Cynllun Cynorthwyo Gwaed wedi'i haentio Cymru
Wales Infected Blood Support Scheme

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# ASSESSMENT OF CHRONIC (STAGE 1) HEPATITIS C INFECTION APPLICATIONS

## Eligible to join the Wales Infected Blood Support Scheme (WIBSS)

It is important to first establish that the applicant (or estate in cases of deceased infected people) is in fact eligible to apply to WIBSS. The majority of beneficiaries will have transferred over from the UK support schemes, but new applicants who are not already allocated to another UK infected blood support scheme will have to demonstrate that they were infected with chronic Hepatitis C in Wales.

## Chronic Hepatitis C

To qualify for a Chronic Hepatitis C payments the applicant (or the deceased infected person) must have been chronically infected (for more than six months) with Hepatitis C as a result of treatment with NHS tissue, blood or blood products prior to September 1991, on the balance of probabilities. The clinician completing the application form must therefore have provided evidence that the applicant was infected with Hepatitis C.

## Balance of probabilities principle

The assessor is required to make their decision on the balance of probabilities. They have to conclude that the chronic Hepatitis C infection is more likely than not to have resulted from NHS treatment with exposure to blood, blood products or tissue before 1st September 1991. The screening of blood for Hepatitis C was introduced across the UK from 1st September 1991, so any treatment received after that date is considered safe from Hepatitis C.

It needs to be probable that the chronic infection arose as a direct result of NHS treatment with blood, blood products or tissue. Probable means that the probability that the event happened is more than 50%. For example, it would be highly probable that a haemophiliac was infected in this way given routine treatment with untreated and unscreened blood products, but it would be improbable that an injecting drug user was infected via a single blood transfusion, even if they did receive one (unless that specific batch was confirmed as infective).

The assessor must be persuaded of the existence of the chronic Hepatitis C infection and that it is likely that the applicant received relevant NHS treatment before the claim can be successful. Each claim will have to be assessed on its own merits and the evidence available. Generally speaking, the standard of proof will not be satisfied by inexact evidence, indefinite witness statements, or indirect references.

If the assessor ranks the possible causes in terms of probability and concludes that one is more probable than the others, then they are entitled to conclude that route is the probable cause of the infection.

**Benefit of the doubt**

In borderline cases, where there is viewed to be around a 50% chance of the infection having occurred as a result of infected NHS blood, tissue or blood products, the benefit of the doubt should be given in favour of the applicant. That is, if the applicant's story is on the whole coherent and plausible, any remaining element of doubt should not prejudice the assessor's decision. The claim should be coherent and plausible, not contradicting generally known facts, and, on balance, capable of being believed.

No facts should be discounted in the evidence gathering exercise, unless they are found to have a lack of credibility. Every facet of the applicant's statement should be taken into account in the evaluation of the probability of infection. The burden of proof lies with the person submitting the claim, but the duty to ascertain and evaluate all the relevant facts is shared between the applicant and the assessor.

Although it is ultimately for the applicant to substantiate the application, in borderline cases where aspects of the applicant's statements are not supported by documentary or other independent evidence, the assessor may judge that those aspects shall not need confirmation when the following 5 conditions are met:-

(a) the applicant has made a genuine effort to substantiate his or her application;
(b) all relevant elements at the applicant's disposal have been submitted, and a satisfactory explanation regarding any lack of other relevant elements has been given;
(c) the applicant's statements are found to be coherent and plausible and do not run counter to available specific and general information relevant to the applicant's case;
(d) the applicant has applied to the relevant UK or Wales scheme at the earliest possible time following diagnosis, unless the applicant can demonstrate good reason for not having done so; and
(e) the information provided suggests that the applicant is generally credible.

The requirement that the need for documentary or other independent evidence, such as medical records, should not always be too strictly applied (where appropriate) does not however mean that unsupported statements must necessarily be accepted as true if they are inconsistent with the general account put forward by the applicant or their clinician. The credibility of the applicant will be called into question by contradictions, inconsistencies and omissions in their application.

