NZBS HAEMOCHROMATOSIS & THERAPEUTIC VENESECTION POLICY

REASON FOR ISSUE: New Document for TV Clinic

1. INTRODUCTION

NZBS will provide a venesection service for people in New Zealand who require venesection for conditions that are known to benefit from therapeutic venesection. These include hereditary Haemochromatosis, Polycythaemia / Erythrocythaemia, and Porphyria Cutanea Tarda. (Other indications, such as pathological iron loading in non-alcoholic fatty liver disease, may become accepted on the basis of clinical studies.)

People requiring venesection may, under certain circumstances, be acceptable as blood donors; otherwise blood collected for therapeutic purposes is discarded. Such blood may be used for research, calibration, or quality control purposes as appropriate, provided written consent and where required ethics approval for such use has been obtained. People who are not eligible for NZ health care will not be accepted for venesection.

People requiring venesection must be referred to NZBS by a general practitioner or a specialist. The referring doctor retains primary responsibility for the patient's care, and the responsibility of NZBS is limited to:

- ***Accepting*** the patient onto the venesection programme.
- ***Deciding*** the number and frequency of venesections in accordance with current guidelines.
- ***Monitoring*** the patient around the venesections to ensure that harm is avoided and that intended therapeutic targets are achieved.
- ***Communicating*** with the referring or primary clinician to ensure continuity of care.
- ***Avoiding*** gaps in care, emphasizing in particular that NZBS is not responsible for management of complications, including follow up of liver disease/risks from fibrosis, or for conducting or following up of family studies, or for regular follow up where the patient is treated by attendance at regular blood donor clinics.
- ***Ensuring*** that the patient is comprehensively communicated with in the management of their condition.

2. HEREDITARY HAEMOCHROMATOSIS

2.1 Accepting the patient onto the venesection programme.

The patient must be referred in writing by a General Practitioner, Specialist or a Nurse Practitioner may also refer. The referral shall include the basis for the diagnosis of hereditary Haemochromatosis. NZBS shall not be obliged to perform venesections for Hyperferritinaemia where the diagnosis of a pathological iron loading condition has not been established to accepted criteria:

- A genotype known to be associated with pathological iron loading (C282Y homozygosity, compound heterozygosity for C282Y and H63D, Ferroportin disease or other established genotype)

OR

- Evidence of pathological iron loading in the presence of negative tests for the known genotypes – this evidence can consist of either diagnostic liver biopsy findings, or a positive trial of venesection (see Section 5 below). (Hyperferritinaemia of whatever level is not diagnostic of Haemochromatosis or of pathological iron loading.)

AND

- Hyperferritinaemia above the normal range, and transferrin saturation > 45%.
- If the patient meets these criteria, and is not excluded from treatment at NZBS on the basis of the exclusion criteria in Section 6.0 or if a trial of venesection is warranted, (see Section 5) the patient is commenced on venesection therapy. If not, a letter is sent to the referring practitioner outlining why the referral has been declined. Where the referral is declined the referring letter and the reply are recorded for subsequent retrieval as needed.

2.2 Deciding the number and frequency of venesections.

The final decision on the implementation of the schedule rests with the NZBS physician. Tolerance of the procedure by the patient, venous access etc. may mandate changes in the schedule at the discretion of the NZBS physician.

The venesection schedule will depend on the clinical circumstances, but in general:

- *Where the initial serum ferritin is greater than 1000µg/L* an aggressive programme of weekly venesections will be performed until the ferritin is reduced to <50µg/L. In the presence of abnormal liver function tests, and especially in the presence of fibrosis, this level of venesection may be seen as a minimum, unless the patient tolerates the rate of venesection poorly. In the absence of C282Y homozygosity there may be an alternative cause for the liver inflammation and very high serum ferritin other than iron loading; regular serum ferritin monitoring will reveal if this is the case.
- *Where the initial serum ferritin level is <1000µg/L* and liver function is normal then the initial rate of venesection may be modified. Further clinical trial evidence may become available to guide therapy in this region.
- Where there is evidence of hepatic inflammation and the serum ferritin has not been >1000µg/L, an alternative cause for the elevated LFTs must be established; however venesection is still indicated.
- *Where the initial serum ferritin is within the normal range* (the patient having been identified as having a haemochromatosis genotype on incidental testing or family studies) or
- *Where the patient's serum ferritin has been reduced to the target level of 50 – 100µg/L,* then 3 monthly venesections with annual serum ferritin review is acceptable. There is no evidence to guide more aggressive therapy in this setting. Lower frequencies of venesection can be applied if indicated by serum ferritin levels.

