Clinical practice guidelines

Management of patients with *HFE*-related haemochromatosis (Type 1 haemochromatosis)

July 2005

Synopsis

Title	Management of HFE-related haemochromatosis
Publication date	July 2005
Requested by	*Association française pour l'étude du foie (AFEF)*
Produced by	*Haute Autorité de santé* (HAS) - Guidelines Department
Intended for	All healthcare professionals who may be involved in managing patients with haemochromatosis, i.e. mainly hepatologists, gastroenterologists, specialists in internal medicine, rheumatologists, diabetologists, endocrinologists, cardiologists, non-specialist clinicians, haematology technologists, haematologists, and state registered nurses (SRNs)
Objectives	To provide guidelines on how to manage individuals with haemochromatosis who are homozygous for the C282Y mutation (treatment of iron overload; complications; counselling; treatment in the home)
Assessment method	Agreement among professionals obtained by a formal consensus method derived from the nominal group technique adapted by RAND/UCLA
Literature search	Period: 1966 – Jan 2005 (117 references selected among 396 analysed)
HAS project leader(s)	Fréderic de Bels (Head of Dept: Patrice Dosquet MD) (Literature search: Emmanuelle Blondet with the help of Maud Lefèvre, under the supervision of Rabia Bazi)
Authors of report	Dr Michaël Bismuth, hepatologist/gastroenterologist, Montpellier Dr Edith Peynaud-Debayle, haematology technologist, Colombes
Collaborations and participants (Annex 1)	- Learned societies - Steering committee - Preparatory group (Chair: Professor Pierre Brissot, hepatologist, Rennes) - Expert panel - Peer reviewers
Internal validation	Validated by the Committee for Practice guidelines and Practice Improvement (HAS Board) on 12 July 2005
Related publications	French reports posted on the HAS website (www.has-sante.fr): - Évaluation de l'opportunité d'un programme national de dépistage : l'exemple de l'hémochromatose génétique (October 1995) - Evaluation clinique et économique de l'intérêt du dépistage de l'hémochromatose génétique en France (1999) - Évaluation clinique et économique du dépistage de l'hémochromatose HFE1 en 2004 (April 2004)

Contents

I. Introduction

The aim of these guidelines is to report on the current state of knowledge on family screening of HFE gene-related haemochromatosis (type 1 haemochromatosis), so that a minimum set of formal guidelines can be drafted and practice in managing patients with haemochromatosis can be standardised in France.
The guidelines only concern the management of individuals with haemochromatosis who are homozygous for the C282Y mutation. They address:
1- treatment of iron overload;
2- procedures for detecting complications in relation to stage and risk factors;
3- procedures for counselling the family, notably genetic counselling for parents and children;
4- eligibility criteria and appropriate procedures for at home treatment.

The guidelines do not address the use of blood bags as blood donations for subsequent transfusions. The working group considered this a peripheral issue.

II. Assessment method

These guidelines are based on agreement among professionals obtained by a formal consensus method (Fig. 1) derived from the nominal group technique adapted by RAND/UCLA. When scientific evidence was of a low level or scarce, the working group recommendations (preparatory group and expert panel) are proposals and related in particular to organisational matters.

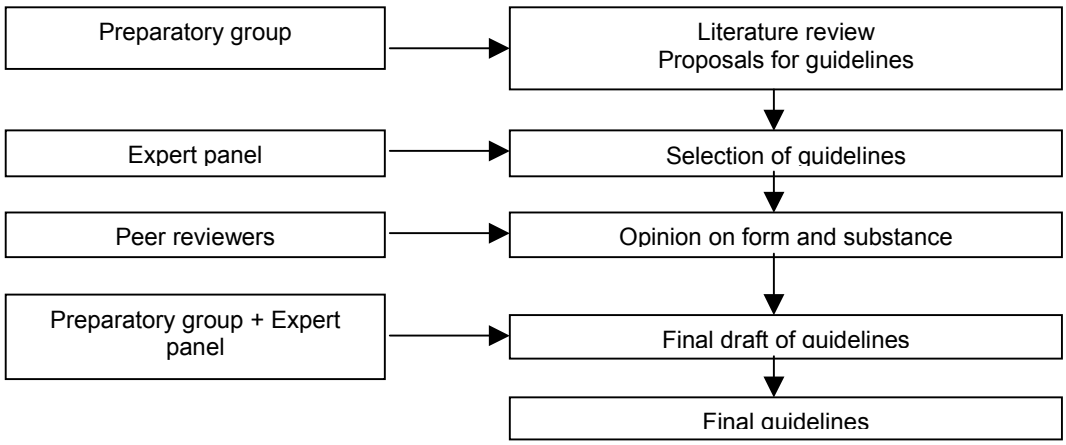


Figure 1. Working method for drafting the guidelines

III. Classification of haemochromatosis by severity

The working group established a classification of the disease on the basis of clinical and laboratory values in haemochromatosis (Table 1).