**Probability of infection**

The number of historically infected individuals is very difficult to estimate; however, we know that the proportion of people receiving a blood transfusion during January -

September 1991 who acquired HCV was approximately **1 in 1500**. A report on the issue of the estimated number of undiagnosed people remaining can be found at:

http://www.gov.scot/Publications/2016/09/5853/0

The majority of patients infected via treatment for bleeding disorders were registered with haemophilia centres, and consequently were traced quickly and would likely have already joined the UK support schemes. A small number of people, with mild blood factor conditions, who only received occasional treatment, are being traced and contacted. Even if they only received a single treatment with blood products historically to treat their bleeding disorder, this would have a very high chance of HCV infection given that these products were pooled from large numbers of donors.

**The assessment for a primary beneficiary**

The assessment essentially consists of three elements:

(1) Is there, or was there, a chronic Hepatitis C infection as confirmed by the applicant's clinician? If so:
(2) Is there evidence of an eligible exposure or potential eligible exposure (prior to 1st September 1991) to NHS blood, tissue or blood products? If so:
(3) Is the infection a probable result of the identified exposure or potential exposure to NHS blood, tissue or blood products, rather than having been caused by other risk factors?

The assessor needs to be able to answer yes to all three elements above. Assessors will be relying upon the applicant's clinician to provide a diagnosis of chronic Hepatitis C and an assessment of the likely length of infection and likelihood of NHS exposure, given the medical procedure(s) or products involved.

**Conclusion**

In short, for an application to be successful the assessor must be satisfied that it is probable that the chronic Hepatitis C infection was caused by the apparent exposure to NHS blood, blood products or tissue. There has to be a probable causal link between the chronic Hepatitis C infection and the alleged NHS exposure in question.

**Secondary infection**

The following categories of people are eligible to make an application to the scheme as a secondary infectee:

- heir spouse or civil partner (or at least they were their spouse or civil partner at the likely time of infection);
- a long-term cohabiting partner – this is a person who was living with the person from whom the virus was transmitted in a relationship which had the characteristics of a marriage or relationship between civil partners at the likely time of infection (or if the person from whom the virus was transmitted was in hospital immediately before death, had been so living when that person was admitted to hospital);

- where the person from whom the virus was transmitted was a mother, a son or daughter of the mother where they were likely to have been infected by their mother at birth.

In all cases a successful Chronic Hepatitis C infection application must have been made by the person who was the alleged source of the infection. Determining if a person was the source of infection will also be dealt with on the balance of probabilities. Where a person was married to or cohabiting with a person who has fairly recently been diagnosed as infected and accepted onto the scheme, then, on the balance of probabilities, you should normally accept that they received the infection from their partner if the secondary infectee has chronic Hepatitis C with a matching genotype to that of their spouse/partner, unless there is evidence which suggests another more likely cause of the secondary infectee's Hepatitis C infection.

However, where a primary beneficiary has been diagnosed with Hepatitis C for a long-period, new secondary infection claims should be treated with caution given that they should have been well aware of Hepatitis C transmission risks and prevention advice. Therefore normally secondary infection applications would only be accepted where it is thought that the person was secondarily infected before the person they were infected by was diagnosed with Hepatitis C. If they were likely to have been infected after their spouse/partner was diagnosed with Hepatitis C, then they may still qualify as long as they can provide a reasonable explanation regarding what precautions they were taking at the time – for example if they can confirm that they always used a condom, but that it failed on a particular occasion – again any such evidence would need to be considered on the balance of probabilities.

**Evaluation**

The evaluation of the application should identify:

- What is known;
- What is not known;
- Consistencies in the account and evidence (e.g. between the applicant's account and that of their clinician or any other supporting statements);
- Conflicts in the account and evidence .

The assessor should consider:

- The overall strength of the case;
- Whether sufficient evidence exists that infection via eligible NHS treatment was probable.

