(MODERATE)**<br><br>• One RCT (Molavi et al 2014) reported mean ± SD ALT at baseline and one year follow-up of 70.21 ± 46.32 g/dl and 61.60 ± 29.75 g/dl in patients taking DFO/DFX (n=46) and 58.25 ± 29.84 g/dl and 54.85 ± 20.01 g/dl in patients taking DFX only (n=48). There was *no statistically significant difference* between groups at 12 months (p value for between-group difference at 12 months =0.185). They also reported mean ± SD AST at baseline and one year follow-up of 66.76 ± 36.17 g/dl and 59.19 ± 21.02 g/dl in patients taking DFO/DFX (n=46) and 56.45 ± 25.99 g/dl and 51.81 ± 18.63 g/dl in patients taking DFX only (n=48). There was *no statistically significant difference* between groups at 12 months (p value for between-group difference at 12 months =0.075). **(LOW)**<br><br>• One prospective case series (Arandi et al 2015) (n=32) reported a severe skin rash after taking DFO in 1 patient. They also reported mean ± SD ALT of 45.18 ± 51.14 IU/l (range not reported) at baseline and 41.59 ± 44.58 (range |

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| | 8–178) IU/l at 12 months (*no statistically significant difference*, p=0.567), and mean ± SD AST of 33.68 ± 19.29 IU/l (range 7–92) at baseline and 37.5 ± 31.99 (range 11–143) IU/l at 12 months (*no statistically significant difference*, p=0.452). The same study also reported mean ± SD creatinine of 0.59 ± 0.24 (range 0.3–1.6) mg/dl at baseline and 0.64 ± 0.23 (0.3–1.3) mg/dl at 12 months in patients taking DFO/DFX (*no statistically significant difference*, p=0.215), and mean ± SD BUN of 13.87 ± 4.79 (range 4–25) mg/dl at baseline and 14.31 ± 4.99 (range 6–30) mg/dl at 12 months (*no statistically significant difference*, p=0.623) (lower values better). **(VERY LOW)**<br><br>**At 6 months**:<br>• One prospective case series (Keikhaei 2011) (n=62) reported headache, skin rash, abdominal pain, diarrhoea, anorexia and proteinuria each in 1 to 2 patients taking DFO/DFX (1% – 3%). They also reported that 10 (16%) patients taking DFO/DFX had an elevated AST, that 11 (17%) patients had an elevated ALT and that 13 (21%) of patients had a rising creatinine (no definitions or significance measures reported for any of these outcomes). **(VERY LOW)**<br><br>One RCT reported that patients taking DFO/DFX and DFX had similar rates of mild gastrointestinal symptoms (39% and 40% respectively) and transient skin rashes (14% and 18% respectively) but no statistical comparisons were reported. One prospective case series provided very low certainty evidence that headache, skin rash, abdominal pain, diarrhoea, anorexia and proteinuria each occurred in only 1% to 3% of patients. In contrast, a second prospective case series provided very low certainty evidence that 90% of 60 patients taking DFO/DFX had had any adverse event (AE) within 2 years, including 29 (48.3%) patients in whom AEs had led to dose adjustment or interruption; these AEs included UPCR increase, abdominal pain, diarrhoea, pyrexia, nausea, influenza and blood creatinine increase.<br><br>One RCT provided moderate certainty evidence of increases from baseline in ALT and AST at 12 months in both DFO/DFX and DFX only treatment groups with the increase statistically significantly higher in the DFX group, and of statistically significantly higher bilirubin at 12 months in the DFO/DFX group than the DFX group. A second RCT provided low certainty evidence of no statistically significant difference between DFO/DFX and DFX only treatment groups in ALT or AST at 12 months. One prospective case series provided very low certainty evidence of no statistically significant difference in either ALT or |

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| | AST at 12 months compared with baseline in patients treated with DFO/DFX.<br>One RCT provided moderate certainty evidence of no statistically significant increase in creatinine in either the DFO/DFX or DFX groups at 12 months compared with baseline.<br>One prospective case series provided very low certainty evidence of no statistically significant difference in creatinine or blood urea nitrogen at 12 months compared with baseline in patients taking DFO/DFX. |

**Abbreviations**
AE: adverse event; ALT: alanine aminotransferase; AST: aspartate transaminase; BMD: bone mineral density; BUN: blood urea nitrogen; CI: confidence intervals; DFO: desferrioxamine or deferoxamine; DFP: deferiprone; DFX: deferasirox; dl: decilitre; DRESS: drug rash with eosinophilia and systemic symptoms; dw: dry weight; Fe: iron; Gmean: geometric mean; IU: international units; l: litre; LIC: liver iron concentration; LVEF: left ventricular ejection fraction; mg: milligrams; ms: milliseconds; mT2*: myocardial T2*; ng: nanograms; RCT: randomised controlled trial; SD: standard deviation; TDT: transfusion-dependent thalassaemia; ULN: upper limit of normal; UPCR: urinary protein/creatinine ratio; µg: micrograms

### In the Population what is the cost effectiveness of the Intervention compared with Comparator?

| Outcome | Evidence statement |
|---|---|
| Cost effectiveness | No evidence was identified for cost effectiveness |

### From the evidence selected, are there any subgroups of patients that may benefit from the intervention more than the wider population of interest?

| Outcome | Evidence statement |
|---|---|
| Subgroups:<br>• Gender<br>• Splenectomy or no splenectomy<br>• Previous type of iron chelation therapy<br>• Baseline liver iron concentration<br>Baseline serum ferritin | In total, two studies (two prospective case series) provided evidence relating to subgroups of patients that may benefit from the combination of DFO and DFX more than the wider population of interest. The subgroups considered were gender, previous splenectomy or no splenectomy, previous type of iron chelation therapy, baseline liver iron concentration and baseline serum ferritin.<br><br>***Gender***<br>• One prospective case series (Arandi et al 2015) reported that the mean ± SD decrease (improvement) in serum ferritin between baseline and one year follow-up was 1575 ± 1831 ng/ml for males (n=12) and 1637 ± 1307 ng/ml for females (n=20). There was |