The prevalence of individuals homozygous for the C282Y mutation is estimated to be between 0.2 and 0.8% of the general population. Approximately 1% will progress to Stage 4

but this estimate needs to be confirmed and weighted in view of improvements in patient management.

Table 1. Classification of disease severity for individuals homozygous for the C282Y mutation

Stage	Serum transferrin saturation (STS) (%)	Serum ferritin (µg/L)	Clinical expression
0	<45	Normal	Asymptomatic stage in terms of clinical symptoms or abnormal laboratory values
1	> 45	No higher than normal < 300 (men) < 200 (women)	Preclinical stage
2	> 45	> 300 (men) > 200 (women)	No clinical signs or abnormal laboratory values suggesting organ damage or metabolic disorder (preclinical stage)
3	> 45	> 300 (men) > 200 (women)	Impact on quality of life (asthenia, impotence, muscle or joint signs and symptoms, diabetes, early liver disease, arrhythmia, skin pigmentation)
4	> 45	> 300 (men) > 200 (women)	Life-threatening symptoms (cirrhosis, hepatocellular carcinoma, insulin-requiring diabetes, diastolic heart failure)

IV. Treatment of iron overload

The aim of treatment of iron overload is:
- to remove excess iron (induction or “attack” phase)
- to avoid excessive iron building up again (maintenance phase).

The treatment strategy should also include:
- advice on limiting iron intake: avoiding prescription of iron, iron-containing medicines or medicines containing vitamin C (which encourages intestinal absorption of iron);
- symptomatic treatment of any complications such as organ damage or metabolic disorders.

The working group considered that there was no evidence for complications other than hypogonadism and diastolic heart failure (i.e. insulin-requiring diabetes, cirrhosis, etc) requiring special management in a patient with haemochromatosis. Complications should therefore be managed as in patients without haemochromatosis.

IV.1 What methods can be used to remove iron?

- **Phlebotomy** (also called venesection) is the gold standard therapy. It has been shown to be effective in terms of patient survival (level of evidence 4) and regression (variable) of some of the complications associated with iron overload. Phlebotomy can

avoid the onset of irreversible complications (level of evidence 4) although this depends on the degree of compliance.

- **Red-cell apheresis** uses a cell separator that extracts a larger volume of red blood cells in a single pass than does phlebotomy. More iron is thus removed at each session. The method is suitable for patients with no anaemia or heart failure. It can restore normal iron levels in a few sessions and is a useful alternative in patients with poor compliance, patients who find it hard to take time off work and patients who live a long way from the treatment centre. However, because phlebotomy is cheaper and simpler, phlebotomy should be the first-line therapy.

- **Iron chelation** is a second-line therapy to be used in the rare cases when removal by the venous route is contraindicated or not feasible (when the veins are in poor condition). Desferrioxamine (Desferal®) is the only drug that has been licensed to treat primary haemochromatosis. Its drawbacks, related to the parenteral route of administration, its potential side effects and its cost, mean that it may only be prescribed in forms of HFE gene-related haemochromatosis that cannot be treated by phlebotomy, eg central anaemia, or when the veins are in very poor condition.

IV.2 When to start iron removal therapy?

Because of the link between excess iron and onset of complications (insulin-requiring diabetes, fibrosis, cirrhosis, asthenia) and increased risk of mortality (level of evidence 3), induction therapy should be started as soon as serum ferritin exceeds the threshold of 300 µg /L in men and 200 µg /L in women, i.e. for disease stages 2, 3 or 4, ie

- stages 0 and 1 do not require any iron removal therapy
- stage 2 requires treatment of iron overload
- stages 3 and 4 require treatment of iron overload and treatment and prevention of organ damage and metabolic disorders.

IV.3 How to remove iron?

- **Rapid desaturation to normal levels** appears to improve the prognosis (level of evidence 3). During induction therapy, weekly phlebotomy is recommended. This should be tailored to:
  - serum ferritin level (the desaturation process may be slower when excess serum ferritin is not too high [borderline values around the treatment threshold]);
  - the patient's ability to tolerate treatment.

- **The recommended maximum volume of blood to be removed** varies with weight (7 ml/kg) but should not exceed 550 ml per phlebotomy. The volume removed depends on the patient's ability to tolerate treatment, age, and state of health (notably cardiac function).