It is customary to maintain serum ferritin levels in the range of 50 – 100µg/L; however there is no evidence at the time of writing to indicate that this is better than at any level <1000µg/L. At present a range of 50 – 100µg/L represents a pragmatic target level in patients who have had previous evidence of iron loading. Some recent guidelines accept any level within the normal range as adequate, and clinical studies are in progress to attempt to establish an evidence base for future

guidance. *In particular, where a patient has been identified by screening testing before developing Hyperferritinaemia, there is no requirement to maintain the serum ferritin below the upper limit of the normal range by venesection.*

Transferrin saturation is used by some clinicians to manage iron status in patients who have genetic haemochromatosis, although this approach has not been addressed to date in clinical trials. The goal is to reduce transferrin saturation to be consistently <50%. Most patients with genetic haemochromatosis (homozygous C282Y mutation of the HFE gene) and iron overload achieve a transferrin saturation <50% when the ferritin level is reduced to 50 – 100mcg/L. A small subset of patients require the serum ferritin to be below 30 – 40mcg/L to achieve a transferrin saturation <50%. A further subgroup may achieve transferrin saturation values <50% when ferritin levels are in the range 100 – 150mcg/L.

- *Symptomatic patients at lower levels of serum ferritin.* A number of patients assert that they experience fatigue, pains in joints, difficult in concentrating or similar symptoms when their serum ferritin levels are rising, but still well within the normal range, and that these symptoms are predictably relieved by venesection. It is impossible to separate attenuation of some low level of iron-associated inflammatory disease from a placebo effect at the current state of knowledge. It is reasonable to venesect these patients (in the presence of a firm diagnosis of an iron loading disorder) at a frequency that keeps them feeling well, ensuring that the patient does not become iron deficient.

2.3 Monitoring the patient around the venesections to ensure that harm is avoided and that intended therapeutic targets are achieved.

All patients are assessed for fitness to undergo venesection by the clinic nursing staff, who shall refer to an NZBS doctor at their discretion. All patients have a point of care haemoglobin test performed to ensure that they are not anaemic below a level of 110g/L (on a venous sample if a finger-prick blood sample has a haemoglobin level <110g/L).

- Serum ferritin levels are assessed at a frequency depending on the phase of de-ironing, the clinical diagnosis and the rate of venesection. In general testing ferritin levels after every 6 to 8 venesections will be adequate to monitor response in patients undergoing aggressive venesections; yearly checks will suffice in patients in stable phases.
- Patients with unexplained and unexpected low levels of serum ferritin during monitoring in stable phase require referral for investigation for occult causes of blood loss.
- Patients with unexpectedly rapid falls in serum ferritin or haemoglobin levels in initial phases of venesection require reassessment of their diagnosis.

2.4 Provision of therapeutic venesection as a blood donor

When a patient with genetic haemochromatosis has achieved the target ferritin level then they may be considered for suitability for the community venesection programme. This applies for those donors who meet standard donor selection criteria and who agree to be manged in this way. Where these criteria are met the individual will be discharged from the clinic and advised to

- donate blood every 3 months
- have their ferritin level checked by the their General Practitioner on an annual basis.

NZBS will monitor the number of blood donations given and contact the donor, and their General Practitioner, in the event that none are given in any year. If the health status of the individual changes and they are no longer eligible to donate then they should be re-referred to the therapeutic venesection clinic.

2.5 Communicating with the referring or primary clinician to ensure continuity of care.

The patient's general practitioner or the referring clinician maintains overall responsibility for the care of the patient. This is particularly important when the patient's venesection requirement is to be managed as a normal blood donor, without any further input from the haemochromatosis clinic at NZBS. It must be clear to both patient and their GP that ongoing monitoring is necessary and that NZBS is no longer providing that monitoring, nor is NZBS providing annual reports of venesections in this setting.
Formal standardised communication with the GP (and referring clinician if desirable or necessary) is required:

- At acceptance onto the programme/commencement of therapy
- Where the referral is declined
- At every major change in treatment – when a programme of aggressive venesection is completed and replaced by stable-phase management, when the donor is discharged to GP follow up.
- Annually in stable phase as a type 11 (undergoing phlebotomy at a blood centre, blood not suitable for transfusion) and a type 26 (undergoing phlebotomy at a blood centre, blood is suitable for transfusion). Where the patient has not attended during the year this will be communicated to the referring clinician by copy of a letter to the donor/patient (this also applies to type 33 donors as identified in 2.4 above) - GPs will be asked to inform NZBS where a patient has no further need of NZBS services.

