

*This Policy replaces
POL195/5*

Copy Number

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Summary of Significant Changes

- Amendments re closure of the service evaluation to register patients with sickle cell hepatopathy to the liver waiting list
- Changes to the Appeals process

Policy

This policy has been created by the Liver Advisory Group on behalf of NHSBT.

The policy has received final approval from the Transplant Policy Review Committee (TPRC), which acts on behalf of the NHSBT Board, and which will be responsible for annual review of the guidance herein.

*Last updated: **April 2017***

*Approved by TPRC: **April 2017***

The aim of this document is to provide a policy for the selection of adult and paediatric patients on to the UK national transplant list and, where necessary, criteria for their de selection. These criteria apply to all proposed recipients of organs from deceased donors.

In the interests of equity and justice all centres should work to the same selection criteria. Non-compliance to these guidelines will be handled directly by NHSBT, in accordance with Non-Compliance with Selection and Allocation Policies.

http://www.odt.nhs.uk/pdf/non_compliance_with_selection_and_allocation_policies.pdf.

It is acknowledged that these guidelines will require regular review and refreshment. Where they do not cover specific individual cases, mechanisms are in place for selection of exceptional cases (see section 3).

Liver transplantation is an established treatment in patients who have a likelihood of poor survival or impaired quality of life secondary to acute or chronic liver disease.

Selection criteria for adult transplantation are largely based on outcome measures. While the same general principles apply to children there are notable differences:

- The success of liver splitting allows many children to benefit from liver transplantation with little net effect on the overall donor organ pool
- In some circumstances a smaller probability of long-term success may be a very worthwhile outcome for some children and their families

1. Conditions that are considered for transplantation

1.1 Adult patients

Most adult patients with liver disease are not managed in transplant centres. Patients referred for assessment for liver transplant will include those with the following broad categories of conditions:

- Acute liver failure
 - Multi-system disorder in which severe acute impairment of liver function with encephalopathy occurs within 8 weeks of the onset of symptoms and no recognised underlying chronic liver disease
- Chronic liver disease; any cirrhosis which may be due to:
 - Alcoholic liver disease
 - Non-alcoholic fatty liver disease
 - Chronic viral hepatitis B, C, D
 - Autoimmune liver diseases: primary biliary cirrhosis, primary sclerosing cholangitis, chronic active liver disease and overlap syndromes
 - Genetic haemochromatosis
 - Wilson's disease
 - α -1 antitrypsin deficiency
 - Congenital hepatic fibrosis and other congenital or hereditary liver diseases
 - Secondary sclerosing cholangitis
- Liver tumours
 - Hepatocellular carcinoma
- Variant syndromes
 - Diuretic resistant ascites
 - Chronic hepatic encephalopathy
 - Intractable pruritus
 - Hepatopulmonary syndrome
 - Familial amyloid polyneuropathy
 - Familial hypercholesterolaemia
 - Polycystic liver disease
 - Hepatic epithelioid haemangioendothelioma
 - Recurrent cholangitis

Patients not falling within these categories may be considered through the National Appeals Panel route.

1.2 Paediatric patients

- Acute liver failure
 - Multi-system disorder in which severe acute impairment of liver function with encephalopathy occurs within 8 weeks of the onset of symptoms and no recognised underlying chronic liver disease
- Chronic liver disease
 - Biliary atresia
 - α -1-antitrypsin deficiency
 - Autoimmune hepatitis
 - Sclerosing cholangitis
 - Caroli's syndrome
 - Wilson's disease
 - Cystic fibrosis
 - Progressive familial intrahepatic cholestasis (all types)
 - Alagille's syndrome
 - Glycogen storage disease types 3 and 4
 - Tyrosinaemia type 1

- Graft versus host disease
- Budd-Chiari syndrome
- Any aetiology leading to hepatopulmonary syndrome or portopulmonary hypertension
- Liver tumours
 - Unresectable hepatoblastoma (without active extrahepatic disease)
 - Unresectable benign liver tumours with disabling symptoms
- Metabolic liver disease with life-threatening extra-hepatic complications
 - Crigler-Najjar syndrome
 - Urea cycle defects
 - Hypercholesterolaemia
 - Organic acidaemias
 - Primary hyperoxaluria
 - Glycogen storage disease type 1
 - Inherited disorders of complement causing atypical haemolytic uraemic syndrome

2. Assessment of patients

2.1 Adult patients

Adults are assessed and reviewed by the multi-disciplinary team, as outlined in the Introduction.

2.1.1 Illicit drug use

2.1.1.1 Assessment

Due to the potential risk of recurrent disease or poor adherence leading to graft loss, and with the increasing number of assessments for patients with viral hepatitis C (HCV) secondary to intravenous drug use (IVDU) there is a growing requirement for careful assessment of illicit drug use and potential impact on outcomes after organ transplantation. In particular, it is important to consider poly-substance use and drug dependence due to the potential for both a direct effect upon the liver and also indirect consequences such as poor programme adherence or initiation/resumption of harmful alcohol use. These guidelines are complementary to those for patients with harmful alcohol consumption.

Illicit drug use is not a contraindication to transplantation, if the patient will comply with the required management schedules. However, continued intravenous drug use is considered a contraindication owing to the possible risk of infection in an immune-suppressed patient.

Patients admitted for a transplant assessment irrespective of diagnosis should be screened for current and past illicit substance use as part of the clinical interview. This should include misuse of over-the-counter medications and apparent misuse of pain relief medication.

- Any patient considered to have a significant drug-taking history should be assessed by a specialist in substance misuse; the term 'significant' must be interpreted by the clinical multidisciplinary team
- Adequate time and resources should be made available to allow this specialist to undertake this process
- Assessment should include problematic or dependent use as well as recent use. It should also identify substance use and stability within the patient's wider social support network, and take into account mental health and criminal justice issues as appropriate
- Services should endeavour to develop and implement joint screening and assessment protocols between hepatology and substance misuse services to ensure effective care pathways are in place

2.1.1.2 Illicit drug use and substitute prescribing

The recommendations regarding this area are given in the context of limited research data. Small studies are favourable to consideration of transplantation whilst on a substitute prescription, e.g. methadone maintenance therapy (MMT).

In such patients analgesia post transplantation will need careful consideration and will require an agreed plan between the anaesthetist, pain team and substance misuse specialist.

Awareness of potential issues relating to patient-controlled analgesia will also be required, and risk factors should be assessed and a local management plan effected accordingly.

The potential for misuse should be balanced with the knowledge that opiate-tolerant patients are likely to need higher doses than an opiate-naive patient.

a. Methadone maintenance therapy (MMT)

MMT is a safe, well-evidenced treatment for patients unable to become opiate-free. It is commonly a long-term treatment. Patients on a stable MMT should be offered assessment for transplantation where medically indicated. Stability (individually measured as a continuum, not an absolute) indicates abstinence from other illicit drug use (predominantly other opiates and stimulants – including cocaine and crack cocaine).

There should be engagement with a drug treatment service and the patient should have an agreed care plan and a named key worker (though it should be acknowledged that it is now common practice to transfer stable patients to GP management). MMT patients should not be asked to reduce their methadone simply for the purpose of transplantation as this has the potential to destabilise them and provoke a relapse to other drug use.

Evidence suggests the likelihood of a prolonged ITU stay post transplant and the requirement for larger doses and longer treatment for post-operative analgesia.

b. Buprenorphine

The same requirements apply in the context of substitute prescribing as for MMT. Due to its method of action as a partial opioid agonist antagonist there will be issues around peri-operative analgesia. Where possible, conversion to methadone peri-transplant will assist with this issue. This should be undertaken in consultation with a substance misuse specialist.

c. Prescribed IV diamorphine or phylseptone

Where clinically possible, conversion to oral substitution therapy should be considered, in view of concerns including venous access and sepsis. This decision needs consideration and team discussion incorporating the patient and substance misuse specialist.

d. Benzodiazepines

Careful assessment should be made where there is past or current significant use of benzodiazepines – whether prescribed or illicit – and the context of this use. Replacement of opioids and alcohol with benzodiazepines can occur, and thus their use might mask a relative risk to relapse. It is worth noting that benzodiazepines are also associated with high risk behaviours and cognitive and memory impairment, and so their use may actively trigger relapse.

2.1.1.3 Drug screening

Drug screening should be arranged where there is concern about concurrent illicit drug use. Where a patient is on MMT they should be undergoing drug screening as part of their programme with the substance misuse team, and consent to obtain drug test results from the substance misuse team should be given. A positive screen for illicit drugs (except cannabis) prior to transplant is a contraindication to listing. Post transplant, a positive screen is a clear prompt for intervention and support. Whether drug testing is via mouth swab or urinalysis, and whether it is a supervised process or not will depend on the practice of individual centres.

2.1.1.4 Drug screening and alcohol agreements

These should be undertaken on the basis of past history or where there is perceived risk of alcohol being used to substitute for other drugs (commonly opioids). This approach to testing requires each centre to consider its approach to the process of screening questions for alcohol and drug use and referral to the substance misuse specialist. Blood alcohol levels can be taken during blood tests or randomly requested. A “drugs of abuse” screen can be undertaken with a urine sample via the toxicology laboratory. All patients assessed for transplant listing should give explicit consent to future drug and alcohol testing from this period onward, as considered appropriate by the centre.