- **Duration of depletion therapy** depends on the initial iron overload, the rate of iron mobilisation and the patient's compliance. Induction therapy should be continued until serum ferritin is reduced to 50 µg/L. The working group did not reach a consensus on whether or not there is any benefit in normalising STS or on a target value to be achieved.

IV.4 What monitoring methods should be used?

Patients undergoing phlebotomy should be monitored regularly to:
- monitor progress in reducing iron overload (and therefore treatment efficacy);
- avoid the onset of iron deficiency anaemia or anaemic syndrome;
- prevent and/or manage at the earliest stage the onset of rare immediate events (feeling faint or local manifestations) associated with venepuncture in general.

- **Monitoring reduction in iron overload**. Serum ferritin should be monitored monthly (every 4 phlebotomies) at the start of the induction phase and until the upper limit of normal is reached, i.e. 300 µg/L in men and 200 µg/L in women. Below these values, it should be monitored every 2 phlebotomies. Samples should be taken via the tubing attached to the bag.

- **Avoiding iron-deficiency anaemia**. If serum haemoglobin falls below 11 g/dL, phlebotomy should be discontinued until the value returns to normal. The cause should be sought. Iron supplementation to correct the value is contraindicated. The working group did not reach a consensus on the optimum frequency of serum haemoglobin testing.

- **Prevention and management of immediate events.** Phlebotomy should be performed in a safe environment, the patient should have been fully informed about the procedure, and the staff should be properly trained. A doctor should be in attendance or immediately contactable, particularly for the first phlebotomies or for patients who have already felt faint.

Monitoring the patient's tolerance of treatment should include the following, before and after each phlebotomy:
- measurement of heart rate and blood pressure;
- assessment of the patient's clinical status;
- investigation for any factors indicating poor tolerance or route-related complications.

Other measures to prevent fainting due to hypovolaemia are:
- using suitable equipment (a reclining chair that can be adjusted to a fully reclined position; scales to ensure the correct volume of blood is taken);
- adequate patient hydration (providing the same volume of cold drinks as the volume of blood to be taken);
- and, if necessary, making up the volume of blood taken (with starch solution, macromolecular solution, etc.) in patients with unstable haemodynamic values.

If the veins become inflamed, phlebotomy should be postponed or performed on the other arm. The inflammation should be treated in the usual way.

IV.5 Contraindications

Permanent and temporary or transient contraindications are given in Box 1.

In patients whose haemodynamic state is unstable for a reason unrelated to haemochromatosis, phlebotomy may be performed under specific conditions (patient lying with their head lower than their feet, specialist facilities, etc), once a cardiologist's opinion has been obtained.

Box 1. Contraindications to phlebotomy

Permanent contraindications

- any disease likely to compromise the patient's health during phlebotomy
- sideroblastic anaemia or any other form of anaemia caused by inadequate haemoglobin production and not by deficiency
- thalassaemia major
- severe or uncontrolled heart disease not secondary to haemochromatosis
- unstable or severe coronary disease, severe cardiomyopathy, left heart valve disease, uncontrolled heart failure, poorly-tolerated ventricular or supraventricular arrhythmias, etc. (a cardiologist should be consulted to establish the severity of the disorder).

Temporary and/or transient contraindications

- major iron deficiency anaemia (< 11 g/dL, particularly when this may be the result of previous phlebotomies)
- hypotension (SBP < 100 mmHg)
- severe occlusive arterial disease of the lower limbs, history of acute thrombotic ischaemia of a limb artery, or recent stroke (< 6 months)
- heart rate < 50 or > 100 bpm
- pregnancy (the working group considered there was no major risk in suspending treatment for 9 months; during the 6 months following delivery, the reference serum haemoglobin threshold established by the French National Blood Service for blood donations is 12.5 g/dL
- if the veins of the upper limbs are in very poor condition or inaccessible
- intercurrent disease leading to deterioration in general health.

IV.6 Maintenance therapy

Maintenance phlebotomies should be performed regularly every 2, 3 or 4 months to maintain stable serum ferritin ≤ 50 µg /L (the interval is a function of each individual patient). Serum ferritin should be monitored every 2 phlebotomies and serum haemoglobin should be monitored during the week preceding treatment.

IV.7 Phlebotomy facilities

The working group considered that, except in exceptional circumstances, the procedure and the disease do not justify day hospitalisation in a healthcare organisation or other care facility authorised to perform phlebotomy. They strongly advised against day hospitalisation if special management was not required or if the fees charged were not justified They considered that there should be a standard national tariff for phlebotomy (cost study to be performed), irrespective of where the phlebotomy is performed.