The acceptance and annual report letters shall remind the GP that family studies or hepatic follow up is not being managed by NZBS.

The patient shall be copied in all correspondence with the GP, or at least notified that correspondence has taken place. Correspondence shall be documented in the patient's record, and shall be done using controlled document templates.

2.6 Avoiding gaps in care

- *Management of complications*, especially follow up of liver disease/risks from fibrosis. All annual reports as well as the initial letters will contain reminders that the management and follow up of complications of haemochromatosis remain the responsibility of the primary or referring team.
- *Family studies.* Sibling follow up and family tracing will similarly be pointed out as the responsibility of the referring or primary teams on the acceptance letters as a standard inclusion.

2.7 Ensuring that the patient is comprehensively communicated with in the management of their condition.

This is managed through patient & donor information leaflets and copies of annual reports as above.

3. POLYCYTHAEMIA / ERYTHROCYTOSIS

3.1 Accepting the patient onto the venesection programme.

The patient must be referred in writing by a specialist; specialist nurse practitioners may refer. The referral shall specify the diagnosis of polycythaemia, and whether from Polycythaemia Rubra Vera or other cause. The benefit of and the therapeutic targets for, venesection in other forms of erythrocytosis are not as well established as for PRV; cases and their venesection schedules will be individually considered in discussion with the referring clinician. (Patients with high haemoglobin levels as a complication of testosterone replacement therapy do not require therapeutic venesection.)

3.2 Deciding the number and frequency of venesections in agreement with the referring clinician.

The clinician will usually state the level of haematocrit required. For PRV this should be 0.45 for both men and women. For secondary Erythrocytosis and for apparent Polycythaemia different target levels may be defined. The frequency of venesection may be determined by the referring clinician; if not, a decision can be made by the NZBS physician and reviewed depending on response in the haematocrit level. For very high levels of haemoglobin at diagnosis daily venesection may be indicated. Erythrocytapheresis may be preferable in such circumstances.

3.3 Monitoring the patient around the venesections to ensure that harm is avoided and that intended therapeutic targets are achieved.

All patients are assessed for fitness to undergo venesection by the TV clinic RN in consultation with an NZBS physician. Prior to venesection a full blood count result from a recent blood sample should be available from the referring clinician; this removes the need for pre-venesection testing of haemoglobin if performed within the previous ten days. Where very frequent venesections are being performed for high haematocrit, a point of care test of haemoglobin is required prior to each venesection, with a cut-off of 110g/L before venesection can proceed.

3.4 Communicating with the referring clinician to ensure continuity of care; avoiding gaps in care.

Patients must have regular follow-up appointments at the referring clinic.

3.5 Ensuring that the patient is comprehensively communicated with in the management of their condition.

This is managed through the referring clinic.

4. PORPHYRIA CUTANEA TARDA (PCT)

Patients with PCT may develop iron overload and associated liver disease; therapeutic venesection is a treatment of choice. It may take approximately six months to achieve full remission through venesection of 1 unit two weekly, though skin lesions may improve after approximately six venesections. The therapeutic goal is to induce remission of symptoms and/or to reduce the serum ferritin to <20µg/L. Response to venesection can occur without pre-existing Hyperferritinaemia, so that a diagnosis of PCT with abnormal liver function may be considered sufficient indication for venesection. There may be associated homozygosity or heterozygosity for haemochromatosis mutations, and there is a strong association with hepatitis C infection. Alcohol ingestion and oestrogens are also well-recognised aggravating factors. 20% of cases are familial.

4.1 Accepting the patient onto the venesection programme.

The patient must be referred in writing by a specialist – specialist nurse practitioners may refer. The referral shall include the basis for the requirement for therapeutic venesection, and should specify the frequency of venesections.

