INFECTED BLOOD INQUIRY

EXHIBIT WITN7660003 TO THE STATEMENT OF DR AILEEN MARSHALL

This is the Exhibit marked **"WITN7660003"** referred to in the Witness Statement of Dr Aileen Marshall

Signed GRO-C Dated 28 February 2023

NHS England

Clinical Commissioning Policy Statement: Treatment of chronic Hepatitis C in patients with cirrhosis

Reference: NHS England B07/P/a

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Description	Hepatitis C is a serious infectious disease caused by blood borne hepatitis C virus (HCV) and is an important cause of liver disease. There are a range of new oral treatments becoming available. The new treatments are better tolerated than current treatments and have been shown to be effective in curing hepatitis C. Policy statement sets out hepatitis tratments that will be routinely commissioned.
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Contact Details for further information	NHS England Specialised Commissioning - Operational Delivery Skipton House London, SE1 6LH www.england.nhs.uk/commissioning

Document Status

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NHS England

Clinical Commissioning Policy Statement:
Treatment of chronic Hepatitis C in patients with cirrhosis

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Prepared by NHS England Clinical Reference Group for Infectious Diseases

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POLICY STATEMENT: **Treatment of chronic Hepatitis C in patients with cirrhosis**	**Reference:** **NHS England** B07/P/a

Plain English Summary	Hepatitis C is a serious infectious disease caused by the blood borne hepatitis C virus (HCV) and is an important cause of liver disease. Over time, patients with chronic hepatitis C can develop complications such as cirrhosis or liver cancer which can, in turn, lead to the need for a liver transplant. There are a range of new oral treatments becoming available. The new treatments are better tolerated than current treatments and have been shown to be effective in curing hepatitis C. A number of these treatments are being evaluated by the National Institute for Health and Care Excellence (NICE). This policy statement sets out the hepatitis treatments that will be routinely commissioned by NHS England for the treatment of chronic hepatitis in patients with cirrhosis. It also sets out how access to treatments will be organised with the setting up of Operational Delivery Networks from August 2015 and arrangements in the interim.
Background:	A number of new Hepatitis C treatments are subject to NICE technology appraisal review during 2015. This interim policy statement sets out the commissioning criteria for treatment of chronic Hepatitis C in patients with cirrhosis and those with advanced liver disease. Liver disease is the 5th biggest cause of mortality in England and Wales after cancer, heart disease, stroke and respiratory disease. Liver disease is the only major cause of mortality and morbidity which is increasing in the UK, whilst decreasing elsewhere in Europe. Hepatitis C is a serious infectious disease caused by the blood-borne hepatitis C virus (HCV) and is an important cause of liver disease. Around 75% of people infected with hepatitis C will develop chronic infection. Chronic infection with hepatitis C, if left untreated or if unsuccessfully treated, can cause cirrhosis and liver cancer in a significant proportion of patients. Once cirrhosis has developed,

	hepatic decompensation and other potentially fatal complications can occur and liver transplantation may be required. An estimated 160,000 people in England are chronically infected with hepatitis C. There are 6 different genotypes of hepatitis C. The most common genotypes in the UK (~90%) are genotype 1 (GT1) and genotype 3 (GT3). GT2, 4, 5, and 6 make up the rest of the remaining identified genotypes. Due to the asymptomatic nature of the infection in its early stages, many people are unaware they are infected with hepatitis C until the disease is severe. The primary goal of chronic hepatitis C treatment is to cure the infection by eradicating the hepatitis C virus (HCV), denoted by achieving a sustained virological response (SVR) at week 12 post-treatment (SVR12). Treatment - especially for genotype 1 - has evolved rapidly with the recent regulatory approvals of sofosbuvir (SOF) and simeprevir (SMV). These medicines result in SVR rates of >90% with 12 weeks of SOF, or >80% with 12 weeks of SMV when combined with pegylated interferon (Peg-IFN) and ribavirin (RBV) for 12 or 24–48 weeks respectively. Regimens containing SOF +/- SMV represent treatment options for patients with cirrhosis and chronic hepatitis C GT1, GT4 and GT3 (SOF-based regimens only), based on the most recent UK and European guidelines. Whilst some patients may benefit from interferon (IFN)-free regimens containing SOF plus either ribavirin or SMV, the majority of patients in England are currently treated with an IFN-containing option as there are no IFN-free options recommended by NICE for GT1 and GT4 patients, or GT3 patients who do not have cirrhosis. In addition, the introduction of Ledipasvir/Sofosbuvir (LDV/SOF) allows more GT1 and GT4 patients to be cured without the need for IFN. The combination therapy of ombitasvir/paritaprevir/ritonavir +/- dasabuvir +/- ribavirin also provides options for GT1 and GT4 patients who are not able to tolerate an interferon-based regimen. Additionally, the combination of sofosbuvir + daclatasvir +/- ribavirin provides an all-oral treatment option for GT3 patients who are intolerant of an interferon based regimen. The primary limitation of Peg-IFN and ribavirin-containing regimens is the association with severe side-effects including influenza-like