2.1.1.5 Treatment agreement

If the opinion of the multidisciplinary team is that the patient should be listed, then the patient may be asked to sign an agreement that they will not drink alcohol post transplant and will comply with follow-up if the team feel that will promote long-term abstinence. A treatment agreement is recommended as a useful process for a number of reasons; it can outline a statement of intent including treatment engagement, commitment to the programme and consent to share appropriate information with relevant agencies. Any potential consequences to non-concordance with the treatment agreement (e.g. non-attendance, refusal of, or positive, drug screens) should be made clear in the agreement. Past behaviour documented in a comprehensive assessment is a better guide to stability and engagement than the signing of a treatment agreement. Consent should be part of a treatment plan.

It is recommended that follow-up with the local drug/support services, where required, is explicit in the agreement and should also form part of the care plan at the substance misuse service. Follow-up within the transplant programme should also clearly monitor and document substance use – preferably with monitoring by a substance misuse specialist – and the transplant team should actively encourage referral to and engagement with substance misuse services in the event of a relapse. This is likely to be expedited more successfully where contact with local substance misuse services has already occurred. As stated above, good data collection for the purpose of clinical audit is necessary to inform this area of transplantation.

2.1.1.6 Predictors of relapse

Research data in this field is currently limited. Guiding principles require referring to good practice and clinical “common sense”. Dependence on substances such as opioids and alcohol is a relapsing condition and harmful patterns of drug use may be repeated. However, behaviour change can occur and be sustained though may take many years and numerous treatment attempts. Reasons for abstinence as well as relapse are numerous and individual.

2.1.2 Alcohol consumption

2.1.2.1 Assessment process

A history of excess alcohol is relevant in regard to potential or actual significant damage to cardiovascular and neurological tissue, to the risk that patients might revert to alcohol abuse or might not comply with medication or follow-up schedules and thus damage the new liver. A multidisciplinary approach is required to select patients who are likely to comply with follow-up and not return to a damaging pattern of alcohol consumption after transplantation and may include psychological/psychiatric assessment.

Patients admitted for assessment where alcohol has contributed to their liver disease should be assessed by a specialist team in substance misuse. This team should have dedicated time for this purpose. This assessment should include careful attention to risk factors associated with predicting a relapse to drinking and advising the transplant team on follow-up requirements to prevent this.

2.1.2.2 Factors to be considered in assessment

At present, there is conflicting evidence that a fixed period of abstinence will predict adherence post transplant. However, it is important to recognise that with abstinence, many possible candidates will improve to such an extent that transplantation is no longer indicated. A period of abstinence is also required to allow the addiction team to assess the patient and organise any support measures that may be required. Those factors that have been identified in meta-analyses as being associated with relapse include:

- A shorter period of abstinence
- A family history of alcoholism
- Absence of social back-up
- Repeated behavioural lapses to harmful drinking

The presence of one of these is not a veto to transplantation. Use of single predictors to identify patients who are liable to drink following transplant should be used with caution because of the weak inconsistent evidence base and the fact that most patients who drink following transplantation do so without harm. Robust criteria for predicting a return to heavy drinking (and its consequences on graft function and with adherence) must:

- Discriminate consistently and be clinically meaningful
- Be objective, measurable and fair
- Cannot be, or unlikely to be, modified

2.1.2.3 Alcohol as a co-factor

The same process of assessment and listing should be applied to patients where alcohol has contributed to the progression of another chronic liver disease. This is definitely the case if alcohol consumption is >100 units per week and very likely to be the case if consumption lies between 50–100 units. A separate agreement indicating alcohol as a co-factor should be used.

2.1.2.4 Living-related liver transplantation

These considerations should be applied to all potential liver transplant recipients regardless of the type of donor, living or cadaveric.

2.1.2.5 Advice to recipients with hepatitis B or C

As alcohol contributes to the progression of hepatitis C recurrence it is expected that all recipients with chronic hepatitis C, irrespective of whether they have misused alcohol or drunk normally, should ensure that their alcohol consumption remains within safe limits. As these limits are unknown, the safest approach is to advise all such patients to abstain totally from alcohol.

2.1.2.6 Alcohol advice to other transplant recipients

Available evidence and clinical experience suggests that a liver allograft is more susceptible to alcohol injury and therefore the following recommendations are given for recipients not transplanted for alcohol-related liver disease or those with hepatitis C infection.

Male recipients – a maximum of 3–4 units on one day, two alcohol free days per week

Female recipients – a maximum of 2–3 units on one day, two alcohol free days per week

2.1.3 Paracetamol hepatotoxicity

Self-inflicted conditions such as resulting from an overdose of paracetamol would only be contraindicated if there were good reason to believe that the patient would, despite appropriate support, return to a behavioural pattern that would lead to liver failure or result in a quality of life unacceptable to the patient. The views of the family doctor and other support agencies and the family may have to be taken into account.

2.1.4 Medical and psychiatric comorbidity

Concurrent extra-hepatic comorbid medical or psychiatric conditions are relevant if they will affect the patient's quality of life, prospect for survival post transplant or likelihood of compliance with medical treatments and clinic follow up. The comorbidities that should be considered will include: prior cardiac, peripheral or cerebral vascular disease, chronic lung disease and diabetes mellitus, although this list is not exhaustive. If there is a history of prior psychiatric disease, albeit without illicit drug or alcohol use, the advice of a psychiatric team, preferably the patient's own team, should be sought to assess the potential impact of such diagnoses on compliance and outcomes. Where uncertainty remains, evaluation should be considered in discussion with other transplant centres and, where appropriate, the Chairman of NHSBT Liver Advisory Group.

2.1.5 Age

Age itself is not a contraindication to liver transplantation; although the survival rate in the over 65s is significantly worse than that of younger patients.

2.1.6 Re-transplants

Re-transplants will need special consideration dependent on the circumstances that gave rise to the need for re-transplant, as results after re-transplant are worse than for first transplants and only limited benefit may be achieved. However, the principles for listing that apply to primary grafts should also apply to re-transplants.

2.1.7 Prior non-hepatic malignancy

Where potential liver allograft recipients have suffered from prior non-hepatic malignancy, the decision to proceed for liver transplantation should depend, in part, on the probability of malignancy recurring and failing to respond to treatment following liver transplantation. Some immunosuppressive agents may encourage the growth of malignancy. Patients should be considered in the light of their anticipated quality and length of life.

Selection criteria for patients with primary hepatic malignancy are considered in section 3, below. Cholangiocarcinoma and secondary hepatic malignancy are not appropriate indications for transplantation.

2.2 Paediatric recipients

Most children with liver disease who are candidates for transplant will have already been referred to one of the three paediatric liver transplant centres: King's College Hospital, London, The Children's Hospital Birmingham and Leeds General Infirmary. Well-established referral pathways exist for this.

For the more frequent indications listed in the selection criteria (see section 3.3) it is usually clear whether these criteria are met, and if so, they should be offered transplantation if there is an expectation that they have a >50% probability of survival at 5 years after transplantation with a quality of life acceptable to them and their families.

Assessment is carried out by the transplant multidisciplinary team and will involve the patient and their family. These initial procedures often follow outpatient review and are usually undertaken over 4–5 working days.

The decision whether or not to register a patient on the transplant list will be made after discussion with the multidisciplinary team, the patient's family and, with age-appropriate language, the patient themselves. This should allow informed consent to be given by the patient's family and where appropriate the patient themselves.

The ability of the child's family to comply with instructions and follow-up plans are relevant factors that must be considered in the transplant assessment process. However, the aim of the process is to identify support required to enable successful transplantation. Children should not be disadvantaged by family factors beyond their control.

Age is not itself a contraindication, but the outcome of transplantation in the neonatal period is inferior to transplantation later in childhood.

3. Selection criteria

Eligible patients can be placed on the UK national transplant list only following registration with NHSBT. Patients who have not been registered should not be offered an organ. Patients are required to consent to transfer of their data onto the UK Transplant Registry, which is maintained by NHSBT on behalf of transplant services in the UK and holds detailed information about each patient awaiting any organ transplant in order that they may have an up-to-date status of the transplant list.

Patients will be placed on the national transplant list on the day on which details are received at NHSBT. Discrepancies or missing information will be followed up with the local centre and might cause a delay.

In an emergency, as defined in section 3.4, a super-urgent recipient registration can be made by telephone and a temporary form will be completed at NHSBT. Centres must ensure that a replacement form is completed and sent to NHSBT at the first opportunity following the telephoned registration.

Recipients are categorised as Group 1 or Group 2 (as defined by The NHS Blood and Transplant (Gwaed a Thrawsbkniadau'r GIG) (England) Directions 2005 - Guidance). It should nevertheless be noted that nationals of a non-UK country may only be registered on a transplant list after they have been accepted by a consultant as suitable for treatment. It is the responsibility of the consultant registering such a patient on the transplant list to confirm that they have been accepted under E112 or similar arrangements.

3.1 Rationale for two different types of selection criteria

Separate selection criteria have been devised for those cases requiring emergency transplantation (super-urgent transplantation criteria, section 3.4) compared to those who require an elective procedure. The two groups have a different range of aetiologies with markedly different short-term prognoses; different criteria are required to define that prognosis. Similarly, allocation processes are different for super-urgent and elective transplantation, reflecting those patient groups with a different risk of death without transplantation.

3.2 Selection criteria for adult elective transplantation

- Selection will be based primarily on risk of death without a transplant. Patients can be considered for elective transplantation if they have an anticipated length of life or survival in the absence of transplantation that is less than that obtained with a liver transplant
- All patients selected for the elective adult liver transplant list must have a projected 5-year survival after transplantation of >50%. That figure may change in the future if/when donor numbers alter
- Selection will be assessed secondarily on ability of transplantation to improve quality of life
- All patients will need to be regularly reviewed to ensure that they continue to meet criteria and have not improved or become too sick to benefit from transplantation
- When the clinical situation alters such that a patient no longer meets these criteria, the patient's name must be removed from the national list

3.2.1 Criteria for selection

Patients can be selected if they fulfil one of the following criteria:

- Chronic liver disease or failure
 - Projected 1 year liver disease mortality without transplantation of >9%, predicted by a United Kingdom Model for End-Stage Liver Disease (UKELD) score of ≥ 49 . The UKELD score is derived from the patient's serum sodium, creatinine and bilirubin and International Normalised Ratio (INR) of the prothrombin time
 - Patients with porto-pulmonary hypertension (mean PAP ≥ 25 mmHg, < 50 mmHg; PVR ≥ 120 dynes/s/cm⁻⁵; PCWP < 15 mmHg) should have had a clinically significant response to one of long-acting prostacyclin (or analogues), sildenafil, or bosentan
 - See **Appendix A** for the details of a service development evaluation to transplant patients with severe acute alcoholic hepatitis.
- Hepatocellular carcinoma (HCC)
 - Radiological assessment should include both MDCT and MRI with size being assessed by the widest dimensions on either scan. A tumour (for the purposes of counting numbers) will require to be identified as an arterialised focal abnormality with portal phase washout on MDCT or Gd enhanced MR. Other tumours are considered indeterminate and do not count. Tumour rupture and an α -fetoprotein (AFP) $> 1,000$ iu/ml are absolute contraindications to transplantation, as are extra-hepatic spread and macroscopic vascular invasion. The following are criteria for transplantation listing:
 - A single tumour ≤ 5 cm diameter or
 - Up to 5 tumours all ≤ 3 cm or
 - Single tumour > 5 cm and ≤ 7 cm diameter where there has been no evidence of tumour progression (volume increase by $< 20\%$) and no extra-hepatic spread and no new nodule formation over a 6-month period. Locoregional therapy +/- chemotherapy may be given during that time. Their transplant list place may be considered from the time of their first staging scan
 - Locoregional therapy should be considered for all transplant list patients who have a hepatocellular carcinoma

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- It is recognised that different imaging modalities may identify differences both in number and size of tumour, but to qualify as an HCC will require a congruent lesion to be seen on a minimum of two different radiological modalities. There must be no radiological evidence of vascular invasion and no distant metastasis
- See **Appendix B** for the details of a service development evaluation of orthotopic liver transplantation for HCC patients undergoing “down-staging”.
- A variant syndrome in patients whose UKELD score is <49
 - Diuretic resistant ascites:
Ascites unresponsive to or intolerant of maximum diuretic dosage and non-responsive to TIPS or where TIPS deemed impossible or contraindicated, but in whom UKELD score at registration is <49.
 - Hepatopulmonary syndrome:
Arterial pO₂<7.8, alveolar arterial oxygen gradient >20 mmHg, calculated shunt fraction >8% (brain uptake following TC macroaggregated albumen), pulmonary vascular dilatation documented by positive contrast enhanced transthoracic echo, in the absence of overt chronic lung disease
 - Chronic hepatic encephalopathy:
Confirmed by EEG or trail-making tests, with at least two admissions in one year due to exacerbations in encephalopathy, not manageable by standard therapy. Structural neurological disease must be excluded by appropriate imaging and, if necessary, psychometric testing
 - Persistent and intractable pruritus:
Pruritus consequent on cholestatic liver disease, which is intractable after therapeutic trials. Exclude psychiatric co-morbidity that might contribute to the itch. Lethargy is not an accepted primary indication for orthotopic liver transplantation
 - Familial amyloidosis:
Confirmed transthyretin gene mutation in the absence of significant debilitating cardiac involvement, or autonomic neuropathy
 - Primary hyperlipidaemia:
Homozygous familial hypercholesterolaemia, absent LDL receptor expression and LDL receptor gene mutation
 - Polycystic liver disease:
Intractable symptom due to mass of liver or pain unresponsive to cystectomy, or severe complications secondary to portal hypertension
 - Recurrent cholangitis:
Recurrent significant cholangitis not responsive to medical, surgical or endoscopic therapy
 - Hepatic epithelioid haemangioendothelioma:
Histological confirmation; not a single lesion amenable to resection; extra-hepatic spread confined to abdominal lymph nodes only.

Any cases not falling within these criteria may be referred to the National Appeals Panel (see section 4).

3.3 Selection criteria for paediatric elective transplantation

3.3.1 Criteria for selection

Indications for elective liver transplantation in children are:

- Chronic liver disease
 - Life expectancy: anticipated length of life <18 months (because of liver disease)
 - Unacceptable quality of life (because of liver disease)
 - Growth failure or impairment due to liver disease
 - Reversible neuro-developmental impairment due to liver disease
 - Likelihood of irreversible end organ damage (which may be renal, respiratory or cardiovascular depending on the underlying disorder)
- *Rarer indications:*

A complicating factor in paediatric practice is that many of the conditions affecting children are individually rare and decisions have to be based on general principles rather than condition-specific data. Particular rare indications for liver transplantation that paediatric centres would feel are reasonable, but for which there is limited outcome data, would include the following conditions:

 - Liver transplantation for organic acidaemia
 - Unresectable hepatic malignancies without extra-hepatic spread (to include selected hepatocellular carcinoma and epithelioid haemangioendothelioma)
 - Diffuse hepatic haemangioendothelioma unresponsive to alternative treatments
 - Langerhans cell histiocytosis
 - Mitochondrial respiratory chain disorders with chronic liver disease (selected) but without discernible disabling extrahepatic disease
 - Intestinal failure associated liver disease
 - Hepatoblastoma: children hepatoblastoma should be discussed at a Multi-Disciplinary Team which should include a paediatrician with an interest in liver disease, a paediatric oncologist, a hepatobiliary surgeon and liver transplant surgeon.

The use of transplantation for the rarer indications should be audited regularly and new indications should in general be developed by consensus.

Patients can be placed on the UK national transplant list only following registration with NHSBT. Patients who have not been registered should not be offered an organ.²

3.4 Selection criteria for adult and paediatric super-urgent transplantation

3.4.1 Process for super-urgent registration

Initial registration on the super-urgent liver scheme must be made by telephone to the Organ Donation and Transplantation (ODT) Duty Office, who will then place the recipient on the super-urgent liver scheme and notify all liver transplant centres in the UK and the European Organ Exchange Organisations by telephone and facsimile. The recipient centre must immediately complete a super-urgent registration form that must be counter-signed by the clinician and sent to the ODT Duty Office by facsimile or if necessary by urgent courier. On receipt, the ODT Duty Office will facsimile an anonymised copy of the form to all designated liver transplant centres.

Centres wishing to seek clarification of the details of a recipient on the super-urgent liver scheme must notify the ODT Duty Office by facsimile. The clinician from the centre seeking clarification will make direct contact with the registering centre and discuss the case clinician to clinician. In cases where clarification has been sought, the ODT Duty Office will seek confirmation of the patient's status from the registering centre 24 hours after a registration. Where there remains a dispute this should be discussed with the Chairman of the Liver Advisory Group and possible referral to the National Appeals Panel considered.

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A summary of recipients on the super-urgent liver scheme will be sent by facsimile to all designated centres by the ODT Duty Office each day. The summary will show the date and time of registration on the super-urgent liver scheme.

A patient suspended from the super-urgent list can be reactivated within 5 days and maintain their position on the list. Once the patient is suspended for over the 5 days, the patient will then be removed from the super-urgent list and will not automatically be moved to the elective list. If the patient is removed from the super-urgent list and needs to be registered on the elective list then an elective registration form must be completed.

3.4.2 Adult and paediatric super-urgent selection criteria

The super-urgent liver scheme is available to Group 1 patients only in the UK and Republic of Ireland. To be registered on the super-urgent liver scheme, at least one of the following criteria must be met:

- Category 1
Aetiology: Paracetamol poisoning: pH <7.25 more than 24 hours after overdose and after fluid resuscitation
- Category 2
Aetiology: Paracetamol poisoning: Co-existing prothrombin time >100 seconds or INR >6.5, and serum creatinine >300 µmol/l or anuria, and grade 3–4 encephalopathy
- Category 3
Aetiology: Paracetamol poisoning: Significant liver injury and coagulopathy following exclusion of other causes of hyperlactatemia (e.g. pancreatitis, intestinal ischemia) after adequate fluid resuscitation: arterial lactate >5 mmol/l on admission and >4 mmol/l 24 hours later in the presence of clinical hepatic encephalopathy.
- Category 4
Aetiology: Paracetamol poisoning: Two of the three criteria from category 2 with clinical evidence of deterioration (e.g. increased ICP, FiO₂ >50%, increasing inotrope requirements) in the absence of clinical sepsis
- Category 5
Aetiology: Favourable non-paracetamol aetiologies such as acute viral hepatitis or ecstasy/cocaine induced ALF: the presence of clinical hepatic encephalopathy is mandatory and: prothrombin time >100 seconds, or INR >6.5, or any three from the following: age >40 or <10 years; prothrombin time >50 seconds or INR >3.5; any grade of hepatic encephalopathy with jaundice to encephalopathy time >7 days; serum bilirubin >300 µmol/l.
- Category 6
Aetiology: Unfavourable non-paracetamol aetiologies such as seronegative or idiosyncratic drug reactions: a) prothrombin time >100 seconds, or INR >6.5, or b) in the absence of clinical hepatic encephalopathy then INR >2 after vitamin K repletion is mandatory and any two from the following: age >40 or <10 years; prothrombin time >50 seconds or INR >3.5; if hepatic encephalopathy is present then jaundice to encephalopathy time >7 days; serum bilirubin >300 µmol/l.
- Category 7
Aetiology: Acute presentation of Wilson's disease, or Budd-Chiari syndrome. A combination of coagulopathy, and any grade of encephalopathy
- Category 8
Hepatic artery thrombosis on days 0 to 21 after liver transplantation
- Category 9
Early graft dysfunction on days 0 to 7 after liver transplantation with at least two of the following: AST >10,000, INR >3.0, arterial lactate >3 mmol/l, absence of bile production
- Category 10
The total absence of liver function (e.g. after total hepatectomy)

- Category 11
Any patient who has been a live liver donor (NHS entitled) who develops severe liver failure within 4 weeks of the donor operation
- Category 20
Acute liver failure in children under two years of age: INR >4 or grade 3-4 encephalopathy. Definition: Multisystem disorder in which severe acute impairment of liver function with or without encephalopathy occurs in association with hepatocellular necrosis in a child with no recognised underlying chronic liver disease. Children with leukaemia/lymphoma, haemophagocytosis and disseminated intra-vascular coagulopathy are excluded

No other causes of liver failure may be considered appropriate for registration on the super-urgent liver scheme.

3.5 Multiple organ transplants

3.5.1 Simultaneous liver and kidney (SLK) transplantation

Simultaneous liver and kidney transplantation is only undertaken when there is evidence of kidney failure that will not recover with a liver transplant alone.

The indications for SLK are:

- Genetic liver kidney syndromes, including hereditary oxalosis and Glycogen storage disease type 1
- Chronic liver disease meeting at least one of the three current criteria for liver transplant selection + end-stage renal disease on long-term dialysis program
- Chronic liver disease meeting at least one of the three current criteria for transplant selection + hepato-renal syndrome with serum creatinine >200 and dialysis >6 weeks
- Chronic liver disease meeting at least one of the three current criteria for transplant selection + GFR <30 ml/min (isotope or MDRD v6) or renal biopsy showing <30% fibrosis and/or glomerulosclerosis

All other cases should be referred to the National Appeals Panel.

3.5.2 Combined lung/liver patient transplantation

Please refer to the guidelines for combined cardiothoracic and liver transplantation in the UK.

3.6 Multi-visceral transplantation

Please refer to the selection policy for bowel transplantation.

3.7 Contraindications to selection

Any patient who does not fulfil the criteria listed in section 3 is contraindicated for selection. This is also the case for paediatric patients.

3.7.1 Absolute contraindications

3.7.1.1 Alcohol-related liver disease

Some factors have been accepted, currently, as a contraindication to registration on the transplant list:

- Alcoholic hepatitis
- More than two episodes (within 2 years) of non-adherence with medical care where there was not a satisfactory explanation. Non-adherence with medical care should not be confined to management of their liver disease, but includes management of their alcohol abuse as well
- More than two episodes (within 2 years) of return to drinking following full professional assessment and advice

- Concurrent or consecutive illicit drug use (except occasional cannabis use)
- Evidence of drinking whilst on the transplant list will result in permanent removal from the list. Patients should be informed on entry to the list that this will occur if they drink whilst waiting for their transplant

3.7.1.2 Illicit drug use

Contraindications to listing for transplantation include the following:

- Current ongoing intravenous use of illicit or non-prescribed substances
- More than two recent incidences of unexplained and significant non-adherence with treatment – not necessarily confined to the management of liver disease
- Current failure to comply with the assessment and treatment process for transplantation, including refusal to provide consent for gaining access to information pertaining to drug treatment and prescribing
- Recent history of cross dependency (substituting from one drug to harmful/problematic use of another), within the last 2 years; this requirement could be relaxed for patients who have switched drugs within 2 years but have been stable since maintaining engagement in substance misuse services

3.7.2 Relative contraindications

Relative contraindications are those which, while not absolute contra-indications, may preclude transplantation in individual cases and allow issues of concern to be factored in without necessarily attempting to weigh issues against one another in the absence of good evidence. The importance of potential contraindications should be discussed between the transplant team and substance misuse specialist and interpreted with clinical judgement on a case by case basis:

- Current legally prescribed intravenous drug use (i.e. diamorphine or phylsephone). Some patients are long term yet stable IVDUs and their use of prescribed IVDU opiates is as part of a long term agreed treatment plan. Others may be more recent presentations who have failed on an optimum treatment programme but are a high risk group. Assessment here needs to be undertaken by a specialist
- Insufficient social support network to remain abstinent from illicit drugs, and where it is not possible to work with the patient to facilitate a suitable and acceptable social support package
- Lack of motivation to move away from drug using culture/area, within the confines of opportunity
- Current illegal drug use
- Past history of cross dependency (substituting from one drug to harmful or problematic use of another) within the last 2–5 years
- Reluctance to agree to drug treatment and after-care or to sign a treatment agreement
- Active ongoing alcohol use in the presence of HCV, where there is clear evidence of medical advice to become abstinent

3.8 De-selection criteria

Following selection, certain criteria are indications for de-selection:

- In the category of chronic liver disease, sodium, creatinine, bilirubin and INR present and UKELD score <49
- Tumour rupture occurred
- α -fetoprotein (AFP) greater than 1,000 iu/ml
- A single tumour >7 cm, more than 5 tumours, between 2 to 5 tumours any one >3 cm or a single tumour >5 cm and \leq 7 cm and a volume increase \geq 20% within a 6-month time period, all judged by USS or CT scan, radiological evidence of vascular invasion, extra-hepatic tumour spread. Tumour size will be assessed by serial scanning 3-monthly using the scan, which demonstrates the largest diameter

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- Failure of adherence with guidelines relating to alcoholic liver disease and illicit drug use
- The development of comorbidities sufficient to impact on expected 50% probability of survival at 5 years

It has not been possible to define other universally acceptable de-selection criteria either for super-urgent or electively listed candidates. The Organ Donation and Transplantation (ODT) Directorate of NHSBT will continue to collate clinical and laboratory data on all patients that are de-selected to try to identify common themes within the separate centres.

3.9 Selection for re-transplant

Registrations for second or subsequent transplants will require a different set of criteria as different factors affect risk and outcome and so are not subject to these criteria and decisions are at left, at present, to the discretion of each transplant centre. Re-transplants are only undertaken when there is evidence of irreversible graft failure and the risk of mortality from that exceeds the increased post-operative mortality after re-transplantation.

Re-transplant patients are also expected to achieve a 50% probability of an acceptable survival and quality of life 5 years after transplant.

4. Appeals process

The above criteria have been agreed by the Liver Advisory Group in order to be placed on the national transplant list. It is recognised that these criteria may exclude a small group of patients who would otherwise be appropriate candidates; the purpose of the National Appeals Panel is to determine whether such excluded patients should be placed on the national transplant list.

If a centre wishes to register a patient, adult or paediatric for an elective first or subsequent liver transplant who does not satisfy any of the above criteria, a request should be made in writing/electronically to the Chair of the Liver Advisory Group who will forward it to members of the National Appeals Panel.

4.1 Composition of the National Appeals Panel

The panel will consist of an independent non-voting Chair and two representatives from each of the seven UK Liver Transplant Centres. Only one vote will be allowed per centre. The centre proposing a case may not vote but the appeal will be allowed if four or more centres are in favour.

The chair of the Appeals Panel will be the Chair of the Liver Advisory Group. The centres will nominate one representative and one substitute.

4.2 Criteria for acceptance

4.2.1 Criteria

The Panel may place a patient on the transplant list if they do not meet any of the current criteria and, on the evidence provided to them, one or more of the following conditions are met:

- Greater than 50% probability that the patient will be alive and with an acceptable quality of life 5 years after transplant
- **and** probability of death from liver disease of >9 % at 1 year
- **or**
- Unacceptable quality of life because of the liver disease that would be corrected by transplantation that occurs despite full therapeutic intervention

4.2.2 Hepatocellular carcinoma

The panel will not allow exceptions purely on the basis of cases being outside number or size criteria. Nevertheless, if a unit believes that it can make a case that the specific circumstances of their candidate demonstrates tumour biology that meets the criteria in 4.2.1 then the Appeal Panel will consider the appeal.

4.2.3 Paediatric candidates

Paediatric candidates for the transplant list outside current criteria may be referred to the Appeals Panel, where the two other paediatric transplant centres will give their opinion.

4.2.4 Live Donor Liver Transplantation (LDLT)

NHSBT is responsible under its Directions for criteria for deceased organ transplantation but is not responsible for national criteria for LDLT which are laid down by commissioners at NHS England and the devolved Health administrations. Current criteria are that LDLT criteria are the same as for deceased donor transplantation. Units wishing to undertake LDLT outside of deceased liver transplantation criteria should seek the advice/ permission of their commissioners and use this Appeals Panel process as a means of external peer review of their decision. Emergency deceased re-transplantation, should that be required, would not be possible after "out of criteria" LDLT.

4.3 Process

- Any clinician working in a designated transplant centre may apply to the Panel for a patient to be considered for either a super-urgent or an elective transplant listing
- There will be no appeal from the Panel's decision
- ODT (NHSBT) will maintain records of all proposals, decisions and the proportion of each centre's transplant list that are referred to the National Appeals Panel, and the outcome of all applications will be tabled at the next LAG meeting
- The Panel may make recommendations to the Core Group of the Liver Advisory Group to revise the agreed criteria. The terms of reference of the Panel will be reviewed annually.
- As far as possible, the Panel will conduct its business electronically and by telephone
- The physician responsible for the patient may present the case to the Panel, but the representative(s) of the region where the application is from will not vote.

4.3.1 Elective cases

- The process will be managed and overseen by NHSBT, who will keep a record of applications and to provide the Panel with the information required
- The Panel should reach a decision within 5 working days of receipt of all relevant information. The appeal will be allowed if four or more centres are in favour. If a decision has not been reached by members of the Panel after 7 working days, an executive decision will be made by the Chair (or his deputy if the Chair is away or if there is a potential conflict of interest).
- The Chair will notify the applicant's clinician of the decision.

4.3.2 Super-urgent cases

- A case will be submitted by the centre, in writing, to the Chair of the National Appeals Panel.
- The Chair will respond to as a go/no-go. If Chair deems it as a valid appeal case, the centre will submit to NHSBT a Super-urgent Liver Recipient Registration, including the details of the appeal spelled out at the form Appendix.
- NHSBT will circulate the Appendix with the appeal details by the agreed methods to each centre. The centres will be responsible for seeking a response from their appeal panel representatives.
- Centres will respond to NHSBT within 12 hours.
- A super-urgent appeal case will be deemed as approved if either four positive responses are obtained or 12 hrs have elapsed and three or more centres have not objected.

- NHSBT will inform centre of the outcome. If a favourable outcome, NHSBT will carry out the super-urgent registration.

4.4 Second opinion for patients with alcohol-related liver disease

As with all potential transplant candidates, if a potential recipient is deemed not to be a suitable candidate by the multidisciplinary team then the opportunity for a second opinion from a different liver transplant centre can be considered and should not be refused. This may initially be in the form of a case notes review with full reassessment to follow if appropriate.

5. Reassessment on a transplant list and post transplant follow-up

All patients undergoing organ transplantation require lifelong follow-up and should have that explained at the start of their assessment process.

5.1 Re-assessment on list

It has to be recognised that patients awaiting a liver transplant are, by definition, ill and their condition may deteriorate to the extent that the probability of a 5-year survival may fall below 50%. In these circumstances, the patient will be removed from the transplant list but only after full discussion with them. Such patients, although in greatest need, are at greatest risk of not benefiting after transplantation.

Paediatric patients should be kept under review while on the transplant list as their condition may deteriorate to the point that transplantation becomes inappropriate or unnecessary. In these circumstances the patient would be removed from the transplant list only after discussion with their family and, where appropriate, the child themselves.

5.2 Post-transplant monitoring of alcohol consumption

The expectation is that all patients who are transplanted for alcoholic liver disease will remain abstinent following liver transplantation. To encourage this, follow-up for alcohol use will be separate from and additional to the transplant follow-up and should be carried out by specialists in substance misuse. Ideally this would be the same individual/s that were involved in the initial assessment. It is anticipated that as time from the liver transplant increases, frequency of follow-up will decrease, and that shared care arrangements with alcohol services in the patient's locality will often be appropriate. The type and frequency of follow-up will depend on the patient's needs.

In order to monitor the outcome of transplant listed patients with a significant illicit drug history, appropriate clinical data should be recorded. Consent for this to occur should be given at the same time as the drug and alcohol screening.

6. Audit

6.1 Policy audit and updates

The details of any policy concerning selection and allocation will inevitably change with time. Any new versions of protocols will be updated and published only twice per year in April and October following ratification at Liver Advisory Group Meetings. All changes to the guidance must first be agreed with the Liver Advisory Group, usually after discussion within the Core Group. Regular reports will need to be produced to assess the success or failure of any new selection, allocation and distribution policy.

6.2 Policy outcomes

The purpose of all liver transplant policies and guidelines is to ensure equitable access to organ transplantation in all transplant centres in the UK and the best possible outcomes when judged from the point of registration. All policies will be judged against those standards. Six monthly audits of outcomes will be undertaken by the Statistics and Clinical Studies department at NHSBT. The Liver Advisory Group will decide which additional topics are to be included in the Interim and Annual Report.

7. Recipient registration

7.1

All patients awaiting a transplant must be registered on the National liver transplant list at NHSBT. A standard registration form must be completed and sent to NHSBT via ODT online or by post. Patients will be placed on the National liver transplant list on the day on which details are received at NHSBT. Discrepancies or missing information will be followed up with the local centre and might cause a delay.

7.2 Multivisceral grafts

7.2.1

For recipients awaiting small intestine grafts, paediatrics will be given priority; offering criteria will be defined by size, age and geography.

7.2.2

For recipients awaiting composite liver and small intestine grafts, offering will be in line with the liver allocation sequence. Priority will be given to paediatrics; offers for paediatric patients will be made following offers to Super Urgent Liver Scheme recipients.

7.3 Combined lung/liver patient transplantation

If a suitable combined lung/liver patient is identified through the lung allocation, the liver (if suitable and not required by a super-urgent, hepatoblastoma or multivisceral patient) will be offered with the lung.

7.4 NHS Group

Recipients are categorised as Group 1 or Group 2 (as defined by The NHS Blood and Transplant (Gwaed a Thrawsbkniadau'r GIG) (England) Directions 2005 - Guidance). It should nevertheless be noted that nationals of a non-UK country may only be registered on a transplant list after they have been accepted by a consultant as suitable for treatment. It is the responsibility of the consultant registering such a patient on the waiting list to confirm that they have been accepted under E112 or similar arrangements.

7.4.1

Group 1 patients have priority for available organs above Group 2 patients. Group 2 patients registered in the UK and Republic of Ireland will be offered liver or liver and small intestine before offers are made to European Organ Exchange Organisations or Group 2 countries abroad. No organ should be offered to a Group 2 patient in the UK or Republic of Ireland if there is a clinically suitable Group 1 patient in the UK or Republic of Ireland.

7.5 Super-Urgent liver scheme

Initial registration on the super-urgent liver scheme can be made by telephone to the ODT Duty Office or a form may be faxed to the ODT Duty Office. Centres must ensure that a super-urgent registration form is counter-signed by the clinician and sent to the ODT Duty Office by facsimile or if necessary by urgent courier at the first opportunity following the telephoned registration. On receipt, the ODT Duty Office will facsimile an anonymised copy of the form to all designated liver transplant centres and the ODT Duty Office will place the recipient on the Super-urgent Liver scheme and notify all liver transplant centres in the UK and the European Organ Exchange Organisations by telephone and facsimile.

7.5.1

Centres wishing to seek clarification of the details of a recipient on the super-urgent liver scheme must notify the ODT Duty Office by facsimile. The clinician from the centre seeking clarification will make direct contact with the registering centre and discuss the case clinician to clinician. In cases where clarification has been sought, the ODT Duty Office will seek confirmation of the patient's status from the registering unit 24 hours after a registration.

7.5.2

A summary of recipients on the super-urgent liver scheme will be sent by facsimile to all designated centres by the ODT Duty Office each day. The summary will show the date and time of registration on the Super-urgent Liver Scheme.

7.5.3

A patient suspended from the super-urgent list can be reactivated within 5 days and maintain their position on the list. Once the patient is suspended for over the 5 days, the patient will then be removed from the super-urgent list and will not automatically be moved to the elective list. If the patient is removed from the super-urgent list and needs to be registered on the elective list then an elective registration form must be completed.

References

1. NHS Blood & Transplant and British Transplantation Society. Guidelines for consent for solid organ transplantation in adults.
http://www.odt.nhs.uk/pdf/guidelines_consent_for_solid_organ_transplantation_adults.pdf

APPENDIX A

Liver Transplantation in Severe Acute Alcoholic Hepatitis - Protocol

Introduction

1. Liver transplantation for cases with the severest forms of acute alcoholic hepatitis was previously considered by the Liver Advisory Group (LAG) in 2008, and rejected as an indication for selection to the transplant list. More recently the issue has arisen again firstly when a young patient with Severe Acute Alcoholic Hepatitis (SAAH) was being considered for transplantation and secondly as a consequence of recent published results of transplantation in these cases.
2. Liver transplantation in abstinent patients with inactive alcoholic liver disease (ALD) is well accepted and the survival rates in the UK and elsewhere are excellent¹. For instance, the most recent guidelines of the American Association for the Study of Liver Disease state that rejection, graft failure, and the need for retransplantation all are less common in patients with ALD compared with patients transplanted for other conditions, with the exception of an increased post-transplant incidence of pharyngeal, esophageal, and gastric malignancies² in patients with ALD.
3. In contrast, SAAH is not an indication for liver transplantation in most countries, so there has been little data on which to judge the issue. In a number of retrospective studies^{3 4 5 6} the outcome from transplantation in patients with histological or clinical evidence of alcoholic hepatitis in their explant has been similar to that in cases with the well accepted definition of inactive abstinent alcoholic cirrhosis. This has included similar survival rates and rates of return to harmful drinking. More recently a prospective study from France of carefully selected cases with SAAH reported better survival when compared to matched non-transplanted patients and similar survival to other cases with inactive abstinent alcoholic liver disease.⁷ Rates of resumption of alcohol use were similar to those reported in other series of patients following transplantation for alcoholic liver disease⁸.
4. As a consequence of this a number of international authorities have raised this issue again, calling for a reappraisal of liver transplantation in this selected cohort of patients^{9 10 11}.

¹ Lucey MR. Liver transplantation for alcoholic liver disease: past, present, and future. *Liver Transpl* 2007;13:190-192

² Murray KF, Carithers RL Jr. AASLD practice guidelines: evaluation of the patient for liver transplantation. *Hepatology* 2005;41:1407-1432.

³ Shakil AO, Pinna A, Demetris J et al. Survival and quality of life after liver transplantation for acute alcoholic hepatitis. *Liver Transpl Surg* 1997; 3: 240-244

⁴ Jennifer T. Wells, Adnan Said, Rashmi Agni et al. The Impact of Acute Alcoholic Hepatitis in the Explanted Recipient Liver on Outcome After Liver Transplantation. *Liver Transplantation* 13:1728-1735, 2007

⁵ Immordino G, Gelli M, Ferrante R, et al. Alcohol abstinence and orthotopic liver transplantation in alcoholic liver cirrhosis. *Transplant Proc* 2009; 41: 1253-1255.

⁶ Tomé S, Martínez-Rey C, González-Quintela A et al. Influence of superimposed alcoholic hepatitis on the outcome of liver transplantation for end-stage alcoholic liver disease. *J Hepatol* 2002; 36: 793-798

⁷ Mathurin P, Moreno C, Samuel D et al. [Early liver transplantation for severe alcoholic hepatitis](#). *N Engl J Med*. 2011 Nov 10;365(19):1790-800

⁸ Pageaux GP, Bismuth M, Perney P, et al. [Alcohol relapse after liver transplantation for alcoholic liver disease: does it matter?](#) *J Hepatol*. 2003 May;38(5):629-34

⁹ Ashwani K Singal, Andrea Duchini. Liver transplantation in acute alcoholic hepatitis: Current status and future development. *World J Hepatol* 2011 August 27; 3(8): 215-218

¹⁰ Robert S. Brown, Transplantation for Alcoholic Hepatitis — Time to Rethink the 6-Month “Rule” *N Engl J Med* 365;19 1836-7

¹¹ Burroughs A. Liver transplantation for severe alcoholic hepatitis saves lives *J Hepatol* 2012 (in press)

5. Critical to this re-assessment will be the ability to accurately identify those cases with SAAH who have the highest risk of mortality. A number of methods of assessing disease severity in SAAH have been described. A Maddrey score of ≥ 32 ¹², or a MELD score > 18 ¹³ both describe a poor outcome with approximately 60% hospital mortality. A Glasgow Alcoholic Hepatitis score¹⁴ of ≥ 9 and the Lille model¹⁵ of response to corticosteroids also predict a poor prognosis. These scores are moderately accurate in predicting those cases with the worst potential outcome (c-statistic 0.75-0.8) and may be used within the first week of admission.
6. Current therapy for SAAH is unsatisfactory and the subject of a new national trial - STOPAH. Therapies include nutritional support, corticosteroids¹⁶ ¹⁷ and pentoxifylline¹⁸. Although such therapies have been recommended for only those with very severe disease it has also been suggested that they may not be appropriate for the most severe cases¹⁹ and those that do not respond with 7 days of starting treatment. There remains a need to identify further treatments for those with the most severe forms of SAH.
7. The arguments in favour of liver transplantation in such cases are that when carefully selected they undoubtedly have a very poor prognosis and both retrospective and prospective studies described above demonstrate that they will benefit from such life-saving therapy. When identifying the principles underlying selection to the UK liver transplant waiting list at a Consensus Conference in October 2006, (now accepted in the recent NHS BT policy document *Liver Transplantation: Selection Criteria And Recipient Registration*) the following criteria were agreed:

3.2 Selection criteria for adult elective transplantation

- Selection will be based primarily on risk of death without a transplant. Patients can be considered for elective transplantation if they have an anticipated length of life or survival in the absence of transplantation that is less than that obtained with a liver transplant
- All patients selected for the elective adult liver transplant list must have a projected 5-year survival after transplantation of $>50\%$. That figure may change in the future if/when donor numbers alter
- Selection will be assessed secondarily on ability of transplantation to improve quality of life

¹² Carithers RL Jr, Herlong HF, Diehl AM, Shaw EW, Combes B, Fallon HJ, et al. Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial. *Ann Intern Med* 1989;110:685-690

¹³ Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001;33:464-470.

¹⁴ Forrest EH, Evans CD, Stewart S, Phillips M, Oo YH, McAvoy NC, et al. Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow alcoholic hepatitis score. *Gut* 2005; 54:1174-1179.

¹⁵ Louvet A, Naveau S, Abdelnour M, Ramond MJ, Diaz E, Fartoux L, et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. *HEPATOLOGY* 2007;45:1348-1354. www.lillemodel.com

¹⁶ Rambaldi A et al. Systematic review: glucocorticosteroids for alcoholic hepatitis—a Cochrane Hepato-Biliary Group systematic review with meta-analyses and trial sequential analyses of randomized clinical trials. *Aliment Pharmacol Ther* 2008;27:1167-1178.

¹⁷ Mathurin P, O'Grady J, Carithers RL, Phillips M, Ramond MJ, Louvet A, et al. Corticosteroids improve 28-day survival in patients with severe alcoholic hepatitis: individual data analysis of the last 5 randomized controlled trials. *Hepatology*. 2008;48:170A

¹⁸ O'Shea R, Darasathy S, McCullough A. Alcoholic liver disease; AASLD practice guidelines *Hepatology* 2010;51; 307-327

¹⁹ Mendenhall C, Roselle GA, Gartside P, Moritz T. Relationship of protein calorie malnutrition to alcoholic liver disease: a reexamination of data from two Veterans Administration Cooperative Studies. *Alcohol Clin Exp Res* 1995;19:635-641

- All patients will need to be regularly reviewed to ensure that they continue to meet criteria and have not improved or become too sick to benefit from transplantation
- When the clinical situation alters such that a patient no longer meets these criteria, the patient's name must be removed from the national list.

Selected patients with SAAH would meet those criteria.

8. Arguments against such a policy include the fact that up to 40% of patients initially presenting with SAAH may survive as with abstinence recovery is significant with improvement in liver function. Nevertheless, with current selection criteria this figure is much lower. A second concern here is that the adverse publicity of a transplant community being prepared to transplant cases with SAAH might have a detrimental effect on organ donation and the public's perception of organ transplantation. That may be a major concern at a time when publicity campaigns are in place to promote donation and increase transplants by 50% over a five year period. In fact when this topic has been discussed with patient groups and liver disease charities on two occasions there has been unanimous support. When previous cases with SAAH were described in the press some commentators and press coverage was favourable to transplantation in this context as well as others which were not. That divergence emphasises the importance of a carefully constructed communications plan involving NHS BT and the transplant centres, should this study proceed.
9. Another concern has been that introducing new indications for adult elective transplantation without any expansion in the donor pool might impact on the chance of other potential recipients with more accepted indications for transplantation from receiving an organ. In fact there has been a small increase in organs for donation over the last two years, and it is important to note that donor shortage has not been considered a barrier to the recent extension of the UK Selection Criteria to include extended criteria Hepatocellular carcinoma (2008) and Hepatic Epithelioid Haemangio-Endothelioma (2010). This criticism implies restricting access to the transplant list such that the number of potential recipients matches the number of potential organs available. That has not been an accepted selection process in the UK.
10. Patients transplanted with SAAH will not have had a prolonged period of abstinence prior to transplantation, currently a requirement prior to transplantation for alcoholic liver disease in UK (albeit without any rigid "six month rule"). That also applies within the USA. Nevertheless, there is a diversity of opinion on the relevance of prior abstinence as sole criterion for predicting long term sobriety. Not all studies have demonstrated that the duration of abstinence is a strong predictor of recidivism, and other factors including psychiatric co-morbidities, social support networks, poly-substance misuse and age at onset of abuse are also critical^{20 21 22 23}. Some countries have moved away from a 6 month rule, as in France²⁴, to a comprehensive psycho-social assessment, similar to that required in this protocol. The absence of abstinence does not reliably predict recidivism and other factors, which we believe we can identify, are more important.

²⁰Mackie J, Groves K, Hoyle A, Garcia C, Garcia R, Gunson B, et al. Orthotopic liver transplantation for alcoholic liver disease: a retrospective analysis of survival, recidivism, and risk factors predisposing to recidivism. *Liver Transpl* 2001;7:418-427.

²¹Pfizzmann R, Schwenger J, Rayes N, Seehofer D, Neuhaus R, Nussler NC. Long-term survival and predictors of relapse after orthotopic liver transplantation for alcoholic liver disease. *Liver Transpl* 2007;13:197-205

²²Dew MA, DiMartini AF, Steel J, De Vito Dabbs A, Myaskovsky L, Unruh M, Greenhouse J. Meta-analysis of risk for relapse to substance use after transplantation of the solid organs. *Liver Transpl* 2008;14: 159-172.

²³[Are preoperative patterns of alcohol consumption predictive of relapse after liver transplantation for alcoholic liver disease?](#) Perney P, Bismuth M, Sigaud H, et al. *Transpl Int*. 2005 Nov;18(11):1292-7.

²⁴Consensus Conference; indications for liver vtransplantation19/01/05. Lyon-Palais des Congres; text of recommendations. *Liver Transpl* 2006;12; 998-1011.

11. Although there is little doubt that transplantation can offer better survival in those with SAAH with the highest risk of death, there remains uncertainty as to whether it would be feasible to identify quickly in referral units, transfer, assess fully and extensively as described in this proposal and then finally list for transplantation in time for that procedure to be effective before irreversible deterioration will occur. It is in the light of the present uncertainty on that issue, that a carefully audited evaluation in a small UK pilot study is recommended and described here.

A proposal

We propose that 20 cases with SAAH are identified with criteria described below and offered elective liver transplantation and followed for a two year period. There would be no change to the current Adult Elective Liver Transplantation Selection criteria until the cases had been evaluated over a two year period from the date of the first case's transplant and at least 90 days from the last enrolled case's transplant.

This study is considered to be a service evaluation and audit and not a research study as there have been prior papers describing transplantation in this context. The evaluation is to identify potential numbers of such cases in UK, the feasibility of listing and allocation of donors in time to impact on the outcome of this disorder and to monitor longer term outcomes in a UK setting.

Study End-points: Primary;

1. Identify numbers of eligible patients who can be assessed and placed on the transplant list before deterioration occurs.
2. Duration of waiting prior to transplantation and numbers eventually receiving transplantation when using proposed selection criteria.

Study End-points: Secondary;

All patients will be followed up and reviewed in an identical manner to current adult liver transplant recipients and be included in the twice yearly audits of graft and patient survival. That includes 90 day, 1, 3 and eventually 5 year graft and patient survival as well as re-transplantation rates. All patients transplanted with alcoholic liver disease or other substance use are required to have extensive follow up of substance misuse behaviour as described in current national protocols (*Liver Transplantation: Selection Criteria And Recipient Registration 2012*). Patterns and quantity of alcohol consumption including harmful consumption will be recorded as usual.

Patient clinical selection criteria

1. First presentation with alcoholic liver disease.
2. Acute Severe Alcoholic Hepatitis – Lille score ≥ 0.45 with no response to a trial of corticosteroids over a 7 day period started within 7 days of initial hospitalisation.
3. Liver biopsy confirmation of diagnosis (transjugular)
4. Patient ≤ 40 years old
5. No other comorbidities related to brain, heart or pancreatic function (low dose inotropes for renal support do not constitute a co morbidity issue)
6. Absence of prior participation in any program to stop alcohol consumption and absence of prior refusal to participate in an offered program.
7. Agreement to enrol in a formal alcohol management program with local psychiatric support services both before (whilst waiting) and after transplantation.
8. Good family/network support as currently assessed for other patients with inactive alcoholic liver disease
9. No other substance abuse (including cannabis)

10. Absence of infection at the time of the diagnosis of resistance to steroids including fungal infection (screening for infection with at least : chest X-ray, 3 blood cultures, 1 urine culture and systematic ascites culture and fungal infection)

Any patient who has had a previous hospital admission for alcoholic liver disease (and who would have been told to stop alcohol consumption) on a separate occasion will be excluded from the study.

All patients identified under selection criteria will be enrolled into the observation study and will undergo:

Patient psychiatric selection criteria

- a. Evaluation by a Consultant Psychiatrist in substance Misuse and/or an alcohol support team, as is current practice.
- b. Evaluation to assess their understanding of the nature of their disease, prospects for adherence to an alcohol management protocol including future abstinence by both the patient and his family.

Transplant unit selection criteria

- a. Be given factual information including to their relatives concerning the prognosis of the disease and the presence of a national pilot study in SAAH. Patient to be informed that transplantation is usually not offered without a period of abstinence, that it will only be offered after careful review and unanimous agreement by the whole team and after meeting nationally agreed criteria for enrolment in the pilot study.
- b. If the patient is interested in liver transplantation, a local consensus has to be reached, involving the same decision making process at the selection MDT as for other non super urgent patients; there should be
Transplant Surgeons
Nurses - recipient co-ordinators
Consultant Hepatologists
Consultant Psychiatrist in Substance Misuse and/or alcohol specialist nurses
Liaison with Specialist alcohol services will include assessing the likelihood of the patient not returning to a damaging pattern of alcohol use if given the appropriate support and complying with follow-up, with respect to medication follow-up clinics, alcohol and substance abuse teams The agreement of the Consultant Psychiatrist as to the overall appropriateness of transplantation in the management of the case is necessary.
- c. If a case is not selected as appropriate then they continue in an observation study to examine mortality in non-transplant cohort
- d. Once deemed appropriate on above criteria for transplantation the case will be notified to all other transplant units for the purposes of confirming that all requirements have been met. A form describing selection criteria and how they are met in each case will be developed. This is to demonstrate compliance with all entry requirements and if all have been met other units will not have a right to veto the case.
- e. Cases will then be registered by NHSBT ODT.
- f. Once a case has been accepted onto the transplant list the patient will be informed that they are currently waiting transplantation unless their liver spontaneously improves.

Pre-transplant Screening

1. Laboratory screening :

- group, rhesus
- HLA, Coombs,
- PT in seconds, INR,
- Na, k, urea, creatinine
- CRP, fibrinogen
- Protein electrophoresis
- Liver function tests
- Creatinine clearance
- Arterial blood gas
- CEA, CA19-9, AFP
- Screening for autoimmune disease
- α 1 anti-trypsin
- caeruloplasmin, copper
- iron studies, folate ,B12, vit D,
- Screening for: HAV, HSV, CMV, EBV, HBV, HCV, HEV HIV, Legionella, Aspergillosis, Candidosis, Toxoplasma gondii

2. Radiological screening :

- Abdominal CT scan or abdominal MRI (according to kidney function)
- Gastroscopy to screen for oesophageal cancer
- Trans thoracic echocardiography
- Thoracic CT scan

(Screening to be adapted according to the past medical history of each patient)

Transplant Listing

Cases will join their participating Unit's elective adult transplant list and will be prioritised within that Unit's own protocols which in most cases is by ranked need (MELD or UKELD)

Prophylactic antibacterials and anti fungals

Prophylactic antibiotics for 5 days

Prophylactic IV antifungals (started when failed steroids or ab initio according to unit policy - the antifungal must be active against Aspergillus).

Patients will be listed to a centre's transplant list but will only be eligible for a zonal DCD/DBD or a DCD not accepted by a non-participating centre (whereby not impacting on donor availability in the two non-participating centres).

Currently, for the purposes of assessing the size of a unit's donor zone, each unit's % share of new elective adult registrants over 12 months is compared to that unit's % share of zonal donors. Current cases with SAAH selected for an elective transplant list by a unit will not be included in that calculation.

Immunosuppression

IL 2 R blockers if renal impairment (Basiliximab day 0 and 4)

Low dose tacrolimus (levels close to 5ng/l) and steroids (20 mg pred /d)

Audit and Registry (to include all SAAH from start of protocol)

Units will keep records of:

- Cases initially reviewed
- Cases meeting clinical selection criteria
- Patients meeting psychiatric selection criteria
- Patients meeting transplant unit selection criteria
- Patients registered for transplantation for SAAH.
- Patients transplanted
- Patient follow up and alcohol recidivism

Forms will be developed for each of these aspects

Ongoing project scrutiny

1. A total of 20 cases will be assessed with review after every 5 cases by the Data Monitoring Committee and a 6 monthly progress report sent to the Medical Director (Prof Neuberger).
2. Data Monitoring Committee will consist of an independent chair, a representative of those units not involved in the trial (Dr A Holt), a representative from the British Liver Trust, and an international representative.
3. Participating centres will be required to complete all data monitoring forms and return those to ODT NHS BT for their retention.

Patient Follow-up

As part of contract the follow up visits must be adhered to and patients called back if they do not attend. The same rules and screening and follow up should pertain to these patients as other alcoholics so that an assessment can be made if a similar management results in any differences for the return to drinking pattern and other outcomes.

Table 1. Components of Scoring Systems Used to Assess Prognosis in Alcoholic Hepatitis.*

Scoring System	Components							
	Bilirubin	Prothrombin Time or INR	Creatinine	Age	White-Cell Count	Urea Nitrogen	Albumin	Change in Bilirubin between Day 0 and Day 7
Maddrey's discriminant function†	Yes	Yes	No	No	No	No	No	No
MELD score‡	Yes	Yes	Yes	No	No	No	No	No
Glasgow score§	Yes	Yes	No	Yes	Yes	Yes	No	No
Lille score¶	Yes	Yes	Yes	Yes	No	No	Yes	Yes

* Maddrey's discriminant function, the Model for End-Stage Liver Disease (MELD) score, and the Glasgow score are used to decide whether to initiate corticosteroid therapy, whereas the Lille score is used to decide whether to stop the use of corticosteroids after 7 days or complete a 28-day course. INR denotes international normalized ratio.

† Maddrey's discriminant function is defined as $[4.6 \times (\text{patient's prothrombin time} - \text{control prothrombin time, in seconds})] + \text{serum bilirubin level, in milligrams per deciliter}$. A score of more than 32 indicates severe alcoholic hepatitis and is the threshold for initiating corticosteroid treatment.