V. Detecting complications (patient follow-up)

As there is a wide range of possible symptoms, care should be coordinated, with multidisciplinary care if necessary (hepatologist/gastroenterologist, endocrinologist, rheumatologist, cardiologist, internal medicine specialist, haematology technician, haematologist, etc).

The patient's own doctor and, if appropriate, the state-registered nurse (SRN) in charge of the patient outside hospital are key members of the care team who can monitor the onset or progress of complications.

The patient and care team should be given detailed information about the symptoms suggesting complications and the conditions under which they occur. When the patient is being treated with iron depletion therapy, they should be given information about ways of improving symptoms and the importance of compliance.

V.1 History and initial tests

After a genetic diagnosis, a history is taken and baseline tests are performed to:
- establish a baseline record of symptoms;
- detect risk factors for the onset or aggravation of complications.

The clinician should be looking out for complications relating to general health (physical asthenia), the skin (pigmentation), liver (hepatomegaly, fibrosis, cirrhosis, hepatocellular carcinoma), joints (joint disease, articular chondrocalcinosis, osteoporosis), endocrine functions (diabetes) or the heart (restrictive cardiomyopathy).

- *If serum ferritin level is not raised (stages 0 and 1)*, there is no need for any further investigations after a clinical examination and standard iron tests.
- *If serum ferritin level is raised (stages 2, 3 and 4)*, tests should be performed - in addition to clinical examination and iron tests - to look for the following types of disease:
  - pancreatic (fasting blood glucose);
  - liver (transaminases, ultrasound imaging in the event of clinical signs or cytolysis);
  - heart, particularly in stages 3 and 4 (cardiac ultrasound);
  - gonads, in men (looking for warning signs, testosterone assay);
  - bone if there are concomitant predisposing factors for osteoporosis such as hypogonadism, menopause, etc. (bone densitometry)

In the event of abnormal results or suspected complications, particularly when serum ferritin is ≥ 1 000 µg/L, the patient should be referred to the appropriate specialist for further tests (see current guidelines on the relevant disorders).

V.2 Monitoring and follow-up

The working group considered that checkup frequency (Table 2) and further investigations should depend on:
- **severity of initial iron overload** and the presence of one or more complications, particularly fibrosis, cirrhosis or diabetes at the time haemochromatosis is diagnosed (ie disease stage at diagnosis);
- **presence of risk factors** for onset or aggravation of complications (eg excessive alcohol consumption, HCV or HBV infection, family history of diabetes, phenotypic expression of haemochromatosis in the family or siblings, sex, age, etc);
- **whether or not iron depletion therapy has been started.**

The diagnosis of new complications and the monitoring of existing complications do not call for any special procedures. The current guidelines for diagnosis and monitoring of these complications should be referred to, particularly those for screening for hepatocellular carcinoma (HCC).

Table 2. Recommended checkup frequency

Stage	Tests	Frequency
0	Consultation, clinical examination and iron tests	Every 3-5 years depending on age and risk factors
1	Consultation, clinical examination and iron tests	Yearly
2	- Consultation and clinical assessment (including at least monitoring haemodynamic values, checking that the last phlebotomy was well tolerated, and checking that there are no contraindications)	At each phlebotomy session
	- Serum ferritin and serum haemoglobin	As recommended for induction or maintenance therapy (see section II)
3 or 4	- Consultation and clinical assessment, iron tests and complete blood count depending on whether current treatment is induction or maintenance therapy	At each phlebotomy session
	- Monitoring of laboratory values including transaminase and fasting blood glucose (particularly to monitor onset of new complications)	Twice yearly

The working group stressed that:

- if fibrosis or cirrhosis is diagnosed during initial tests, the risk of subsequent HCC is not removed by restoring iron overload to normal levels by iron depletion therapy;
- no predictive scores for fibrosis or cirrhosis have been validated as yet in the context of haemochromatosis;
- glycated haemoglobin is unreliable in patients being treated with regular phlebotomy (underestimating the real blood glucose balance);
- the benefit in providing advice about risk factors such as alcohol abuse and viral liver disease during monitoring for complications. The initial haemochromatosis treatment plan should provide for specialist management of these factors and their prevention, if possible (eg by withdrawal therapy, psychological care, anti-HBV vaccination, etc.).

VI. Managing the family. Genetic counselling

A patient found to have *HFE*-related haemochromatosis should be informed of the benefits and drawbacks of screening of members of their family and of the likelihood of each of them being homozygous and having the disease.

Preferably, all of the proband's[1] siblings should be informed on the appropriateness of biochemical and genetic screening. The proband should be informed of whether screening is appropriate for children who are above the age of majority and for natural relatives. It is the responsibility of the proband alone to inform their relatives.