The assessor should consider the use of a clinical advisor in complex cases, for example to check the likelihood of a certain medical procedure requiring a blood transfusion.

**Evidence gathering**

The assessor should consider:

- Has all the available material been gathered?

- Does the assessor understand all the material?
- Are there any lines of enquiry which have not yet been pursued and which could generate more material. For eample could WBS be contacted to check for records of a transfusion or could the applicant be encouraged to contact any other NHS Board/GP sources to check if any records are held.

**Relevance and reliability of evidence**

The assessor should always look for independent corroboration of the account provided by the applicant.

The following may assist the assessor to determine the appropriate weight a piece of material should be given:

- Material that can be corroborated by an independent source (i.e. someone who is not related to the applicant and does not have any material interest in the outcome of their application) will have high reliability;
- Material that cannot be corroborated and conflicts with other material gathered will have less reliability.

There may also be other factors which may cast doubt on the reliability of the material, such as inconsistency in the reporting of the infection event.

**Key facts**

For applications from primary beneficiaries, the assessor should determine:

- *What has occurred?* It is important to establish what happened, particularly the fact that the applicant was infected with chronic Hepatitis C. This may be immediately obvious, but in some cases the assessor will have to piece together the available material and request further information if necessary.
- *When did the alleged infection take place?* Did this happen prior to the introduction of Hepatitis C inactivation (usually heat treatment) for blood products (generally from May 1987 in Wales); or the introduction of Hepatitis C screening for blood and blood products (from September 1991)?
- *Why was this treatment given to the patient at this time?* Concentrated blood products administered to those with bleeding disorders carried a very high risk of infection (up to 100% risk) given that they were produced from large pools of donors. So a person with a bleeding disorder would be very likely to be infected by this route, even if they could not provide evidence of a specific infected batch of treatment.
- *How was the infection transmitted*? What blood component or blood product, and in what volume, did the person receive? Generally a higher dosage of a product would be more likely to result in an infection. Different blood products carried different risks of infection, and some were made safe before others, generally through heat treatment. Whole blood and blood components were not heat treated and remained potentially infective, although high risk donors were deferred from 1983 onwards (deferral protocol steadily improved) and screening for Hepatitis C across the UK was introduced from 1 September 1991.

## Interpretation

There are a number of ways in which assessors can test the validity of their interpretation of the evidence:

- Self review: assessors should thoroughly check their work and review any assumptions they have made during the evaluation process;
- Peer review: Checks by supervisors or scheme colleagues provide a second opinion on the interpretation of material;
- Expert Review: Where there are difficult clinical matters to interpret, they should consult a clinical expert to ensure that the outcome of the evaluation is consistent;
- A rejected applicant will also have the option of review of the decision by the appeals panel.

## Confirming the applicant has/had chronic Hepatitis C

An application cannot be considered unless a diagnosis of chronic Hepatitis C infection has been made. Those who have been diagnosed as having been infected with Hepatitis C, but have cleared the virus in the acute phase (first six months) of the disease without the use of treatment are not eligible to claim from WIBSS.

WIBSS is only aboe to consider applications in respect of chronic hepatitis C infection. Hepatitis B infection os not covered by the scheme.

Detection of viral ribonucleic acid (RNA) by nucleic acid tests (NAT) indicates current infection. Detection of antibodies indicates resolved or current infection. If Hepatitis C RNA is detected, that indicates current Hepatitis C infection. If Hepatitis C RNA is not detected, that indicates either past, resolved Hepatitis C infection, or false Hepatitis C antibody positivity (in rare cases false positive results occur—when someone tests positive but is not actually infected). False positive results would be picked up by confirmatory testing with another Hepatitis C antibody test – the person would not be eligible in that case.