4.2 Deciding the number and frequency of venesections in agreement with the referring clinician.

The clinician will usually state the number and rate of venesections required; in default fortnightly venesections until the serum ferritin is less than 20µg/L is the usual schedule. Therapy following remission or when the serum ferritin is <20µg/L is decided by the referring specialist – this is because additional measures such as the identification and avoidance of precipitating factors may make further treatments unnecessary.

4.3 Monitoring the patient around the venesections to ensure that harm is avoided and that intended therapeutic targets are achieved.

All patients are assessed for fitness to undergo venesection by the TV clinic RN. All patients have a haemoglobin finger prick test performed to ensure that their haemoglobin is > 110 g/L(repeat a venous sample if a finger prick blood sample has a haemoglobin level <110g/L). Continuing venesections when the haemoglobin level is below 110g/L can be approved by the NZBS physician if considered necessary.

4.4 Communicating with the referring clinician to ensure continuity of care; avoiding gaps in care.

Patients must have regular follow-up appointments at the referring clinic. At the end of the initial course of treatment (patient in remission, or serum ferritin <20µg/L) the patient is discharged back to the referring clinician.

4.5 Ensuring that the patient is comprehensively communicated with in the management of their condition.

This is managed through the referring clinic.

5. OTHER CONDITIONS; TRIAL OF VENESECTION.

Patients may be referred with Hyperferritinaemia associated with inflammatory conditions without Haemochromatosis, including Hepatic Steatosis, Hepatitis C, and Metabolic Syndrome. Often the referral will be for Hyperferritinaemia without evidence of Haemochromatosis, and without evidence of a clinically recognisable source of inflammation. However, no evidence exists that demonstrates consistent benefit from venesection in any of these conditions, and venesection is not currently incorporated in guidelines for these conditions. ***People with Hyperferritinaemia of uncertain cause are not acceptable as blood donors.***

Therapeutic venesection may have a powerful psychological effect independently of any direct effect on a disease process – it will be impossible to separate these effects in individual patients, making it very difficult to stop a therapy in a patient who has derived symptomatic benefit, once started in the absence of a clear indication. In addition, where there is no clear indication for therapeutic venesection, patients and clinicians may be misled into relying on a useless therapy for an underlying disorder that has not been properly diagnosed.

In the absence of new, persuasive clinical trial evidence, venesection for these conditions should be declined, or at most offered as a trial of venesection to determine if a true, not-currently-categorised form of iron loading disorder is present – a course of 16 full venesections over a year, which is considered positive (evidence of iron loading) if no iron deficiency anaemia develops. If anaemia develops, further venesections should be declined and the patient returned to the referring clinicians' care.

Nevertheless, we do not know why patients with iron loading develop some of the symptoms that they do, nor do we know why venesection ameliorates some of those symptoms in the way that it seems to. It may be that venesections can genuinely improve outcomes or symptoms in some patients with inflammatory disorders in ways that are not recognised at present: future clinical trials may change practices.

6. EXCLUSION CRITERIA

- Age under 16 years
- Absence of proper referral
- Absence of a diagnosis of a clinical disease treatable by venesection, (unless formally accepted for a trial of venesection)
- Symptomatic heart disease or other symptomatic vascular disease (TIAs, claudication, <6 months post myocardial infarction or cardiac procedure, blood pressure >200mmHg)
- Other significant co-morbidities:
    - Patients with significant comorbidities may be accepted for smaller volume venesections at the discretion of the NZBS physician.
    - Newly diagnosed patients with organ damage from haemochromatosis should be managed with standard therapy insofar as possible. Patients on maintenance therapy may continue to benefit from venesections, and age is not an absolute

contraindication to venesection. However, normo-ferritinaemic patients over the age of 75 years are unlikely to develop tissue damage de novo from iron accumulation over their remaining lifetimes and a conservative approach is justified to reduce the risk of cardiovascular events, fainting and falls. Comorbidities causing either inflammatory Hyperferritinaemia or occult blood loss are more likely to arise in older patients.

7. MINIMUM TRAINING REQUIREMENTS *(FOR NZBS USE ONLY)*

☐	Complete Document Sign-Off Sheet (108F060). • Read specified sections: Sections: *(enter section numbers)*
☒	Complete Document Sign-Off Sheet (108F060). • Read and understand whole document
☐	Complete Document Sign-Off Sheet (108F060). • Formal training required. Specify: *(enter details of formal training)*
☐	Complete Training Module *(enter name of module)*
☐	No training required. Specify reason: