UK Position Statement on the use of Organs from Hepatitis C Viraemic Donors and Increased Infectious Risk Donors in Hepatitis C Negative Recipients

Contents

List of Stakeholders

British Viral Hepatitis Group (Lead)

Advisory Committee on the Safety of Blood, Tissues and Organs

British Association for the Study of the Liver

British Liver Transplant Group

British Transplantation Society

Clinical Virology Network

National Health Service Blood and Transplant

National Health Service Scotland

National Health Service Wales

Operational Delivery Networks for HCV in England

Skipton Fund (Special Category Mechanism)

Renal Association

Executive Summary

1. Despite the increase in organ donation in the UK, up to 1 in 6 patients listed for solid organ transplantation will die or become too sick for a transplant. There is, therefore, a need to continuously explore improving the utilisation of organs that are not currently widely used for transplantation.

2. Most organs from donors infected with hepatitis C have hitherto been discarded because of the high likelihood of transmitting the infection to the recipient. Older treatment modalities had poor tolerance and were not sufficiently successful in curing transplant recipients of the infection.

3. Recent advances in the management of hepatitis C infection have meant that more than 95% of infected individuals can now be cured with directly acting antiviral agents. Studies have shown that similar outcomes of hepatitis C clearance can be safely achieved in transplant recipients and small trials have shown excellent outcomes in Hepatitis C negative recipients given hepatitis C infected organs who were subsequently treated and cured of the virus.

4. A recent analysis of the UK Potential Donor Audit has suggested that up to 15 suitable donors are declined every year because of the risk of transmission of hepatitis C. Using organs from such donors could result in up to 75 extra solid organ transplants being performed every year in the UK.

5. Following the recent recommendations by the Advisory Committee on the Safety of Blood, Tissues and Organs that, in some clinical situations, organs from hepatitis C infected donors may be transplanted into uninfected recipients, a group of clinicians, virologists, scientists, health care managers and patient representatives have proposed a UK wide framework for the appropriate use of organs from HCV infected donors.

6. Key elements of the guidelines include selection of appropriate donors, a policy for ensuring the intended recipient gives fully informed consent, guidance for the testing and treatment of recipients as indicated, the formation of a monitoring group to oversee the programme in the

early phases of implementation as well as consideration of some of the headline operational issues that will arise during successful implementation of the pathway.

Introduction

Solid organ transplantation is now well established in routine clinical practice, and transforms lives by reducing morbidity and by preventing deaths. Indeed, it was recently reported that the number of patients alive in the UK following a successful transplant has surpassed 50,000 [1]. National Health Service Blood and Transplant (NHSBT) have made great progress in increasing the number of transplants that happen year on year through their 'Taking Organ Transplantation to 2020' donor strategy [2] . However, a significant number of patients still die due to a shortage of donor organs. In the twelve month period of 2016/17 alone, 457 patients died on UK transplant waiting lists [1]. This confirms the ongoing need to strive to increase the number of organs available for transplantation.

An important strategy is the continuous review of organs that have been discarded, to assess whether advances in medicine could enable such organs to be transplanted. It is now apparent that greater use can be made of organs from hepatitis C (HCV) infected donors. In the past these organs have traditionally been discarded, or only used for transplantation into HCV infected recipients. With the advent and licensing of highly effective and well tolerated direct-acting antiviral (DAA) therapy that can cure more than 95% of patients infected with HCV, regardless of genotype, there is a pressing need to assess whether organs from HCV infected donors may safely be transplanted into HCV uninfected recipients. This strategy could ultimately make more organs available for transplantation, and so reduce the morbidity and mortality of patients on solid organ transplant waiting lists. However it is important to precisely define the serological and virological status of the donor rather than use the term "HCV positive." Further clarity is required, as set out in this position paper.

Introduction to HCV and Clarification of Nomenclature

HCV is a single stranded RNA virus member of the Flaviviridae family. Six genotypes (G1-6) and a large number of sub-genotypes have been characterised in detail [3]. Transmission of HCV generally occurs parenterally (through intravenous drug use (IVDU) or blood products), sexually (predominantly those who have unprotected anal sex with multiple partners) or vertically, from mothers to infants, and can lead to sequelae of acute or chronic hepatitis [4–9]. Acute infection tends to be subclinical, with chronic infection, defined as persistence of HCV RNA in serum for greater than six months after initial

infection. This develops in at least 60% of those infected.

To date, considerable difficulties have arisen due to differences in the nomenclature used in the published literature when reporting the HCV status of both organ donors and organ recipients. This has made the interpretation of published data both difficult and confusing. Figure 1 outlines the changes in the virologic and serologic status of a potential donor following infection with HCV. Serologic tests can detect antibodies to HCV within two to six months of initial infection [10]. However, the most important parameter to be considered when assessing the HCV infectivity of an organ donor or recipient is whether or not active HCV replication is present; i.e. whether they are viraemic, with detectable HCV RNA by sensitive genome amplification methods such as polymerase chain reaction nucleic acid testing or, potentially, antigen testing [11]. It should be pointed out that HCV antibody (anti-HCV) continues to remain positive for a number of years and often indefinitely [12] after spontaneous clearance, or successful treatment of HCV with interferon or DAA therapy resulting in undetectable HCV RNA (SVR; sustained virologic response).

As DAA therapy for HCV becomes more widely available, the prevalence of individuals who are HCV antibody positive but who have undetectable HCV RNA will increase. The identification of these patients as 'HCV positive' donors would be incorrect, as they are no longer ordinarily infectious. However, some individuals could be re-infected if they engage in increased risk behaviours (such as sharing of intravenous drug injecting equipment, unprotected anal sex with multiple partners). Re-infection would be identified by detectable HCV RNA by PCR testing in a person who had documented spontaneous clearance of HCV, or had achieved SVR following antiviral therapy in the past.

The University of Cincinnati has recently reported follow up data of 25 HCV antibody negative recipients who received donor livers from anti HCV antibody positive but HCV RNA negative "HCV high risk" donors. All recipients underwent follow up HCV RNA testing, 4 recipients (16%) developed HCV infection demonstrated by HCV viremia, detectable within three months after transplantation [13]. These data demonstrate a potential risk of HCV transmission from increased infectious risk donors who may be in the window period of reinfection. The presence of occult HCV, i.e residual HCV viral genomes, in donor tissue is also a potential means of HCV transmission. It is, therefore, for the purposes of this document safest to consider all organs from HCV antibody positive donors or organs from those who engage in increased risk behaviours as having the potential to transmit HCV. Hence, careful testing of recipients of these organs is mandatory (see below).

In order to standardise the nomenclature, the term 'HCV viraemic' will be used in this document to refer to donors or recipients who have active HCV infection with detectable HCV RNA, regardless of

HCV antibody status; it also refers to donors that are HCV IgG +ve where the HCV RNA status is not known at the time of organ offering / transplantation. It is important to note however that transmission of infection may still occur from donors during the window period of acute infection as shown in Figure 1.

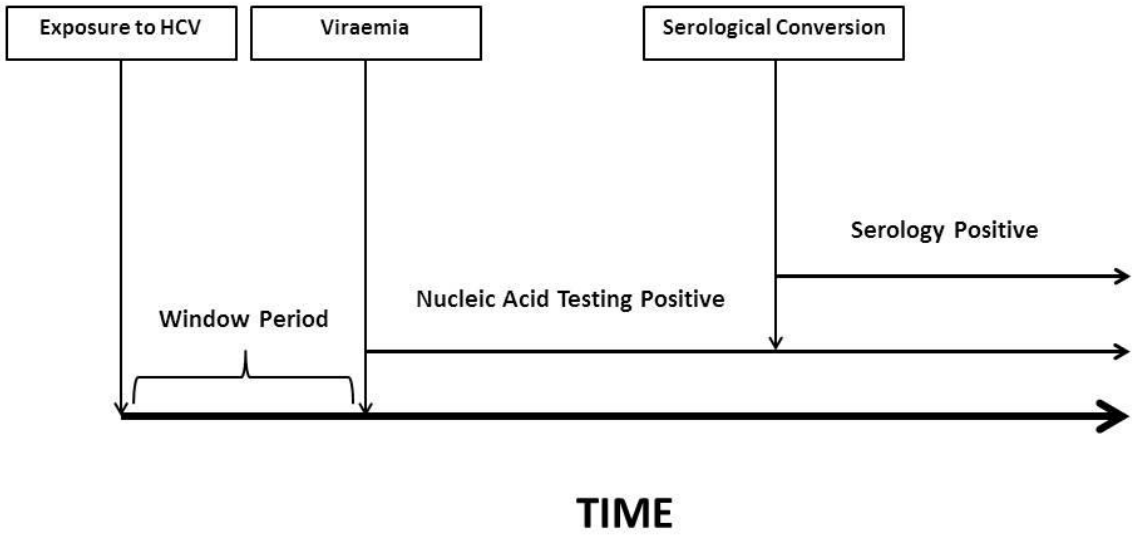

Figure 1. Changes over time in PCR and serology status in an individual exposed to hepatitis C. Serological conversion applies to the development of hepatitis C antibody positivity.

Changes in the treatment of hepatitis C over the past five years

There has been a revolution in the management of HCV in the past six years. This began with the licensing of the first generation protease inhibitors Telaprevir and Boceprevir in 2012. These prototype direct-acting antiviral (DAA) drugs were combined with interferon and ribavirin, and increased cure rates for patients with G1 HCV from 50% to over 80% [14,15]. The pace of drug development has been

rapid, and many agents licensed have now been superseded by better tolerated and more effective regimens. A detailed review of the many DAA regimens is beyond the scope of this paper and has been extensively reviewed elsewhere [16]. Most of the current regimens used in clinical practice are given for between 8 and 16 weeks, and offer cure rates of 95-100% for patients without cirrhosis, regardless of HCV genotype. Most regimens do not rely on the use of ribavirin. There is already substantial UK experience of using two licensed pan-genotypic regimens in the form of Sofosbuvir / Velpatasvir and Glecaprevir/Pibrentasvir. The pan-genotypic triplet of Sofosbuvir, Velpatasvir and Voxilaprevir was licenced in August 2017 [17]. The advantage of Glecaprevir / Pibrentasvir is that it can be given to patients with established renal failure [18]. These regimens also have high efficacy for the treatment of patients who have previously failed other DAA-containing regimens, with the best data currently available for Sofosbuvir, Velpatasvir and Voxilaprevir [19]. The second and third generation DAA regimens have also been shown to be highly effective for patients with cirrhosis, and for patients treated after kidney or liver transplantation [20–24]. Thus the vast majority of patients can be cured post transplant.

This change in the treatment landscape brings into sharp focus the realistic possibility of using HCV RNA viraemic donor (from herein called D+) organs for transplantation for recipients without HCV viraemia (herein called R-), to reduce the morbidity and mortality of those individuals on solid organ transplant waiting lists. Such discussions have already taken place in other developed countries as will be further outlined, and small clinical trials have already reported on the efficacy of this approach [25,26] . This paper seeks to establish a professional consensus to enable the use of HCV viraemic donor organs for HCV negative recipients in the United Kingdom.

Current discard rates for hepatitis C positive donor organs in the UK

Current practice in the UK is to restrict the use of HCV D+ organs to HCV positive recipients (R+), although this is predominantly accepted in the field of liver transplantation. Anecdotal evidence points, however, to very poor utilisation of HCV D+ non-liver organs even for HCV R+ recipients. With declining numbers of HCV R+ patients on transplant waiting lists due to the efficacy of DAA therapy, organ discard rates will increase unless current clinical practice changes. The most up to date UK data available was published in 2017 by Trotter and colleagues. Using data from the UK Transplant Registry

and the National Potential Donor Audit from 2000 to 2015, they identified 244 HCV antibody positive donors during that 16 year time period [27]. Organs from only 76 (31%) of these donors were transplanted into 93 recipients (63 liver, 27 kidney and 2 heart transplants). The quality of the declined organs did not differ from that of the organs that were used, with positive serological tests reported as the reason for decline in 69% of cases. The declined donors often had good kidney and liver function, and, based on validated UK Donor Risk Indices, if they had been used, 77% of kidneys and 80% of livers from the potential donors would be predicted to be functioning 5 years later. Furthermore, even at the list price of DAAs (the actual prices that the NHS pays are lower) the additional costs of transplanting recipients exposed to HCV with a kidney from a HCV antibody positive donor was cost-neutral in comparison with remaining on dialysis within 5 years following transplantation. In reality, it is likely that this cost effectiveness will manifest earlier. Notably, data were not provided as to whether the donors had detectable HCV RNA by PCR testing, as only a minority had HCV RNA status reported.

The UK Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) is responsible for making recommendations to the four UK governments regarding the use of organs for transplant. It has anticipated the potential change in the landscape as discussed in this position statement, and recently issued revised guidance [28]. The most relevant statement in the guidance reads as follows -

'HCV infection in the potential donor does not amount to an absolute contraindication to donation of material for life-preserving transplantation, however the net benefit of transplantation must be considered against the risk of not receiving that specific transplant. This risk/benefit analysis allows for the potential use of a transplant from a HCV infected donor to a non-infected recipient.'

This change in the guidance paves the way for potential D+ to R- transplants.

Experience from outside the UK

The United States has the best data on D+ donor numbers as well as on discard rates, and is leading the way in early clinical trials of D+ to R- transplants. 4.1% (6,567/159,552) of all organ donors in the US between 1995 and 2015 were reported to be HCV antibody positive [25]. Utilisation of HCV antibody positive livers has increased with time but these have been transplanted exclusively into HCV R+ patients. Discard rates for HCV D+ livers have reduced in the US from 25% in 2006 to 10% in 2015

and now roughly mirror the discard rates of HCV D- livers. However, discard rates for other organs are significantly higher despite the fact that they often come from younger donors. Indeed more than 500 HCV positive kidneys are discarded annually in the US [29,30]. Due to the current epidemic of opiate abuse in the US, the median age of HCV D+ in the US has declined from 47 in 2012 to just 35 in 2016 [25]. Notwithstanding this inherent societal tragedy, it is likely that good quality organs are currently discarded in the USA simply because a sizeable percentage of them are from HCV D+ individuals.

As a consequence of this, and given the long waiting times for some individuals particularly on the kidney transplant waiting list, a conference of the American Transplantation Society was held in January 2017 to explore this area [25]. The consensus was in favour of considering D+ to R- transplantation across all solid organs within set criteria, and recommended that such practice should take place within prospective research protocols. The importance of insurance companies guaranteeing funding for DAA therapy for patients knowingly infected with HCV at the time of transplantation was noted at the meeting.

Part of the rationale for this strong recommendation has been emerging clinical trial data from the renal field in particular, in small numbers of patients but with excellent results. Goldberg et al published the first of these in the *New England Journal of Medicine* [26]. In a single centre trial at the University of Pennsylvania involving 10 kidney transplant recipients, all were given HCV D+ kidneys from individuals infected with genotype 1 HCV. All recipients became viraemic by day 3 and all received 12 weeks of treatment with Grazoprevir/Elbasvir as soon as the positive result was obtained. These drugs can be used safely in patients with kidney failure and is one of the currently available treatments for G1 HCV in the UK. All the recipients were cured, as defined by a sustained virologic response (SVR; undetectable HCV RNA) 12 weeks after cessation of therapy. The median wait time for a HCV D+ kidney was reduced to 58 days, and the median eGFR at the end of the study amongst the 10 recipients was 68 ml/min (51-83); an excellent outcome by any measure. The only SAEs noted were as follows: 1 delayed graft function, 2 elevated ALT that resolved with therapy, 1 transient class 1 donor specific antibodies, and 1 patient had proteinuria and focal segmental glomerulosclerosis on renal biopsy. All recipients were assessed by a Hepatologist prior to recruitment; patients with any significant chronic liver disease were excluded. Informed consent was obtained.

A second clinical trial was reported at the American Transplant Congress in 2017 [31]. Dr Niraj Desai has kindly provided data from this, the EXPANDER-1 trial (Exploring Renal Transplants Using Hepatitis-C Infected Donors for HCV-Negative Recipients). Ten patients who underwent kidney transplantation with a HCV D+ organ were included. The difference in this trial was that the donors were known to be HCV RNA positive as determined by PCR testing prior to donation, but the genotype was not known.

For logistical reasons, this is likely to be the case in the UK if the practice is adopted here. Grazoprevir/Elbasvir was started immediately before transplantation, and continued for 12 weeks. If the donor had genotype 2 or genotype 3 HCV, Sofosbuvir was added. If HCV resistance associated substitutions (RAS) were identified in donors with G1a HCV, ribavirin was added and treatment was extended to 16 weeks. The DAA combinations used in this trial reflected the DAA regimens available at the time of the study. Preliminary results from the trial are shown in Table 1 below. At the time of reporting, the 8 patients who had reached the SVR12 time point were all cured. All 10 patients completed their treatment and there were no adverse events related to the treatment in the trial.

These clinical trials are very encouraging, and there are also data emerging on the efficacy and safety of DAA therapy in patients who have undergone organ transplantation and have established HCV. Fernandez et al recently reported on the real world efficacy of different DAA regimens in 103 patients who had undergone kidney transplantation [32]. 75% of these patients were on tacrolimus-based immunosuppression. Although 55% of the patients required dose-adjustment of their immunosuppression, SVR12 rates were 98%. There were three episodes of acute cellular rejection but overall there were no changes in creatinine, eGFR or proteinuria pre- and post- treatment.

Results in a larger cohort of patients were reported by Saxena et al from the HCV-TARGET consortium of Academic US centres [33]. In this paper 443 patients were treated after organ transplantation. There were 347 liver transplant recipients, 60 kidney transplant recipients and 36 dual transplant recipients included in the study. The majority were treated with Sofosbuvir and Ledipasvir (an earlier generation combination), with or without ribavirin. Overall SVR12 rates were 96.3% in liver recipients, 94.6% in kidney recipients and 90.9% in kidney/liver recipients. There were 6 episodes of rejection in total; 4 in the liver recipients and 2 in kidney recipients. It should be noted that 42% of the recipients had liver cirrhosis and 54% had previously failed HCV treatment. These patients would be classified as difficult to treat in a pre-transplant setting and in that context the SVR12 results are in fact quite impressive. If HCV D+ to HCV R- transplants were to proceed, the recipients being treated with DAAs would by definition be treatment naïve and likely (in the absence of other causes of liver disease) non-cirrhotic, and have a high likelihood of achieving SVR12.

DONORS	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Age, yrs	21	26	38	30	42	35	30	23	23	30
Sex	Female	Female	Female	Male	Male	Male	Female	Male	Male	Female
Race	White	White	White	White	White	White	White	White	White	White
Death	Trauma	Overdose	Trauma	Anoxia	Trauma	Overdose	Overdose	Overdose	Overdose	Overdose
KDPI	45	43	60	47	62	41	50	34	45	41
HCV Ab	+	+	+	+	+	+	+	+	+	+
HCV RNA	467	104	<15*	46,733	62,400	4,645,289	2,090,042	1,760,000	131	1,140,000
HCV GT	ND	ND	ND	1a/3a	1a	1a	3a	2	ND	1a
HCV R-	**R1**	**R2**	**R3**	**R4**	**R5**	**R6**	**R7**	**R8**	**R9**	**R10**
Age, yrs	71	71	65	57	72	71	74	61	76	66
Race	White	White	White	White	White	Asian	White	Black	White	White
Sex	Male	Female	Male	Male	Male	Male	Female	Male	Male	Male
Wait time	36	4.1	12.2	4.4	0.8	2.3	34.6	0.9	0.8	18.3
From entry	0.5	0.7	1.0	1.0	0.4	1.4	4.0	2.0	0.9	2.7
HCV RNA on treatment (TW)										
POD 1	<15	<15	<15	<15++	<15	94	<15++	136	<15	32
TW1	<15	<15	<15	<15	<15	<15	<15	55	<15	<15
TW4	<15	<15	<15	<15	<15	<15	missed	<15	<15	<15
TW8	<15	<15	<15	<15	<15	<15	<15	<15	<15	<15
TW12	<15	<15	<15	<15	<15	<15	<15	<15	<15	<15
HCV RNA Follow up off treatment (FW)										
FW2	<15	<15	<15	<15	<15	<15	<15	<15	<15	<15
FW4	<15	<15	<15	< 15	<15	<15	<15	<15	<15	
FW8	<15	<15	<15	<15	<15	<15	<15	<15	<15	
FW12	<15	<15	<15	<15	<15	<15	<15	<15		

N. *Am J Transplant*. 2017;17 (suppl 3). American Transplant Congress 2017. Abstract no 2.

Table 1. Preliminary Results of the EXPANDER-1 trial. Courtesy of Dr Niraj Desai.

Why HCV D+ to R- transplantation should be cost effective

Whilst there are clear morbidity and mortality benefits to increasing organ availability for patients on solid organ transplant waiting lists, there are also sound economic arguments. This is perhaps strongest in the field of kidney transplantation. Dialysis is expensive. This cost would be mitigated by timely transplantation, particularly in individuals who are highly sensitised or otherwise difficult to transplant and who may spend many years on dialysis. More importantly, despite the fact that patients can survive on dialysis for many years, their quality of life is significantly reduced.

Although the exact cost of DAAs to the NHS remains commercially confidential, all stakeholders are reassured that a course of therapy to cure a R- patient receiving a D+ organ would be less than the cost of dialysis for one year. Implementation of the proposal contained within this position statement is likely to lead to substantial cost savings by reducing waiting times and dialysis expenditure. More importantly this should save lives and improve quality of life for patients.

What are the risks of HCV D+ to R- transplantation?

While there are clear economic and health related benefits to HCV D+ to R- transplantation, it is important to consider the potential risks and how these could be mitigated.

The first and perhaps most feared risk is of fibrosing cholestatic hepatitis (FCH) [34,35]. This is an aggressive form of HCV recurrence seen in 10% of D+/R+ liver transplants. Prior to the advent of DAA therapy FCH was associated with a high mortality. It is also reported in kidney transplantation, with an incidence of 1.5% in the largest series from Spain [36]. However, there are now increasing reports of DAA therapy being very effective in the setting of FCH. In the SOLAR-1 and 2 studies the combination of Sofosbuvir and Ledipasvir for 12 or 24 weeks cured all 11 patients treated after liver transplantation with FCH [22,37]. Leroy et al reported similarly impressive cure rates of 100% in 15 patients with FCH treated after liver transplantation using the combination of Sofosbuvir and Daclatasvir [38]. There are many case reports and small case series that have also reported very successful management of FCH with normalisation of LFTs. A particularly intriguing case was reported by Liu et al from Taiwan. In their case a HCV R- patient received a genotype 1b HCV D+ heart [39]. The patient became viraemic by 1 week post transplantation, and developed FCH by 6 weeks post transplantation. He was successfully cured with 12 weeks of Sofosbuvir and Ledipasvir. This and other studies would suggest that early treatment (ideally within 4 weeks) with DAA therapy should prevent the development of FCH. Even if this did develop in an individual patient, modern DAA therapy provides an excellent chance of cure.

The concept of knowingly infecting a patient with an infectious agent poses important ethical issues. However, the high morbidity and mortality rates for patients on the waiting list justify the utilisation of D+ organs. Indeed, infecting individuals with cytomegalovirus (CMV) or Epstein Barr virus (EBV) at the time of organ transplantation is a well-established practice despite the fact that EBV and CMV disease in the transplant recipient can cause both morbidity and mortality [40]. Furthermore, the recipient becomes permanently infected with these viruses as there is no current cure. The risk is mitigated by giving prophylactic treatment in the case of CMV. By contrast, HCV D+/R- transplantation followed by early DAA therapy would result in only a transient, usually rapidly curable infection.

Another theoretical concern is that a minority (in reality <5%) of patients treated after organ transplantation may experience DAA treatment failure, which may be associated with the development of difficult to treat resistance associated substitutions (RAS) especially in the viral NS5A protein, but also, for recipients of a protease inhibitor, in the NS3A region [41]. In the early days of a HCV D+/R- programme, treatment duration could be extended slightly (from 8 weeks to 12 weeks or

from 12 weeks to 16 weeks) to mitigate this risk until more real world data emerges. However, data from the POLARIS-1 trial has shown that 12 weeks of re-treatment with the triple therapy combination of Sofosbuvir, Velpatasvir and Voxilaprevir is highly effective (>95%) in achieving cure of HCV in patients with HCV NS5A RAS at baseline [19]. Thus virtually all HCV D+/R- recipients can be cured with modern DAA therapies, even if this is not achieved at the first attempt at treatment.

Extra-hepatic manifestations of HCV such as cryoglobulinaemic vasculitis or potential increased rates of blood derived malignancy such as PTLD are also theoretical consequences of HCV infection in the post-transplantation phase. However, there are no data in the HCV D+/R+ field to demonstrate an increased risk of these consequences, and early DAA therapy should mitigate against these in any case.

Sexual transmission of HCV to a partner could potentially occur in the HCV D+/R- transplant scenario. The risk can be mitigated by simple lifestyle advice, as well as through the proposed early inception of DAA therapy post transplantation. It is likely this risk will be extremely low (<2% perhaps).

Skipton Fund ex gratia payments were previously granted to individuals infected through NHS treatment. The current Special Category Mechanism (SCM) would require clarification before HCV D+/R- transplants could proceed in the UK. However, it is proposed that SCM payments would not be given to recipients who provide informed consent to receipt of a D+ organ, and have thus accepted the risk versus the benefits. Nevertheless, the current sensitivities given the public enquiry into HCV contaminated blood must be acknowledged.

The Practicalities of Implementing this Policy in the United Kingdom

When the working party met on the 2nd of November 2017 to discuss the initial draft of this position statement there was a clear steer that detailed operationalisation of the policy was beyond the scope of this document and the group as a whole. It was felt however that it would be useful for the group to provide a framework for some of the important practical issues that every transplant unit wishing to adopt this policy should consider prior to proceeding with a HCV D+/R- transplant. In addition the group felt strongly that there should be an oversight committee for the first 20-30 transplants, and this will be discussed further.

Patient Consent

Although patients are currently routinely consented to receive so-called 'marginal' organs including for example CMV-positive organs, it was felt that consent to receive a HCV D+ organ should be specifically obtained by individual transplanting centres. To aid this process, the working group has developed a patient information sheet (see Appendix 1). In addition, the group noted that the British Transplantation Society together with NHS Blood and Transplant is currently reviewing the entire pathway of sharing information with and gaining consent from solid organ transplant candidates, and inclusion of consent for HCV D+/R- transplantation will need to form part of this work.

Patient and Unit Requirements Pre-Transplant

The practice of HCV D+/R- transplantation is relatively new and there are a few theoretical concerns that arise when the breadth of clinical scenarios that transplantation encompasses is considered. In order to err on the side of safety, the working party agreed that HCV D+/R- non-liver transplantation should be avoided in recipients with advanced fibrosis or cirrhosis. Rather than mandate that every patient being consented to receive a HCV D+ non-liver organ be seen by a liver specialist, a more pragmatic approach of screening patients using AST-to-Platelet Ratio Index (APRI) and ultrasound is suggested. APRI scores are easily calculated using on line tools such as https://www.mdcalc.com/ast-platelet-ratio-index-apri. If the APRI score is >0.8 or the ultrasound suggests significant or advanced liver disease, then an opinion from a suitably qualified liver specialist should be sought before the patient is considered for a HCV D+ organ. It was felt that even cirrhotic patients could potentially receive HCV D+ organs safely but that this was not an appropriate risk for the early phases of a new UK HCV D+/R- programme. If the APRI score is <0.8, there is no need for the patient to be seen by a liver specialist.

It was also agreed that a checklist of pre-requisites that must be in place before an individual transplanting centre performs its first HCV D+/R- transplant would be valuable (see Appendix 2).

Whilst not an exhaustive list of requirements, individual units should ensure that these requirements are met in order to minimise the theoretical risk to any individual recipient.

Allocation of HCV D+ Organs on the Waiting List

The working group considered this matter and felt that, once sufficient expertise has accrued, and assuming that outcomes are favourable, HCV D+ organs should be treated in the same way as HCV D- organs within the current allocation rules of the national waiting lists as determined by the individual NHSBT bodies; e.g. Liver Advisory Group, Kidney Advisory Group and Cardiothoracic Advisory Group. During the introductory phase of any HCV D+ to HCV R- programme, Advisory Groups will need to decide how best to offer and allocate such organs in order to optimise organ utilisation. Frequent review of post-transplant outcomes will be needed in order to enable Advisory Groups to alter offering and allocation policies as needed.

Management of the Recipient of a HCV D+ Organ

There was consensus amongst all members of the working party that while donor testing was desirable and should be mandated as outlined below, it was crucial to implement standardized, longitudinal testing for hepatitis C RNA of the recipient following receipt of either a HCV antibody positive graft, a HCV RNA positive graft or a graft from an increased infectious risk donor, to ensure appropriate and early intervention if HCV transmission and infection occurs. A proposed flow sheet for management of the recipients is shown below. Individual units may wish to flesh this out to allow operational details to be adapted to local standard operating procedures. Individual units may also wish to consult with their virology laboratories to enhance testing for HIV and HBV.

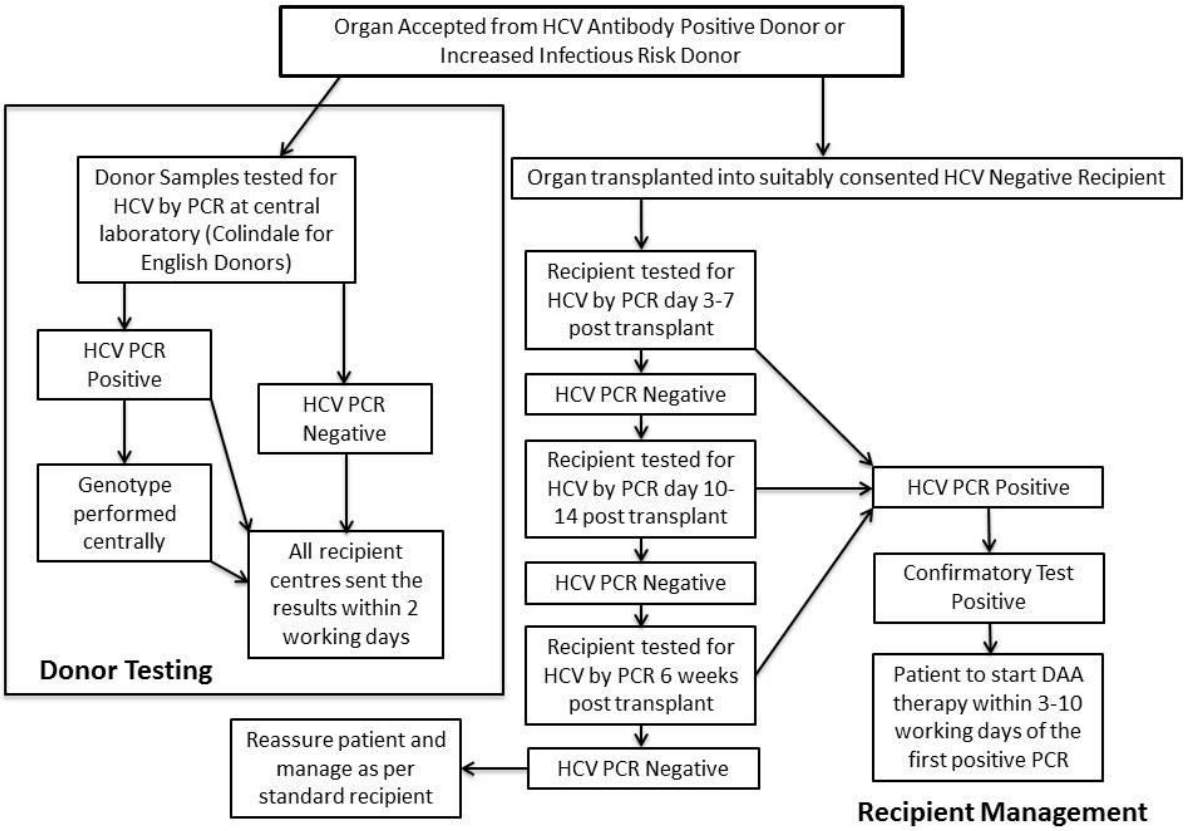

Figure 2. Proposal for Testing of Donors and Management of All Recipients in the UK HCV D+/R- scheme

The exact drug regimens and length of therapy that should be offered to recipients that test positive for HCV after receiving an organ from a HCV D+ donor were discussed. Two alternative regimens should be used as first line agents. These are either the combination of Glecaprevir/Pibrenatasvir or the combination of Sofosbuvir/Velpatasvir. Both should be given for 12 weeks in the context of HCV D+/R- transplants. Both are pan-genotypic, which means that they can be started as soon as HCV PCR positivity is known, without having to wait for a HCV genotype, which can take 3-4 weeks in some areas. Both have very acceptable drug to drug interaction profiles although exposure to the former is increased by ciclosporin, and it may also increase the levels of tacrolimus (CYP3A and P-glycoprotein inhibition); the latter is not recommended in patient with a eGFR <30 mL/min/1.73 m^2 (please refer to the drug SPCs for details). Treatment should be given in liaison with a clinical team with experience of management of HCV but does not necessarily have to be delivered in the transplanting centre. In the rare (expected to be less than 2%) instances where the first course of treatment of HCV is not curative, recipients should be treated with a 12 week course of the combination of

Sofosbuvir/Velpatasvir/Voxaleprevir which, as previously discussed, has high rates of SVR even in those previously exposed to DAA therapy.

Special Additional Considerations

Given the theoretical concerns about the transmission of resistant HCV, the use of organs from donors known to have been treated for HCV with DAA within the last 6 months should be avoided unless there is clear documentary proof at the time of donation of an SVR12 result. Potentially donors engaging in increased infectious risk behaviour are at risk of re-infection post SVR and thus could still transmit HCV. The same donor and recipient testing outlined above should be followed if organs from such individuals are used. The table below indicates which donors should and should not be used for transplantation within the proposed policy.

Acceptable Within Proposed Policy	**Not Recommended Within Proposed Policy**
HCV Ab positive with no history of treatment of HCV	Previously failed DAA therapy with on-going viraemia
HCV Ab positive with documented SVR after treatment	DAA therapy within last year without documented SVR (unless the recipient is at imminent risk of death)
Any HCV Ab negative donor who has exposed themselves to risk but who does not fulfill any of the unacceptable criteria	Multiple documented re-infection with HCV
Any HCV Ab positive donor whose HCV treatment history is unknown – **proceed with caution**	

Until more data is available, any organ from a donor who has been treated for HCV with DAAs but has not achieved SVR12 for any reason should not be considered for transplantation into a negative recipient unless the benefits outweigh the risks (e.g. in a clinically urgent transplant candidate). In such cases early liaison with an experienced hepatitis C clinician with experience of transplantation is mandatory. Resistance testing of the virus at baseline prior to commencing treatment may be required and in such cases the timelines above may be relaxed. The choice of drug regimen in this scenario may have to be tailored in light of this information.

Oversight of the Programme in its Early Days

In order to provide the necessary oversight and to ensure that any clinical experience gained is shared as widely as possible and disseminated through established UK transplant clinical networks, the Working Party felt that an Oversight Committee should be established following endorsement of this position statement. This committee would oversee the implementation of the programme and receive clinical information on the recipients of HCV D+/R- transplantation. It was felt that this should be led and run by BVHG with strong representation from NHSBT and BRITISH TRANSPLANTATION SOCIETY as well as the other main stakeholders involved in this document. The term of the oversight committee should initially be 1 year with further extensions to its remit being subject to the numbers of transplants that have been carried out as well as emerging data from elsewhere. The Working Party has produced a document detailing the minimal dataset that should be collected on the recipients of HCV D+ organs in order to aid the work of the Steering Committee. This dataset is available on request from the lead authors of this statement.

Next Steps in the Process

This document has been out for wider public consultation and was sent to all the organisations listed in appendix 3. Comments were collated and subsequent iterations of this document were modified in light of these. The final paper has been through 7 versions prior to being agreed by members of the working party listed in appendix 4.

It is important to state that transplant units should not seek to implement the proposals contained in this position statement until they are satisfied that there is clear provision for DAA therapy in their local areas that can be accessed according to the timelines outlined in figure 2 above and until they have satisfied all the pre-conditions listed in appendix 2. This document will be launched at the British Transplantation Society Annual Meeting in Brighton in March 2018. Following further negotiations with the commissioners of the UK Health Services, it is envisaged that the 'go-live' date for the programme will be in September 2018. Further operational details will be disseminated by NHSBT using its standard communication channels.

References

1. NHS Blood and Transplant. Organ Donation and Transplantation Activity Report 2016/17. 2017.

2. NHS Blood and Transplant. Taking Organ Transplantation to 2020. A UK Strategy. 2013.

3. Simmonds P, Alberti A, Alter HJ, et al. A proposed system for the nomenclature of hepatitis C viral genotypes. Hepatology. 1994;19(5):1321–4.

4. Nelson PK, Mathers BM, Cowie B, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet. 2011;378(9791):571–83.

5. Alter HJ, Purcell RH, Shih JW, et al. Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis. N Engl J Med. 1989;321(22):1494–500.

6. Tohme RA, Holmberg SD. Is sexual contact a major mode of hepatitis C virus transmission? Hepatology. 2010;52(4):1497–505.

7. Witt MD, Seaberg EC, Darilay A, et al. Incident hepatitis C virus infection in men who have sex with men: A prospective cohort analysis, 1984-2011. Clin Infect Dis. 2013;57(1):77–84.

8. Ohto H, Terazawa S, Sasaki N, et al. Transmission of hepatitis C virus from mothers to infants. The Vertical Transmission of Hepatitis C Virus Collaborative Study Group. N Engl J Med.

1994;330(11):744–50.

9. Zanetti AR, Tanzi E, Paccagnini S, et al. Mother-to-infant transmission of hepatitis C virus. Lombardy Study Group on Vertical HCV Transmission. Lancet. 1995;345(8945):289–91.

10. Kamili S, Drobeniuc J, Araujo AC, et al. Laboratory Diagnostics for Hepatitis C Virus Infection. Clin Infect Dis. 2012;55(Suppl 1):S43–8.

11. Albertoni G, Castelo Girao MJ, Schor N. Mini review: current molecular methods for the detection and quantification of hepatitis B virus, hepatitis C virus, and human immunodeficiency virus type 1. Int J Infect Dis. 2014;25:145–9.

12. Seeff LB. Natural history of chronic hepatitis C. Hepatology. 2002;36(5 Suppl 1):S35-46.

13. Bari K, Luckett K, Kaiser T, et al. Hepatitis C Transmission from Seropositive, Non-Viremic Donors to Non- Hepatitis C Liver Transplant Recipients. Hepatology. 2017;Dec 2(doi: 10.1002/hep.29704.):[Epub ahead of print].

14. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011;364(25):2405–16.

15. Poordad F, McCone J, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011;364(13):1195–206.

16. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017;66(1):153–94.

17. Jacobson IM, Lawitz E, Gane EJ, et al. Efficacy of 8 Weeks of Sofosbuvir, Velpatasvir, and Voxilaprevir in Patients With Chronic HCV Infection: 2 Phase 3 Randomized Trials. Gastroenterology. 2017;153(1):113–22.

18. Gane EJ, Lawitz E, Pugatch D, et al. EXPEDITION-4: efficacy and safety of glecaprevir/pibrentasvir (ABT-493/ABT-530) in patients with renal impairment and chronic hepatitis C virus genotype 1–6 infection [Abstract #LB-11]. Hepatology. 2016;64(6):1125A.

19. Bourlière M, Gordon SC, Flamm SL, et al. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. N Engl J Med. 2017;376(22):2134–46.

20. Colombo M, Aghemo A, Liu H, et al. Treatment With Ledipasvir–Sofosbuvir for 12 or 24 Weeks in Kidney Transplant Recipients With Chronic Hepatitis C Virus Genotype 1 or 4 Infection: A Randomized Trial. Ann Intern Med. 2017;166(2):109–17.

21. Kwo PY, Mantry PS, Coakley E, et al. An Interferon-free Antiviral Regimen for HCV after Liver Transplantation. N Engl J Med. 2014;371(25):2375–82.

22. Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients with Advanced Liver Disease. Gastroenterology. 2015;149(3):649–59.

23. Poordad F, Schiff ER, Vierling JM, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. Hepatology. 2016;63(5):1493–505.

24. Reau N, Kwo PY, S R. MAGELLAN-2: Safety and Efficacy of Glecaprevir/Pibrentasvir in Liver or Renal Transplant Adults with Chronic Hepatitis C Genotype 1-6 Infection. In: EASL International Liver Meeting. 2017.

25. Levitsky J, Formica R, Bloom R, et al. The American Society of Transplantation Consensus Conference on the Use of Hepatitis C Viremic Donors in Solid Organ Transplantation. Am J Transpl. 2017;May 29:doi: 10.1111/ajt.14381. [Epub ahead of print].

26. Goldberg DS, Abt PL, Blumberg EA, et al. Trial of Transplantation of HCV-Infected Kidneys into Uninfected Recipients. N Engl J Med. 2017;376(24):2394–5.

27. Trotter PB, Summers DM, Ushiro-Lumb I, et al. Use of organs from hepatitis C virus positive donors for uninfected recipients: a potential cost-effective approach to save lives? Transplantation. 2017;Nov 22(doi: 10.1097/TP.0000000000002033.):[Epub ahead of print].

28. SaBTO: Advisory Committee on the Safety of Blood Tissue and Organs. Guidance on the microbiological safety of human organs, tissues and cells used in transplantation. 2016.

29. Goldberg DS, Blumberg E, McCauley M, et al. Improving organ utilization to help overcome the tragedies of the opioid epidemic. Am J Transplant. 2016;16(10):2836–41.

30. Reese PP, Abt PL, Blumberg EA, et al. Transplanting Hepatitis C-Positive Kidneys. N Engl J Med. 2015;373(4):303–5.

31. Durand C, Brown D, Wesson R, et al. EXPANDER-1: Exploring Renal Transplants Using Hepatitis-C Infected Donors for HCV-Negative Recipients. American Transplant Congress. 2017.

32. Fernández I, Muñoz-gómez R, Pascasio JM, et al. Efficacy and tolerability of interferon-free

antiviral therapy in kidney transplant recipients with chronic hepatitis C. J Hepatol. 2017;66(4):718–23.

33. Saxena V, Khungar V, Verna EC, et al. Safety and efficacy of current direct-acting antiviral regimens in kidney and liver transplant recipients with hepatitis C: Results from the HCV-TARGET study. Hepatology. 2017;66(4):1090–101.

34. Dickson RC, Caldwell SH, Ishitani MB, et al. Clinical and histologic patterns of early graft failure due to recurrent hepatitis C in four patients after liver transplantation. Transplantation. 1996;61(5):701–5.

35. Yilmaz N, Shiffman ML, Stravitz RT, et al. A prospective evaluation of fibrosis progression in patients with recurrent hepatitis C virus following liver transplantation. Liver Transplant. 2007;13(7):975–83.

36. Muñoz De Bustillo E, Ibarrola C, Colina F, et al. Fibrosing cholestatic hepatitis in hepatitis C virus-infected renal transplant recipients. J Am Soc Nephrol. 1998;9(6):1109–13.

37. Manns M, Samuel D, Gane EJ, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. Lancet Infect Dis. 2016;16(6):685–97.

38. Leroy V, Dumortier J, Coilly A, et al. Efficacy of Sofosbuvir and Daclatasvir in Patients With Fibrosing Cholestatic Hepatitis C After Liver Transplantation. Clin Gastroenterol Hepatol. 2015;13(11):1993–2001.e1.

39. Liu CH, Chen YS, Wang SS, et al. Treatment of de novo hepatitis C virus-related fibrosing cholestatic hepatitis after orthotopic heart transplantation by ledipasvir and sofosbuvir. J Formos Med Assoc. 2017;116(5):407–9.

40. Razonable RR, Humar A. Cytomegalovirus in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):93–106.

41. Pawlotsky JM. Hepatitis C Virus Resistance to Direct-Acting Antiviral Drugs in Interferon-Free Regimens. Gastroenterology. 2016;151(1):70–86.

Appendix 1 - Patient Information Leaflet for the Use of Hepatitis C Infected Organs in Hepatitis C Negative Recipients

Introduction

You are being asked to consider whether or not you would accept a (insert organ here) from a hepatitis C virus infected donor. This leaflet will explain why this option is being considered for you, and will explain the potential benefits and the potential risks that this may involve. It is important to emphasise that it is your choice whether or not you agree to accept a (insert organ here) from a hepatitis C virus infected donor.

What is hepatitis C?

Hepatitis C is a virus that is transmitted in infected blood and body fluids. It lives in the liver and blood of infected individuals and can cause inflammation and scarring of the liver. The scarring can be severe, although on average it takes 30 years for the scarring to become life-threatening in non-transplant patients. Severe scarring may develop more rapidly in transplant patients taking drugs that suppress the immune system.

Treatments for hepatitis C have changed greatly over recent years. It is now possible to cure over 95% of patients who are infected with the hepatitis C virus. Treatment requires taking tablets for 12 weeks. Once the virus is cleared it does not come back and does not affect your long term health.

Why am I being offered a hepatitis C infected (insert organ here)?

There are not enough donated organs in the UK to transplant into all people who may need them. Sadly this means that many people die on the waiting list. This is especially true for those people who are difficult to transplant because they have a rare blood group or tissue type, or if they have a lot of antibodies in their blood against other people's tissue types. These people often wait a long time for a transplant and are more likely to die on the waiting list.

Doctors are therefore trying to find ways to increase the number of organs that can safely be transplanted. Due to recent breakthroughs in hepatitis C virus treatment it is now possible to consider using organs from donors infected with hepatitis C virus for transplantation. These donors are generally younger than average and may be healthier, with lower blood pressure and less heart disease and other medical conditions. Hence their donated organs may be of higher quality than average.

What are the advantages to me of receiving a hepatitis C infected (insert organ here)?

If you agree to accept a (insert organ here) from a hepatitis C virus infected donor, you may receive a transplant more quickly. This may be very helpful if you would otherwise wait a very long time for a transplant. Also, because organ donors who are infected with hepatitis C virus are younger than average, and less likely to have other important health issues, their organs may be of higher quality and therefore more likely to work immediately and may last longer.

What are the risks to me if I receive a hepatitis C infected (insert organ here)?

The main risk of accepting a (insert organ here) from a hepatitis C virus infected donor is that you will become infected with the virus yourself. If hepatitis C virus infection is not treated you may become jaundiced (yellow) and may develop severe inflammation in the liver (fulminant cholestatic hepatitis). In the longer term (3-6 months) hepatitis C may result in kidney injury. However, you will be offered treatment to cure you of the hepatitis C virus as soon as is has been confirmed that you have been infected. This will minimise the risk of any damage to you.

Another important risk to consider is the very small chance that the hepatitis C virus may not disappear after the 12 weeks of treatment (see below). The chances of this happening are less than 2 in 100 (2%). If this were to happen, you would be offered a different course of tablets that has been shown to be highly effective in curing patients whose treatment has failed with other drugs. These drugs achieve 96 to 98% cure rates. This means that it is very unlikely (1 chance in 2,500) that the transplant team will not be able to cure you of the virus if you are infected.

Whilst all donors are routinely screened for the presence of other infections like HIV or hepatitis B in addition to hepatitis C, the screening tests can very rarely miss infections and there remains a very small possibility that these or other infections could also be transmitted at the time of transplantation.

What is the experience of patients who have been infected with hepatitis C at the time of an organ transplant?

There have already been several studies looking at the results of transplanting kidneys from hepatitis C virus infected donors into patients who are not infected with hepatitis C virus. These have mainly taken place in the United States and have required that patients receive treatment for hepatitis C very early (within 4 weeks) after transplantation. These studies show that it is possible to cure every patient of hepatitis C virus after kidney transplantation (100% cure rate). Importantly, the kidneys then went on to work very well, and the overall outcomes were the same for the patients who received kidneys from hepatitis C virus infected donors as those for patients who received kidneys from hepatitis C virus negative donors.

How do I know that the hepatitis C infected (insert organ here) has not been damaged by the virus?

Hepatitis C can cause liver damage, and, in rare cases, kidney damage too. In the UK, livers from hepatitis C virus infected donors have been used safely for more than 10 years to transplant into patients who already have liver damage caused by hepatitis C virus infection. Only livers with very little or no damage from hepatitis C virus infection are used for transplantation, and the same

precautions will apply to hepatitis C virus infected livers that are transplanted into patients that are not infected with the hepatitis C virus.

The health of kidneys that are offered for transplantation is carefully assessed by a series of blood and urine tests that are carried out on the donor before and after they die. Only kidneys with very little or no pre-existing damage are used for transplantation. The same precautions will apply to kidneys from hepatitis C virus infected donors.

Hepatitis C virus does not damage the heart, lungs or pancreas, so these organs should work just as well from a hepatitis C infected donor as from a hepatitis C negative donor.

What are the risks to my family if I receive a hepatitis C Infected (insert organ here)?

The risks to your family are very small. Transmission of the virus is mainly through infected blood and body fluids. Until you are cured of hepatitis C virus, which should happen within the first 3 to 4 months after the transplant, we recommend that you do not share your toothbrush and razor blades with anyone. The virus is not transmitted through kissing and saliva. The virus can be transmitted through sexual intercourse, although it is rare, so we recommend that you or your partner uses barrier contraception (condoms) until you are told that you have been cured of the virus.

How will I be treated if I receive a hepatitis C infected (insert organ here)?

After your transplant you will have a specific and very sensitive blood test to look for the presence of hepatitis C virus in your blood. The first blood sample will be taken within the first 7 days of your transplant, then again within the first 14 days and the last sample will be taken within the first 6 weeks of your transplant. If the virus tests remain negative by that time then your transplant organ has not passed on the infection to you. If any of these tests are positive for hepatitis C virus then the doctors looking after you will start you on highly effective treatment within 3-10 days of the result. This means that you will be prescribed some specific antiviral tablets that you will need to take for a total of 3

months. This will consist of either 1 extra tablet or 3 extra tablets a day. The exact number will depend on what treatment the doctors think is best suited to you. During treatment you will have regular blood tests to make sure that the treatment is working and that the virus is disappearing from your blood. Once the treatment is finished you will have further blood tests to check that you have been cured of the virus. If the virus disappears from your blood and cannot be detected 12 weeks after the treatment has stopped then you have been cured. We predict that more than 95% of patients will be cured. If the first course of treatment does not work then a second 12 weeks course of treatment using a different combination of tablets will be used which cures more than 95% of patients whose first course of treatment has not worked. It is worth mentioning that these new drugs for hepatitis C have very few side effects in recent world experience and are generally very well tolerated by patients taking them.

What happens to me if I refuse to accept a hepatitis C infected (insert organ here)?

It is your choice whether you choose to receive a (insert organ here) from a hepatitis C virus infected donor. If you prefer not to accept an organ from such a donor you will remain on the transplant waiting list as now and you will continue to wait for a suitably matched organ.

Will I be entitled to compensation if I accept a hepatitis C infected (insert organ here)?

No, you will not be entitled to compensation as the current rules stipulate that you are entitled if you have unwittingly been infected. This would not be the case if you knowingly accept a hepatitis C infected (insert organ here).

Where can I find out more information?

Please speak first to your transplant doctor if you have any questions about the information contained in this leaflet.

Other sources of information are also available.

The Hepatitis C Trust is the national charity for people affected by hepatitis C and is patient-led. Staff on their confidential national helpline will be able to answer any questions you may have about hepatitis C and provide support and reassurance about the new treatments available – you can reach them on 0845 223 4424 or 020 79089 6221 and by email helpline@hepctrust.org.uk

There is also a lot of useful up-to-date general information on their website www.hepctrust.org.uk

The British Liver Trust has an excellent publication on hepatitis C that is free to access on the internet. The link to this is https://www.britishlivertrust.org.uk/wp-content/uploads/Hep-C-website.pdf.

Appendix 2 - Checklist for Transplant Units to Go Through Prior to Going Ahead with HCV D+ / R- Transplantation

Please note that all questions have to be answered yes prior to undertaking the first HCV D+/R- transplant.

	Yes	No
Recipient Specific		
Are you able to calculate APRI scores in your unit (requires measurement of AST and platelet count)?		
Are you able to perform high quality liver ultrasounds on potential recipients?		
Does your organisation have a specific consent form for transplantation and if so does it need to be modified to include transplantation of a HCV positive organ?		
Is there a plan to consent your recipients ahead of transplantation?		
Pharmacy Issues		
Does your pharmacy know how to order the HCV DAA drugs and how they get rebated for this?		
Do the HCV drugs need to be on your formulary prior to prescribing? If yes, have they been added to the formulary?		
Is your pharmacy able to get the drugs within the time frames outlined within the position statement?		
Will the whole treatment course be supplied by the transplant unit pharmacy if the patient is repatriated back to the referring centre early? If no have arrangements been made for continuous supply to be provided to the recipient for the duration of the course?		
Does your Trust have access to Blueteq in order to apply for approval of DAAs (England only)?		
Personnel Issues		
Has a lead clinician for this service development been identified? If this individual has not got personal experience of the management of hepatitis C has he/she got easy access to clinicians that do for advice on individual cases?		
Has the clinical lead provided training to your transplant co-ordinators, pharmacy, transplant surgeons, junior doctors and transplant physicians on this proposed service development?		

Does the wider team have a grasp of the following concepts 1. Blood tests to be performed post-transplantation 2. Referral pathway to local HCV MDT 3. Treatment regimens for HCV that are recommended and the importance of consistently checking for drug to drug interactions whilst on DAA therapy 4. Sustained virologic response and definition of "cure" 5. Risks of HCV transmission while patient is viraemic		
Will the clinical lead ensure that the mandatory blood tests are taken post transplantation and that results are actioned within the timelines stipulated within this document?		
Have you reached out to your referral networks to inform them of this potential development? Would your referrers be happy to supervise/delegate management of HCV post-transplant if the patient is repatriated early?		
Do you know who the clinical lead for the local operational delivery network is (England only)? If so, has the lead clinician in your organisation reached out to them and are they able to respond to treatment advice requests within the time frame required in the position statement? Has a formal pathway for management of potential recipients been agreed with the local ODN (England) or Hepatitis C Oversight Committee (in Wales and Scotland)? Has the local ODN lead agreed to report the data on individual recipients to the oversight committee facilitated by BVHG (see above)? For Scotland and Wales have the main oversight HCV committees agreed to report data on individual recipients to the oversight committee facilitated by BVHG (see above)?		
Laboratory Issues		
Have mechanisms been put in place to ensure timely testing of potential recipients within the time frames outlined in the national position statement? Is the lab able to provide a 3-5 day turnaround for HCV PCR results?		
Does the virology lab understand the need for repeated testing in a short time frame in the same patient?		
Is there a robust reporting mechanism in place to ensure timely communication to the relevant members of the transplant team?		

Appendix 3 - List of Consultees

BASL

BHIVA

British Cardiac Patients Association

British Heart Foundation

British Infection Association

British Liver Trust

British Lung Foundation

British Renal Society

BSG

BRITISH TRANSPLANTATION SOCIETY

Cystic Fibrosis Trust

Haemophilia Society

Hepatitis C Trust

Intensive Care Society

Kidney Care UK

Kidney Research UK

Liver Transplant Patient Consortium

NHS England

NHS Northern Ireland

NHS Scotland

NHS Wales

NHSBT

PBC Foundation

PHE Colindale and other testing laboratories

PSC Support UK

Renal Association

Royal College of Pathologists

SaBTO

Skipton Fund

The Haemochromatosis Society

The National Kidney Federation

The Patients Association

Appendix 4 - Members of the working party

Name	Representing (Secondary Affiliation)	Organ Interest
Ahmed Elsharkawy (Chair)	BVHG (Birmingham)	Liver
Will Gelson	BVHG (Cambridge)	Liver
Mary Cannon	Kings	Liver
Mark Harber	Royal Free	Kidney
Rachel Hilton	BTS (Guys)	Kidney
Colin Wilson	BTS (Newcastle)	Liver and Pancreas
Varuna Aluvihare	BTS (Kings)	Liver
Chris Callaghan	BTS (Guys)	Kidney
Stephen Large	BTS	Hearts
Pedro Catarino	BTS	Lungs
Kosh Agarwal	Kings	Liver
Matthew Cramp	ODN Leads (BASL President)	Liver
Derek Manas	BLTG (Newcastle)	Liver and Pancreas
John Forysthe	NHSBT	
James Neuberger	SaBTO	
Graham Foster	NHS England	
Lynne Vernon	Lay Member	
Sarah Matthew	Lay Member	
William Irving	Clinical Virology Network	
Andy Bathgate	Edinburgh and Scotland	Liver
Graham Lipkin	Renal Association (Birmingham)	Kidneys
Brendan Healey	Wales	
Geoff Dusheiko	Skipton Fund	

Chris Watson	Chair of KAG (Cambridge)	Kidneys and Pancreas
Thamara Perera	Birmingham	Liver
Moira Perrin	Transplant Coordinator (Birmingham)	Liver
Alice Workman	SNOD (London Team)	
Christopher Sandford	Patient Representative	