The best laboratory evidence to support a diagnosis of acute Hepatitis C infection is (1) a positive Hepatitis C RNA test in the setting of a negative Hepatitis C antibody test (identification during the “window” period), or (2) a positive Hepatitis C antibody test after prior negative Hepatitis C antibody test (termed seroconversion). There are rare instances in which these approaches may be misleading, such as in immunosuppressed individuals with impaired antibody production.

The PCR (polymerase chain reaction) test is the best test to detect the presence of Hepatitis C virus in the human body. In a minority of people infected with Hepatitis C, the body's immune system successfully fights the virus and clears it from the body with no long-term ill effects. In these cases the PCR becomes negative and the disease does not progress to a chronic (long-term) phase. Patients in whom this occurs are termed “natural clearers”.

In relation to natural clearers the evidence generally accepted by the specialist medical community is as follows. Of patients infected with Hepatitis C virus, up to one third will clear the virus spontaneously – that is without specific treatment - in the first six months (acute phase). Subsequently an additional few patients clear the virus before one year

has elapsed from infection. After one year from infection, spontaneous viral clearance may occur, but it is an exceptional event.

Thus, of those patients who clear the virus spontaneously, the proportion which clear the virus during the first six months is very much higher than the proportion which clear the virus after the first six months have elapsed. Therefore, when the assessor considers an applicant who has spontaneously cleared the virus, the general population data suggests that it is very probable that infection did not last beyond a six-month period and the chronic infection must have lasted for more than 6 months in order for an application to be approved.

Despite this general evidence which is based on overall figures, the assessor should always looks at the particular information that is available in each individual case to see whether there is any evidence of lasting (chronic) infection. If there is, it should be carefully considered so that you can make a judgement on the question of whether infection lasted more than six months. If there is no good individual evidence that there was infection lasting longer than six months the assessor will have to rely upon the general evidence alone.

## INELIGIBLE TREATMENTS

Fluid replacement (saline, glucose, etc.), artificial plasma expanders and intramuscular anti-D immunisation (in pregnancy and miscarriage/abortion) are *not* associated with hepatitis C infection in the UK and will not be considered by the scheme as probable causes of infection. Likewise the scheme is not able to consider infection caused by incidents at work (for example needlestick injuries) in hospital staff. These fall outside the scheme and the applicant will need to take advice from a solicitor or Trades Union in the normal way.

## TISSUE, BLOOD AND BLOOD COMPONENTS

These treatments carried a risk of HCV infection prior to the introduction of HCV screening from 1st September 1991:

**Cryoprecipitate**: a blood component that was not HCV inactivated. Prior to the use of plasma concentrates it was used for treatment of patients with haemophilia, but also in the context of fibrinogen deficiency e.g. during major haemorrhage.

**Whole blood or its components (including platelets, red cells, neutrophils).**

**Plasma/Fresh Frozen Plasma.**

**Bone marrow.**

## BLOOD PRODUCTS (DERIVED FROM PLASMA)

Blood products differ in that they were generally subject to heat treatment to inactivate HCV prior to the introduction of HCV screening. Except for intravenous immunoglobulin and albumin, they carried a very high risk of HCV infection (up to 100%) prior to the introduction of HCV inactivation processes:

**Factor VIII concentrate (used to treat haemophilia A)** – the product manufactured by SNBTS was heat treated and HCV safe from May 1987. About 15% of the Factor VIII concentrate used in Scotland in 1988-1990 was imported and was not safe from HCV (see Penrose Inquiry doc PEN0131125 pp64-65). However, it is extremely unlikely that this product would have been used to treat patients at risk from HCV.

**Factor IX concentrate (used to treat haemophilia B)** – this product was HCV inactivated by heat treatment from October 1985.

**DEFIX** - this product was HCV inactivated from October 1985. It was an SNBTS FIX concentrate (containing coagulations factors II, IX & X) that was primarily used to treat haemophilia B. It was introduced in 1972.

**Fibrinogen** - this was another coagulation factor concentrate produced by SNBTS that carried a risk of HCV transmission. This was introduced in 1956 and discontinued in 1983.

**FEIBA (used to treat haemophilia treatment inhibitors)** – this was a commercial product heat treated from January 1986 (see Penrose SGH0021947, page 430, table 5), although the degree of heat treatment employed may not have been sufficient to inactivate HCV.

**Intravenous immunoglobulin** – This SNBTS IV product was introduced in 1983 and continued to be used until 2005. It was subjected to an acid treatment from the outset, which was effective in inactivating HCV. Four cases of HCV infection were associated with one batch manufactured in 1987 (three were confirmed as HCV). Although the SNBTS IV IgG was never proven to be the cause of these infections, it was generally accepted to have been the most likely cause. This is considered to have been an isolated incident (Penrose Document No. 2011-00082(a.1)).

**Albumin** – Albumin products were introduced by SNBTS in 1965 and were pasteurised from the outset using standard conditions that had been devised in the USA in 1945. These products are considered free from transmission of HCV. The topic was considered in the Penrose Inquiry in relation to the death of Mr GRO-A, where it was concluded that the albumin that he had received (known as SPPS) was not the cause of his HCV infection (see final report GRO-A).

**PPSB -** another type of SNBTS factor IX concentrate (from 1968) which contained coagulation factors II, VII, IX & X. This was used for the treatment of haemophilia B from 1968-1972; thereafter it was prepared in small quantities for the treatment of coagulation disorders where factor VII was required. It is believed that the risk of HCV transmission was probably low, but cannot be discounted. This product did not tolerate heat treatment and was discontinued in the mid-1980s.

If in doubt for more unusual commercial products, try to research the commercial product in question. In some cases the manufacturer could be contacted for advice or SNBTS may be able to provide further information. Please note that if the product was provided in another part of the UK and the assessor is in any doubt, they should contact that country's scheme or, if needed, the manufacturer to check whether the product could have been infective. NHS Factor VIII (8Y) heat treated sufficiently to inactivate HCV was introduced in England in September/October 1985, however due to demand some of these concentrates were still imported commercial products and not safe from

HCV. Factor VIII concentrate from commercial sources which could be considered as essentially safe with respect to HCV was first licensed in the UK in December 1989 (Monoclate Armour) providing an alternative to SNBTS Factor VIII concentrate that could be considered to be safer than cryoprecipitate.

## MEDICAL PROCEDURE OR TRANSFUSION EVENT

If no specific evidence of a blood transfusion is available, consider whether the medical procedure or event mentioned would be likely to result in blood transfusion.

There is no universal transfusion trigger – the decision to transfuse is based on clinical assessment of the patient, supported by the results of laboratory tests and informed by evidence-based guidelines:

- Transfusion is commonly associated with major surgery, childbirth or a severe accident.
- It can take place during critical care, or in cases of major haemorrhage.
- Patients who are anaemic preoperatively are more likely to be transfused.
- Major obstetric (childbirth) haemorrhage was a common cause of transfusion. T
- he use of red cell transfusion in surgery was more common in the past.
- It can be used to treat inherited blood disorders, such as thalassaemia or sickle cell anaemia.
- Platelet transfusions can be given to patients receiving intensive chemotherapy.
- Transfusion recipients were/are often elderly.
- The biggest medical users of blood are haematology, oncology, gastrointestinal medicine (including liver disease) and renal medicine.

More information on transfusion practice can be found at:

**http://www.transfusionguidelines.org.uk/transfusion-handbook**

If in doubt, a clinical opinion should be sought on the likelihood of transfusion in the given circumstances.

## CLINICAL PICTURE: DISEASE PROGRESSION

The assessor should check that the applicant's disease progression does not appear to contradict the alleged date of exposure. For example, if an applicant was suffering from cirrhosis within less than 10 years from the date of exposure, that could indicate an earlier exposure, or another cause of the cirrhosis.

The Hepatitis C Virus (HCV) is a major cause of liver disease. A person can be infected with hepatitis C for many years without having any symptoms. If left untreated, hepatitis C can eventually progress to cause serious liver damage.

Approximately 20% of people will progress to serious liver damage, called cirrhosis, within 20-30 years of infection.This means that patients diagnosed at a late stage are more likely to suffer from serious liver damage given that they have not had access to appropriate care and treatment. New applicants are more likely to be in this situation, as they will have been infected for over 25 years .

Over time, the virus attacks the liver cells causing swelling which can lead to the appearance of scar tissue that is called fibrosis. Scar tissue gradually builds up, becoming permanent, and the liver becomes harder in texture. This hardening is referred to as cirrhosis. There is an increased risk of liver cancer in those who have developed cirrhosis. The link between chronic HCV infection (generally long duration 15+ years) and a subset of B-cell non-Hodgkin lymphomas is also strongly supported by epidemiological studies.

Hardening of the liver affects its ability to function. The liver can repair or compensate for a lot of damage. However, once it can no longer carry out its functions, the liver is said to be decompensated. Symptoms of decompensated cirrhosis may include jaundice, high blood pressure, swelling of the legs and feet, red, blotchy palms, itching, easy bruising and excessive bleeding.

A patient with decompensated cirrhosis will spend more time in hospital as the condition needs to be closely monitored and fluids, nutrition and treatments given.

There are several different strains of hepatitis C, called genotypes. Currently, throughout the world, there are 11 recognised Hepatitis C genotypes. These are numbered simply 1-11. The most common genotypes found in Scotland are genotypes 1, 2 and 3. Patients with HCV genotype 3, when compared with other HCV genotypes, have relatively faster rates of fibrosis progression, higher prevalence of severe steatosis (fatty liver), and a higher incidence of liver cancer. In the current direct-acting antiviral therapy era, patients with genotype 3 infection have been more difficult to treat compared with other genotypes, especially in patients with cirrhosis.

## OTHER POSSIBLE ROUTES OF INFECTION

Applicants who have had a history of exposure to recreational intravenous drug use (IVDU, such as heroin). The assessor should make their own judgement on the relative likelihood of the applicant having obtained Hepatitis C from intravenous drug usage or from NHS treatment taking account of all the general and individual information available. This would include dates and frequency of IVDU, substances injected, circumstances of IVDU, equipment used, etc

Other risk factors that should be considered include:

- medical treatment in other countries outside the UK (particularly developing countries);
- tattoos (particularly if they were thought to have been carried out by a non-licensed tattooist);
- other recreational drug use including snorting cocaine;
- sexual activity involving the exchange of bodily fluids with a person infected with Hepatitis C and/or an intravenous drug user.

## WITNESS STATEMENTS

Witness statements can provide useful information. This is particularly the case where the witness is completely impartial, although witnesses who know the applicant well can still provide useful information, even if they may not be completely impartial. The key question with regard to witness statements is: can you accept the witnesses as reliable? The assessor should avoid developing inferences or expectations about an applicant or

witness early on in the information-gathering process. This can produce biased judgement – for example if a person was resident in an area historically associated with a high prevalence of injecting drug use.

Where different versions of events are presented, for a claim to be successful the version presented by the applicant to substantiate the claim must be found on the whole to be the most probable. This will involve a qualitative assessment of the truth and/or inherent probabilities of the evidence of the witnesses and, secondly, an assessment of how probable their version of events is.

**Recording your assessment**

A "good" assessment would include the following considerations:

(1) Be clear about the infection event that is being assessed and ensure that it is within scheme eligibility criteria;
(2) Ensure you have the concrete details to inform the decision;
(3) Identify the main details the applicant needs to understand/comprehend (ignoring the peripheral and minor details);
(4) If appropriate, demonstrate the efforts the scheme has taken to promote the applicant's ability to gather evidence;
(5) Evidence each element of your assessment.
(6) If appropriate, be clear why this is a rejection decision as opposed to a successful claim. Feedback should be given to the applicant on the decision.

The key general points to remember are:

- Documented, independent evidence is preferable to retrospective recollection;
- "Yes/No" answers are, in most cases, unlikely to be of assistance unless they are supported by a reason for the answer in the application form;
- What is reasonable to expect by way of documentation will depend upon the circumstances under which the treatment in question was conducted. For example, an emergency assessment in an A&E setting will not demand the same level of detail in the assessment or the recording of it. Some blood transfusions will not have been documented historically, and the patient may not have been notified or aware that they received one at the time.
- In many cases the historic medical records may now have been destroyed in line with the record management processes in place at the time.

**Note-taking**

Assessors should take notes as the case progresses so that they are not forced to rely on memory when reviewing the evidence and forming a decision. They should document the reasoning behind a decision before issuing it; and reflect the reasoning in the decision letter. Consistency in decision-making is essential, given that decisions may be challenged if a precedent has been set. Sharing the reasoning up front with the applicant will help ensure that applicants and stakeholders are more confident that everyone is being treated fairly.

## ASSESSMENT OF ADVANCED (STAGE 2) HEPATITIS C INFECTION APPLICATIONS

This payment is for those who have received the Chronic Hepatitis C payment and their Hepatitis C has advanced. Again, this application form must be completed by a registered medical practitioner, preferably a treating consultant.

The key indicators for the Advanced Hepatitis C payment are:

- **to have undergone, or to be on the waiting list to undergo, a liver transplant; or to have been diagnosed with primary liver cancer;**
- **or to have been assessed as having cirrhosis based on medical evidence (e.g. biopsy results, blood tests, ultrasounds, Fibro Scan etc.);**
- **or to have been diagnosed with B-cell non-Hodgkin's lymphoma.**

The applicant must meet one or more of these tests to be eligible**.**

It should be straightforward for the clinician to confirm and evidence that the applicant has developed primary liver cancer or B-cell non-Hodgkin's lymphoma; or that they have undergone or are waiting to undergo a liver transplant.

### Cirrhosis

It is not always easy to diagnose cirrhosis. A doctor will take a careful medical history, carry out a physical examination and make plans for further tests. Liver biopsy is not necessary for diagnosis of cirrhosis, but is helpful for grading the severity of disease and staging the degree of fibrosis and permanent architectural damage.

Fibrosis may exist in an early stage, being confined to the portal tracts, an intermediate stage consisting of expansion of the portal tracts and bridging between portal areas or to the central area, or a late stage of cirrhosis characterized by architectural disruption of the liver with fibrosis and regeneration. Several scales are used to stage fibrosis. One common classification is a scale from 0 to 4 where stage 0 indicates no fibrosis; stage 1 indicates enlargement of the portal areas by fibrosis; stage 2 indicates fibrosis extending out from the portal areas with rare bridges between portal areas; stage 3 indicates many bridges of fibrosis that link up portal and central areas of the liver; and stage 4 indicates cirrhosis.

The tests for cirrhosis include:

- **blood tests**, which among other things measure the liver function and damage. These are most commonly Liver Function Tests (LFTs). These are used to gain an idea of how the different parts of the liver are functioning.
- **ultrasound**, the same technology used to confirm all is well in pregnancy, sends sound waves into the body. The echoes are picked up and used to build a picture of the condition of the liver.
- **MRI** (magnetic resonance imaging) **and CT** (computerised tomography) provide a detailed view of internal organs and are able to generate very detailed cross-sectioned images (or 'slices') of the body area.

- **liver biopsy** in which a tiny piece of the liver is taken to be looked at under a microscope. A fine hollow needle is passed through the skin into the liver and a small sample is withdrawn. The test is usually done under local anaesthetic and may mean an overnight stay in hospital, although most people are allowed home later the same day if they live close by.
- **endoscopy** in which, following sedation, a thin flexible tube with a light and a tiny camera on the end (endoscope) is passed down the oesophagus and into the stomach. This is to check for varices in the oesophagus or stomach which may rupture and suddenly bleed.

**Non-invasive Tests**

While liver biopsy is considered the "gold standard" for assessing the severity of liver disease, it is not always accurate and has several shortcomings. Liver biopsy can under- or over-estimate the severity of Hepatitis C, particularly if the biopsy is small and if it is not read by a knowledgeable expert. In addition, liver biopsy is an invasive procedure that is expensive and not without complications. At least 20 percent of patients have pain requiring medications after liver biopsy. Rare complications include puncture of another organ, infection, and bleeding. Obviously, non-invasive means of grading and staging liver disease are often preferred.

The liver function test is made up of a number of separate examinations, each looking at different properties of the blood. It is used to gain an indication of how much the liver is inflamed or unable to work properly. The test will measure, for example, levels of the liver enzymes ALT and AST as these are increased during inflammation (hepatitis). It will also look at how well their blood clots (referred to as INR time) and how well the kidneys remove a product called creatinine. These are good indicators for how well their liver is working, and how this is affecting the rest of your body.

Alanine aminotransferase (ALT) levels, particularly if tested over an extended period, are reasonably accurate reflections of disease activity. Thus, patients with repeatedly normal ALT levels usually have mild inflammation and liver cell injury on liver biopsy. Furthermore, patients who maintain ALT levels above five times the upper limit of normal usually have marked inflammatory activity. But for the majority of patients with mild to moderate ALT elevations, the actual level is not very predictive of liver biopsy findings.

More important is a means to stage liver disease and measure fibrosis short of liver biopsy. Unfortunately, serum tests are not reliable in predicting fibrosis, particularly earlier stages (0, 1, and 2). When patients develop bridging (stage 3) fibrosis and cirrhosis (stage 4), serum tests may be helpful. The "danger signals" that suggest the presence of advanced fibrosis include an aspartate aminotransferase (AST) that is higher than ALT (reversal of the ALT/AST ratio), a high gamma glutamyl transpeptidase or alkaline phosphatase, a decrease in platelet count (which is perhaps the earliest change), elevations in serum globulins, and abnormal bilirubin, albumin, or prothrombin time. Physical findings of a firm liver, or enlarged spleen or prominent spider angionata or palmar erythema, are also danger signals. While none of these findings are completely reliable, their presence should raise the suspicion of significant fibrosis.

X-ray and imaging studies have been developed that may be able to separate different degrees of fibrosis in the liver. At present, these techniques are experimental and of unproven accuracy, particularly in detecting early stages of fibrosis. The most promising technique is "elastrography," in which sound or magnetic waves are passed through the

liver and the speed with which they return is measured, which provides an index of the elasticity and stiffness of the liver. Liver stiffness is used as an indirect measure of liver fibrosis. Most importantly, measuring the relative stiffness of the liver over time may provide a non-invasive way to monitor the development of fibrosis and help guide recommendations for when therapy should be recommended.

Ultrasound elastrography is currently under evaluation for its reliability in measuring the degree of fibrosis in the liver in patients with Hepatitis C. Ultimately, elastrography may be able to replace liver biopsy as a way of monitoring the progression of disease in chronic Hepatitis C.

In some cases applicants may pay for additional imaging studies to support their application.

**Overall clinical opinion**

The clinician completing the application form will be asked to offer an overall clinical opinion on the probability of the applicant having developed cirrhosis. This will be based on all the available diagnostic test results. The application form includes simple indices predictive of cirrhosis.

Borderline cirrhosis cases (stage 3/stage 4 fibrosis) can be deferred if necessary pending further confirmatory testing.

Given the technical nature of the test results data and associated calculations, clinical advice may be sought in the interpretation of borderline cases.

**Alcohol and other factors**

The assessor should not currently seek to distinguish whether the cirrhosis was in fact caused by Hepatitis C or other factors such as alcohol, obesity or inherited liver disease.