‡ The MELD score is defined as $9.57 \times \log \text{creatinine, in milligrams per deciliter, plus } 3.78 \times \log \text{bilirubin, in milligrams per deciliter, plus } 11.20 \times \log \text{INR plus } 6.43$. The MELD score can be calculated at www.mayoclinic.org/meld/mayomodel7.html. Higher scores indicate worse prognosis.

§ The Glasgow score ranges from 5 to 12. The score for each item is as follows: age, 1 if younger than 50 years or 2 if 50 years or older; white-cell count, 1 if less than 15×10^9 per liter or 2 if greater than or equal to 15×10^9 per liter; urea nitrogen, 1 if less than 5 mmol per liter (14 mg per deciliter) or 2 if 5 mmol per liter or greater; ratio of patient's prothrombin time to control value, 1 if less than 1.5, 2 if 1.5 to 2.0, or 3 if more than 2.0; bilirubin, 1 if less than 125 μmol per liter (7.3 mg per deciliter), 2 if 125 to 250 μmol per liter (7.3 to 14.6 mg per deciliter), or 3 if more than 250 μmol per liter. Higher scores indicate worse prognosis.

¶ The change in bilirubin levels in the Lille model is defined as the difference in bilirubin levels between day 0 and day 7 of corticosteroid treatment. The Lille score is defined as $3.19 - 0.101 \times \text{age, in years, plus } 0.147 \times \text{albumin on day 0, in grams per liter, plus } 0.0165 \times \text{the change in bilirubin, in micromoles per liter,} - 0.206 \times \text{renal insufficiency, rated as 0 if absent and 1 if present,} - 0.0065 \times \text{bilirubin level on day 0 (in micromoles per liter)} - 0.0096 \times \text{prothrombin time (in seconds)}$. In patients who have received albumin infusions, use the last available albumin value before the infusion of albumin occurred. The Lille score ranges from 0 to 1 with the use of the formula $\text{Exp}(-R) / (1 + \text{Exp}(-R))$. The Lille score can be calculated at www.lillemodel.com. A Lille score greater than 0.45 indicates a lack of response to corticosteroids.

Table 2. Therapies for Alcoholic Hepatitis.*

Treatment	Clinical Purpose	Dose	Evidence
Psychotherapy	Maintain abstinence	Optimum approach and frequency not determined	No clear evidence of benefit in patients with alcoholic liver disease; has not been studied in patients with alcoholic hepatitis ⁶⁵
Corticosteroids	Reduce inflammation	40 mg of prednisolone orally, once a day for up to 28 days	Reduces short-term mortality in selected patients with severe alcoholic hepatitis ^{17,18,66-70}
Pentoxifylline	Ablate TNF- α , help maintain kidney function, and many other actions	400 mg orally, three times daily	Improves in-hospital survival in patients with severe alcoholic hepatitis; fewer instances of the hepatorenal syndrome in group receiving pentoxifylline ⁷¹
Infliximab	Ablate TNF- α	Most effective dose has not been determined	May increase risks of infection and death ⁷²
Etanercept	Ablate TNF- α	Most effective dose has not been determined	May increase risks of infection and death ⁷³
Nutritional support	Reverse malnutrition	35–40 kcal/kg of body weight per day, including 1.2–1.5 g protein/kg/day	Improves nutritional status but does not improve short-term survival in patients with severe alcoholic hepatitis ⁷⁴⁻⁷⁶
Oxandrolone	Increase muscle mass	Most effective dose has not been determined	Does not improve short-term survival in patients with severe alcoholic hepatitis ⁷⁷
Vitamin E	Ablate oxidant-mediated liver injury	Most effective dose has not been determined	Does not improve survival in patients with severe alcoholic hepatitis ⁷⁸
Silymarin (milk thistle extract)	Ablate oxidant-mediated liver injury	Most effective dose has not been determined	Does not improve survival in patients with severe alcoholic hepatitis ⁷⁹

* TNF- α denotes tumor necrosis factor α .

APPENDIX B

A service development evaluation of orthotopic liver transplantation for patients undergoing “down-staging” of Hepatocellular Carcinoma

Background

Current UK selection criteria for patients with hepatocellular carcinoma (HCC) are a modification of the Milan Criteria¹. Using size and number of HCC on pre-transplant imaging, these criteria aim to select at time of presentation patients that have HCC with favourable tumour biology and hence good outcome following liver transplantation. However, it is recognised that some patients outwith standard selection criteria based on size and number of HCC at the time of initial presentation have good biology disease and would benefit from liver transplantation. This recognition has led to the development of expanded criteria for listing of patients at presentation and the listing of patients who have undergone specific anti-cancer therapies resulting in apparent good response. This latter approach has been called “down-staging”. At present down-staging of HCC allowing listing for liver transplantation is not permitted under UK liver transplant selection criteria. However a reassessment has been determined to be necessary given the growing body of evidence to support down-staging as an appropriate strategy². Consequently this Service Development Evaluation aims to evaluate and validate down-staging of HCC utilising the selection criteria as developed by Duvoux and colleagues³. Amongst all potential criteria for down staging the Duvoux criteria, which were developed and have been introduced for use in France, have been deemed appropriate for use within the UK at a recently convened consensus conference².

Aims of evaluation

To assess and validate the Duvoux criteria for down-staging of HCC for use within the UK

Inclusion criteria

- Not eligible for elective listing for under standard UK listing criteria for HCC
- Within Duvoux criteria for down-staged HCC³
- Interval of ≥6 months from down-staging treatment to imaging upon which registration based
- Interval of ≥3 months from first imaging demonstrating patient within criteria to registration

Duvoux criteria for listing for HCC

Criteria for listing following “down-staging” treatment will be consistent with that detailed in Duvoux et al³.

¹ Mazzaferro et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med.* 1996 Mar 14;334(11):693-9.

²

http://www.odt.nhs.uk/pdf/advisory_group_papers/LAG/HCC_recommendations_IR_TS_b_NAS_Work_in_Progress.pdf

³ Duvoux et al. Liver transplantation for hepatocellular carcinoma: a model including α -fetoprotein improves the performance of Milan criteria. *Gastroenterology.* 2012 Oct;143(4):986-94

Variable	Points
Largest diameter (cm)	
≤3	0
3-6	1
>6	4
Number of nodules	
1-3	0
≤4	2
AFP (ng/mL)	
≤100	0
100-1000	2
>1000	3

Patients with a score ≤2 points following down-staging treatment will be eligible for registration for liver transplantation.

Either local or systemic anti-cancer therapies may be undertaken in order to achieve down-staging of HCC, but that for patients who have undergone either surgical resection or ablative therapies within 1 year of registration the resected or ablated lesions will continue to be counted with diameter of lesions as determined by the resection pathology or the pre-intervention imaging with the greatest diameter being used.

Exclusion criteria

- Macrovascular invasion – identified at any time on radiological imaging or liver resection pathology
- Nodal metastases at any time
- Extrahepatic metastases at any time
- Ruptured HCC at any time
- Absence of an absolute contra-indication to liver transplantation as defined in the current UK selection assessment and selection criteria for liver transplantation.

Radiological imaging

Patients with presumed HCC should undergo the following imaging modalities during assessment for liver transplantation

1. Contrast-enhanced CT of chest, abdomen and pelvis
2. Contrast-enhanced MRI liver

Imaging for the purpose of diagnosis and assessment must be undertaken within 4 weeks of listing.

Two independent radiologists will review all imaging undertaken prior to listing in order to confirm that imaging demonstrates HCC within the Duvoux criteria with regard to size and number.

For any given lesion the longest axis will be determined and used for assessment purposes. Measurements will be determined from the imaging modality that provides the best definition of the lesions under investigation

Waiting list management of patients

Local or systemic therapy for HCC is allowed whilst the patient is on the waiting list.

The maximum interval between repeat radiological imaging/AFP estimations will be 3 months.

Repeat imaging for estimation of HCC size and number will be with the modality (CT or MRI) that provides the best definition of identified liver lesions. The independent radiologists reviewing the initial imaging will determine the imaging modality to be used during follow up imaging.

CT chest, abdomen and pelvis will be required at 3 monthly intervals to assess the presence or absence of extra-hepatic disease.

Date of repeat imaging and lesion measurements will be provided to NHSBT along with other required variables.

Removal from waiting list

Patients will be removed from the waiting list if they progress beyond the Duvoux criteria or develop an exclusion criterion as listed above.

Cohort Size

A maximum of 40 patients will be recruited.

Major outcome measures

- 2 year disease-free survival
- 5 year disease-free survival
- 2 year patient survival
- 5 year patient survival

Evaluation monitoring

An independent Oversight Committee will be responsible for the running of the evaluation. This committee will consist of both clinicians and lay members.

The Oversight Committee will provide reports to the Liver Advisory Core Working Group.

The Core Working Group will report and be responsible to the Liver Advisory Wider Group at the 6 monthly meetings.

Termination of service development evaluation

The evaluation will be terminated if there is

1. Evidence of poor outcome following liver transplantation
2. Evidence of poor recruitment to the service development evaluation.

Dissemination of details of planned service development evaluation

Patients eligible for inclusion in the present evaluation may not have traditionally been managed within a liver transplant centre raising the possibility of inequity of access to a potentially curative treatment if referring centres are unaware of the proposed evaluation. Consequently details of the evaluation will be circulated to all cancer networks, gastroenterologists and hepatobiliary surgeons. Where possible information will be circulated through relevant professional bodies e.g. British Association for the Study of the Liver (BASL), GB and Ireland HepatoPancreaticoBiliary Association (GBIHPBA).