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|---|---|
| | *no statistically significant difference* between the genders (p=0.454).<br><br>***Previous splenectomy or no splenectomy***<br>• One prospective case series (Arandi et al 2015) reported that the mean ± SD decrease (improvement) in serum ferritin between baseline and one year follow-up was 1823 ± 1290 ng/ml in patients who had undergone splenectomy (n=11) and 1504 ± 1612 ng/ml in patients who had not undergone splenectomy (n=21). There was *no statistically significant difference* between the groups (p=0.307).<br><br>***Previous iron chelation monotherapy***<br>• One prospective case series (Arandi et al 2015) reported that the mean ± SD serum ferritin at baseline and one year follow-up was 3568 ± 950.35 ng/ml and 1756 ± 967.32 ng/ml in patients on previous DFX monotherapy (n=2) (p=0.18), 4050.5 ± 2235.85 ng/ml and 2496.06 ± 1971.16 ng/ml in patients on previous DFO monotherapy (n=16) (p=0.001), and 4074.85 ± 1802.57 ng/ml and 2420.28 ± 1375.69 ng/ml in patients on previous DFP monotherapy (n=14) (p=0.002). The reduction (improvement) was *statistically significant* in those on DFO or DFP monotherapy but not in those on DFX monotherapy.<br><br>***Baseline liver iron concentration***<br>• One prospective case series (Aydinok et al 2015) reported that the Gmean (95%CI) myocardial T2* at baseline and 24 months was 8.04 ms (7.39 to 8.75) in patients with baseline liver iron concentration <30mg Fe/g dw (n=19) and 6.83 ms (6.43 to 7.26) in patients with baseline liver iron concentration ≥30mg Fe/g dw (n=41). They reported that the Gmean ratio (95% CI) of month 24/baseline was 1.35 (1.16 to 1.58) in patients with baseline liver iron concentration <30mg Fe/g dw and 1.26 (1.09 to 1.45) in patients with baseline liver iron concentration ≥30mg Fe/g dw. No p values were reported.<br><br>***Baseline serum ferritin***<br>• One prospective case series (Aydinok et al 2015) reported that the Gmean (95%CI) myocardial T2* at baseline and 24 months was 7.81 ms (6.36 to 9.60) in patients with baseline serum ferritin ≤2500 ng/ml (n=7) and 7.12 ms (6.74 to 7.52) in patients with baseline serum ferritin >2500 ng/ml (n=53). They reported that the Gmean ratio (95% CI) of month 24/baseline was 1.40 (1.07 to 1.82) in patients with |

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|---|---|
| | baseline serum ferritin ≤2500 ng/ml and 1.28 (1.14 to 1.43) in patients with baseline serum ferritin >2500 ng/ml. No p values were reported.<br><br>One prospective case series reported no statistically significant difference in the reduction (improvement) in serum ferritin on treatment with DFO/DFX between males and females, or between patients who had undergone splenectomy and those who had not. The study also reported a similar degree of improvement in serum ferritin on treatment with DFO/DFX in patients previously treated with either DFO, DFP or DFX monotherapy; the improvement was statistically significant in the DFO and DFP groups but not the DFX group. A second prospective case series reported that myocardial T2* improved to a similar degree in patients treated with DFO/DFX regardless of whether they had lower or higher baseline liver iron concentration or lower or higher baseline serum ferritin concentration. |

**Abbreviations**

CI: confidence intervals; DFO: desferrioxamine or deferoxamine; DFP: deferiprone; DFX: deferasirox; dw: dry weight; Fe: iron; Gmean: geometric mean; ml: millilitres; ng: nanograms

**Patient Impact Summary**

**The condition has the following impacts on the patient's everyday life:**

- **mobility:** patients can have moderate - severe problems in walking about
- **ability to provide self-care:** patients can have moderate - severe problems in washing or dressing
- **undertaking usual activities:** patients can have moderate - severe problems in doing their usual activities
- **experience of pain/discomfort:** patients can have moderate - severe pain or discomfort
- **experience of anxiety/depression:** patients can experience moderate to severe episodes of anxiety or depression during their lifetime

**Further details of impact upon patients:**

Chronic inherited anaemias encompass a range of conditions that have a heterogenous impact based on prognosis and individual patient experience. Indeed, the impact of the background and incidence of secondary conditions such as but not limited to endocrine, metabolic and reproductive dysfunction, cardiovascular dysfunction, hepatobiliary diseases, and psychological burden are significantly worsened by presence of iron overload.

All patients have some degree of fatigue and pain that can affect their daily life. Pain and fatigue can often increase before and after transfusion. Patients can also suffer from breathlessness, palpitations, bone and joint pain, skin discolouration,

headaches, lack of concentration, cognition disturbances, low mood and insomnia.

**Further details of impact upon carers:**
Chronic inherited anaemias can lead to a high burden on the carer to help with the daily management of chronic illness and self-care tasks (bathing, dressing, cooking, and preparing meals, ironing, cleaning the house, getting out and about or help using mobility aids) which may be difficult or impossible for the patient depending on prognosis.

| **Considerations from review by Rare Disease Advisory Group** |
| --- |
| **Not applicable** |

| **Pharmaceutical considerations** |
| --- |
| This policy proposition 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.<br><br>Provider organisations must register all patients using prior approval software. |

| **Considerations from review by National Programme of Care** |
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| 1) The proposition received the full support of the Blood and Infection PoC on the 14th June 2022 |