When family screening is envisaged, all genetic testing should systematically be accompanied by STS and serum ferritin tests.

[1] Proband: first subject diagnosed with the disease in a family

In an individual who is heterozygous for the C282Y mutation, no monitoring is necessary unless laboratory values indicate iron overload. Monitoring procedures will depend on the overload and the age and sex of the relative(s). Genetic testing in parents will only be undertaken if the elevated values found in the first laboratory tests are confirmed. For the proband's mother, determining STS and serum ferritin is sufficient if she does not wish to become pregnant or if she is postmenopausal. For second-degree relatives (uncles, aunts, cousins), information provision depends on whether family history data in the genealogical tree suggests that they are likely to develop haemochromatosis.

Biochemical or genetic screening in children of the proband who are minors is only rarely useful in view of the natural history of the disease. According to current legislation, being unnecessary, it is not justified.

Because genetic investigations are not easy to perform and interpret in practice, the working group emphasised that they should be performed in approved centres or networks.

VII. Eligibility criteria and procedures for care at home

The prescribing doctor, generally the specialist, may offer a patient phlebotomy at home:
- if the patient is a long way from a healthcare facility authorised to carry out phlebotomy;
- at the patient's request (eg if it is likely to improve their compliance);
- if specific local care cannot be provided in a healthcare facility authorised to carry out phlebotomy.

VII.1 Criteria related to performing phlebotomy in the patient's home

- **Constant monitoring by the SRN throughout the phlebotomy procedure.** Management at home implies monitoring by the SRN throughout the procedure and the possibility of a doctor being able to intervene. A doctor need not be in attendance provided that they can be contacted and arrive quickly.
- **Healthcare waste carrying a risk of infection.** Whenever a patient is treated at home, there should be a written procedure for waste disposal (packaging and collection from the patient's home, transport and storage before destruction in an approved facility). The working group strongly recommended the use of commercial disposable phlebotomy kits which contain at least tubing and a collecting bag, for routine safe disposal of waste.
- **Biomedical test laboratories**. The working group considered that phlebotomy by biomedical test laboratories should be encouraged even though it is a treatment. The potential benefits are access to a nationwide network of laboratories, a reliable level of safety, and ways of managing waste. However, current legislation would have to be changed.

VII.2 Treatment plan

Phlebotomy may be performed at home once the following conditions are satisfied:
- a written treatment plan has been produced;
- the patient's preference and informed consent for at home care have been obtained;
- the patient accepts their disease and treatment;
- the patient or the patient's family members have acquired the minimum skills required to ensure safety of care;

- a contact doctor has been identified within the healthcare facility where the induction phase was initiated (as an interface, particularly in an emergency);
- a SRN or, if warranted by the patient's health, a Hospital at Home facility structure or care network have agreed to participate in care;
- the patient's doctor or, failing this, an informed general practitioner has agreed to participate in care;
- all other professionals concerned have agreed to participate in care (community pharmacist, medical test laboratory manager, etc);
- safety of care at home is ensured for the patient, their family members and care givers (telephone, space for technical equipment, cleanliness);
- safety of care is ensured in terms of access to care and reliable warning and emergency procedures.

However, other situations besides contraindications to having blood samples taken are likely to complicate care. The working group contraindicated phlebotomy at home in patients with:

- heart failure or uncontrolled heart disease (see Contraindications, section IV.5) ;
- a poor general state of health, eg because of uncompensated cirrhosis (see Contraindications, section IV.5);
- a history of feeling faint during or after blood collection, when a doctor's intervention was required.

Maintenance phase, induction phase? The working group considered that phlebotomy at home is best reserved for the maintenance phase. Phlebotomy during the induction phase could be performed exceptionally at home after side effects have been assessed over a series of phlebotomy sessions (at least 5) in a healthcare facility, provided the patient is monitored regularly by a specialist and there are no contraindications to phlebotomy.

VII.3 Performing and monitoring phlebotomy at home

Whenever patients are treated at home, continuity of care should be ensured between hospital-based and non-hospital based professionals. Care should be permanently available and provisions made for information sharing and circulation.

- **Information sharing and circulation.** All the caregivers involved should be identified: prescribing doctor (generally the specialist), patient's own doctor, contact doctor, SRN, pharmacist, medical test laboratory. Written information should be provided and include the items in Box 2 at least.

Box 2. Items of written information required

- contact details for the prescriber (generally the specialist) and for a contact doctor within the healthcare facility where the induction phase was initiated, to give an opinion and make decisions in any emergency;
- care protocols and protocols on what to do if complications or side effects occur (in particular, informing the prescribing doctor and reporting them to an appropriate vigilance centre);
- protocols defining procedures for provision of the medical devices used;
- the prescription order giving instructions on procedures to be undertaken and the conditions under which they should be suspended (copies for each professional involved in care);
- a procedure describing how to dispose of waste, in particular waste carrying a risk of infection;
- an information sheet and a phlebotomy monitoring record for the patient.

To facilitate information sharing and circulation, a single shared record[2] should be produced, which can be consulted by everyone. Ideally it should be in electronic form. If this is not possible, it should be left at the patient's home to be available for the other professionals involved. The patient should present it at each treatment session or each consultation for updating. It should be based on the model of the nursing care record and should include a section for the use of other members of the care team and, at the very least, the patient's own doctor. Such a record could be standardised at national level.

- **Monitoring.** Monitoring and examination by the SRN at home are the same as for conventional care (see section V.2). In addition to monitoring laboratory values, the following should be carried out before and after each phlebotomy: heart rate and blood pressure measurement, assessment of the patient's clinical condition, investigation for signs of poor tolerance of treatment or complications related to the venous route.

- **Reassessment of care.** In practice, if there are any clinical signs suggesting complications, the SRN and/or the patient should:
  - first of all and if necessary, take the emergency measures specified in the emergency procedure and in the phlebotomy procedure information sheets;
  - alert the patient's own doctor or, if this is not possible, the contact doctor at the healthcare organisation or the specialist who prescribed phlebotomy.

  Any unanticipated rare or life-threatening side effects should be recorded and notified immediately to all those involved.

  Key points which should lead to reassessment of care at home are:
  - no go-ahead from the patient's own doctor. In particular, the go-ahead should take account of how previous phlebotomies were tolerated, the patient's clinical condition, checking laboratory values (serum haemoglobin, serum ferritin) required according to the criteria mentioned in the protocol summary sheet;
  - onset of complications related to the venous route;
  - onset of iron deficiency anaemia;
  - change in the eligibility criteria established in the treatment plan;
  - problem with the technical conditions needed to ensure safety, particularly in terms of permanent availability of care 24/7, warning and emergency procedures, and effective transmission and circulation of information.

  The other criteria for suspending care at home are:
  - choosing a treatment modality that cannot be carried out at home (eg red-cell apheresis);
  - lack of patient satisfaction or at the patient's request; this implies that the patient has been asked their opinion regularly;
  - psychosocial conditions become unfavourable (change in family environment);
  - refusal by the SRN or patient's own doctor to continue to provide care.

VIII. Looking ahead and studies proposed

In view of the current lack of data and the opportunities offered by the introduction of family screening, the working group strongly recommended that prospective and retrospective

studies be carried out to document the natural history of the disease. They would make it possible to adjust care for homozygous individuals better, particularly in the earlier stages.

Annex 1 – Participants

Learned societies consulted

Association française pour l'étude du foie (AFEF)
Société nationale française de gastro-entérologie (SNFGE)
Société française de pédiatrie
Groupe francophone d'hépato-gastro-entérologie et nutrition pédiatrique
Association de langue française pour l'étude du diabète et des maladies métaboliques (ALFEDIAM)
Association Hémochromatose France
Société française de transfusion sanguine (SFTS)

Steering committee

Professor Pierre Brissot, hepatologist, Rennes
Professor Jean-Pierre Bronowicki, hepatologist/gastroenterologist, Nancy
Professor Emmanuel Jacquemin, hepatologist/paediatrician, Le Kremlin-Bicêtre
Professor Véronique Kerlan, endocrinologist, Brest
Professor Henri Michel, chair, *Association Hémochromatose France*, Nîmes
Professor Jean-Luc Wautier, haematologist, Paris

Preparatory group

Professor Pierre Brissot, hepatologist, working group chair, Rennes
Dr Michaël Bismuth, hepatologist/gastroenterologist, report co-author, Montpellier
Dr Édith Peynaud-Debayle, haematology technologist, report co-author, Colombes
Dr Frédéric de Bels, project manager, HAS, Saint-Denis La Plaine

Dr Pierre Broué, hepatologist/paediatrician, Toulouse
Dr Nicolas Ferry, geneticist, Nantes
Dr Bernard Gavid, general practitioner, Neuville-de-Poitou
Dr Étienne Larger, endocrinologist/ diabetologist, Paris
Dr François Lefrère, haematologist, Paris
Professor Pierre Philippe, specialist in internal medicine, Clermont-Ferrand
Dominique Reynaert, senior health manager, Colombes
Dr Pascal Richette, rheumatologist, Paris
Hervé Segalen, patients' representative, Paris
Professor Jean-Luc Wautier, haematologist, Paris

Expert panel

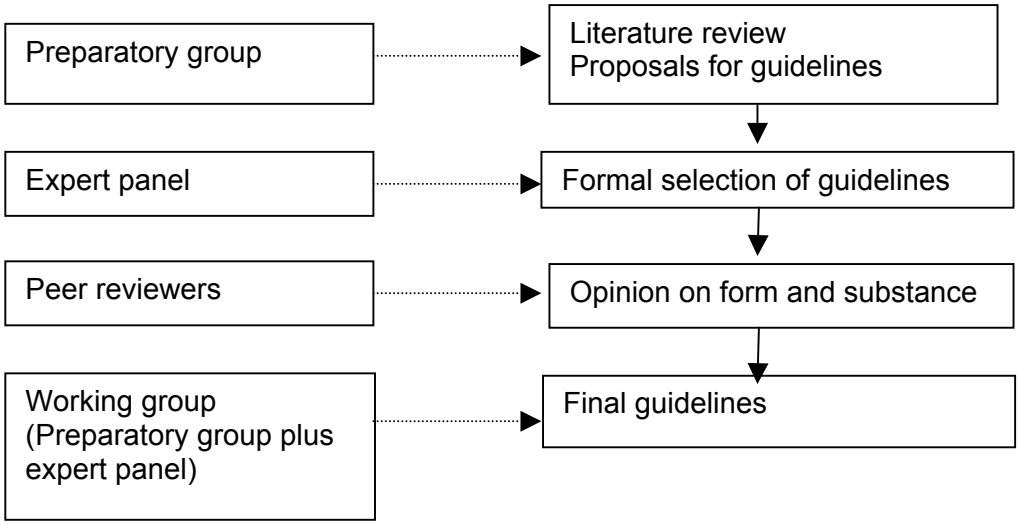
Dr Jean-Claude Barbare, hepatologist/gastroenterologist, Compiègne
Professor Olivier Blétry, specialist in internal medicine, Suresnes
Professor Gérard Chalès, rheumatologist, Rennes
Dr Françoise Courtois, haematology technologist, Paris
Professor Yves Deugnier, hepatologist, Rennes
Dr Rémy Durand, general practitioner, Corgoloin
Professor Claude Ferec, geneticist, Brest
Dr Christine Fourcade, haematologist/laboratory analyst, Argenteuil
Dr Sabrina François, specialist in internal medicine, Lyon
Professor Jean-François Gautier, diabetologist, Paris
Dr Christine Giraud, haematologist, Poitiers
Professor Bernard Grandchamp, geneticist, Paris
Anne Monnier, nurse, Margaux
Dr Olivier Rosmorduc, hepatologist/ gastroenterologist, Paris
Professor Fabien Zoulim, hepatologist, Lyon

Peer reviewers

Dr Armand Abergel, hepatologist/gastroenterologist, Clermont-Ferrand
Dr Patricia Aguilar-Martinez, haematologist/laboratory analyst, Montpellier
Dr Tony Andreani, hepatologist/gastroenterologist, Paris
Professor Thomas Bardin, rheumatologist, Paris
Dr Dominique Bastit-Barrau, haematology technologist, Rouen
Françoise Bourgeois, care manager, Puteaux
Professor Catherine Buffet, hepatologist/gastroenterologist, Le Kremlin-Bicêtre
Dr Valérie Canva, hepatologist/gastroenterologist, Lille
Dr Dominique Capron, hepatologist/gastroenterologist, Amiens
Professor Ariel Cohen, cardiologist, Paris
Dr Christian de Gennes, specialist in internal medicine, Paris
Dr Françoise Degos, hepatologist, Clichy
Dr Philippe Descombes, hepatologist/ gastroenterologist, Amiens
Dr Sabria Djennane, rheumatologist, Argenteuil
Dr Stéphane Durupt, specialist in internal medicine, Chalon-sur-Saône
Dr Thierry Fontanges, hepatologist/ gastroenterologist, Bourgoin-Jallieu
Dr Olivier Guillard, laboratory analyst, Poitiers
Dr Hélène Guntzberger, haematology technologist, Versaille
Professor Emmanuel Jacquemin, hepatologist/ paediatrician, Paris
Dr Dominique Jaulmes, haematology technologist, Paris
Professor Véronique Kerlan, endocrinologist, Brest
Henri-Claude Lauby, insurance agent, member of *Association Hémochromatose France*, Vaux-sur-Seine
Viviane Le Tallec, nurse, Lorient
Dr Patrice Lefèvre, haematology technologist, Marseille
Dr Florence Lévy-Weil, rheumatologist, Argenteuil
Dr Philippe Lore, rheumatologist and specialist in internal medicine, Tulle
Dr Véronique Loustaud-Ratti, hepatologist/ gastroenterologist, Limoges
Professor Richard Maréchaud, specialist in internal medicine, Poitiers
Professor Henri Michel, chair, *Association hémochromatose France*, Nîmes
Isabelle Millogo, nurse, Poitiers
Dr Olivier Nouel, hepatologist/gastroenterologist, Saint-Brieuc
Professor Jean-Baptiste Nousbaum, hepatologist/ gastroenterologist, Brest
Professor Philippe Orcel, rheumatologist, Paris
Dr Michel Perrocheau, haematology technologist, Nantes
John Pinte, nurse, Villejuif
Dr Serge Pissard, geneticist, Créteil
Dr Isabelle Raingeard, endocrinologist, Montpellier
Dr Jean-Loup Renier, haematology technologist, Saint-Germain-en-Laye
Professor Philippe Sogni, hepatologist/ gastroenterologist, Paris
Laurent Thiriot, nurse, Essey-lès-Nancy
Richard Vayn, member of *Association Hémochromatose France*, Verrières-le-Buisson

Annex 2 – Assessment method

The basis for all the guidelines was agreement among professionals using a formal consensus method derived from the nominal group technique adapted by RAND/UCLA[2]. The technique used is illustrated in the diagram below.



Preparatory group. The HAS project manager formed a group of professionals from a number of disciplines, working in public or private practice, from all over the country. Working in tight relation with the group and under the supervision of the chair of the group, he identified, selected, and analysed relevant studies (from a literature search performed by the HAS Documentation Department – see below) and wrote a critical review. This review was then used by the group to propose draft guidelines reflecting all views (even contradictory views) within the group.

Expert panel. Expert panel members were appointed according to the same criteria as above. However, special attention was given to the inclusion of experts who manage patients with haemochromatosis in their practice. The experts scored the draft guidelines (from 1 to 9) on the basis of evidence levels given in the report and of personal experience. They were first consulted by post, then convened to a discussion meeting following which they could modify their scores. Median scores and ranges were calculated. The final selection of guidelines was based on final score (integrating evidence level and agreement among members (this could be a high or a low level agreement)).

External validation (Peer reviewers). Peer reviewers were appointed as above. They were consulted by post, primarily with regard to the readability and applicability of the selected guidelines. The HAS project manager summarised their comments and submitted them to the working group (preparatory group and expert panel) who took the final decisions on guideline selection and wording. Peer reviewers were invited to sign the final document.

[2] *Bases méthodologiques pour l'élaboration de recommandations professionnelles par consensus formalisé* (HAS, January 2006)

Internal validation by HAS Board (Committee for Practice Guidelines and Practice Improvement). The HAS project manager reported to the Committee. The working group finalised the guidelines with due regard to the Board's suggestions.

Literature search and analysis (general procedure)

The scope of the literature search was defined by the steering committee and the project manager. The search was carried out by the Anaes Documentation Department and focused on searching:

- medical and scientific databases over an appropriate period, with special emphasis on retrieving clinical practice guidelines, consensus conferences, articles on medical decision-making, systematic reviews, meta-analyses and other assessments already published nationally or internationally (articles in French or English)
- specific and/or financial/economic databases, if necessary
- all relevant websites (government agencies, professional societies, etc.)
- the grey literature (documents not identified through the usual information distribution circuits)
- legislative and regulatory texts

Further references were obtained from citations in the articles retrieved above and from working group members' and peer reviewers' own reference sources. The search was updated until the project was completed.

The articles selected were analysed according to the principles of a critical appraisal of the literature, using a checklist, to allocate a level of scientific evidence to each study. Whenever possible, the working group based its guidelines on this review of the literature. Guidelines were graded from A to C as shown in Table 1 depending on the level of the evidence of the supporting studies. If no grading is given, they are based on agreement among professionals.

Table 1. Grading of guidelines

Level of published scientific evidence	Grade
Level 1 Randomised controlled trials of high power Meta-analyses of randomised controlled trials Decision analyses based on properly conducted studies	**A:** Established scientific evidence
Level 2 Randomised controlled trials of low power Properly conducted non-randomised controlled trials Cohort studies	**B:** Presumption of scientific foundation
Level 3 Case-control studies	**C:** Low level of evidence
Level 4 Comparative studies with major bias Retrospective studies Case series	