	symptoms, fatigue, psychiatric disorders, skin reactions, bone marrow suppression and anaemia. The need for safety and efficacy monitoring and support, long duration of treatment (up to 48 weeks) and weekly injections has made treatment difficult for many patients. NICE technology appraisal guidance was issued in February 2015 in respect of SOF + Peg-IFN and ribavirin, SOF and ribavirin, and SMV + Peg-IFN and ribavirin. Implementation of the guidance is scheduled for August 2015 for the former and end of May for the SMV containing regimen. Publication of further guidance relating to other treatments / combinations is scheduled throughout 2015.
Commissioning position:	The regimens set out in the table below will be commissioned as an alternative to current therapies when the following apply: <u>For patients with compensated cirrhosis:</u> 1) Treatments are provided to the NHS under a commercial-in-confidence scheme **AND** 2) The patient has compensated cirrhosis defined as: • Evidence of portal hypertension without other obvious cause (e.g. varices on endoscopy or previous ascites in the absence of vascular lesions known to cause portal hypertension), **OR** • APRI score and AST:ALT ratio indicative of cirrhosis (APRI >2.0 with an AST:ALT ratio > 1), **OR** • Imaging (Ultrasound or CT or MRI) reported as showing cirrhosis. **OR** • Fibro Scan or liver elastography showing evidence of cirrhosis (for example, a Fibro Scan score of >11.5kPa, or as determined by an expert panel if required), **OR** • Liver biopsy showing cirrhosis <u>For patients with advanced liver disease</u>: 3) The patient is at significant risk of death or irreversible damage, irrespective of genotype. For example, there are patients listed for liver transplantation and others who are either approaching (but not yet on) a liver transplant waiting list, or who may not fulfil other criteria to allow liver transplantation to be performed. Such patients would be defined as follows: • Evidence of present or previous decompensated cirrhosis with an episode of ascites, variceal bleeding, or encephalopathy • Child Pugh Score ≥ or = 7 • Non-hepatic manifestation of HCV infection likely to lead to irreversible damage imminently AND intolerant of (or failed to

respond to) pegylated interferon-based treatment.

- Exceptional cases: Only patients at high risk of death needing a liver transplant, or likely to suffer irreversible harm who are not suitable for treatment with Peg-IFN-based treatment, will be eligible.

SUMMARY OF TREATMENT BY GENOTYPE		
Status of patient	**Status of liver**	**Commissioned regimens based on available evidence and clinical considerations**
Genotype 1a	Patients with compensated cirrhosis	**Ombitasvir/paritaprevir/ritonavir and dasabuvir and ribavirin** for 12 weeks *(Not the EMA recommended duration)* **Simeprevir Peg-IFN ribavirin** for 12 weeks followed by Peg-IFN and ribavirin for 12 weeks[1,2,3] **Sofosbuvir/ledipasvir +/- ribavirin** for 12 weeks *(Not the EMA recommended duration / regimen for some cohorts)*
	Patients with decompensated cirrhosis	**Sofosbuvir/ledipasvir +/- ribavirin** for 12 weeks *(Not the EMA recommended duration)*
Genotype 1b	Patients with compensated cirrhosis	**Ombitasvir/paritaprevir/ritonavir and dasabuvir and ribavirin** for 12 weeks **Simeprevir/Peg-IFN ribavirin** for 12 weeks followed by Peg-IFN for a further 12 weeks [2,3] **Sofosbuvir/ledipasvir +/- ribavirin** for 12 weeks *(Not the EMA recommended duration for some cohorts)*

	Patients with decompensated cirrhosis	**Sofosbuvir/ledipasvir +/- ribavirin** for 12 weeks *(Not the EMA recommended duration)*
Genotype 3	Patients with compensated cirrhosis	**Sofosbuvir/Peg-IFN and ribavirin for patients who are likely to be IFN-tolerant** for 12 weeks **Sofosbuvir /Daclatasvir and ribavirin (where IFN is contraindicated)** for 12 weeks (*Not the EMA recommended duration*) **Sofosbuvir/ledipasvir and ribavirin (where IFN is contraindicated)** for 12 weeks *(Not the EMA recommended durations)*
Genotype 3	Patients with decompensated cirrhosis	**Sofosbuvir/daclatasvir + ribavirin** for 12 weeks (*Not the EMA recommended duration*) **Sofosbuvir/ledipasvir + ribavirin** for 12 weeks *(Not the EMA recommended duration)*
Genotype 4	Patients with compensated cirrhosis	**Simeprevir/Peg-IFN interferon +/- ribavirin** for 12 weeks followed by Peg-IFN for a further 12 weeks[2,3] **Sofosbuvir/ledipasvir** for 12 weeks *(Not the EMA recommended duration/regimen for some cohorts)*
	Patients with decompensated cirrhosis	**Sofosbuvir/ledipasvir +/- ribavirin** for 12 weeks *(Not the EMA recommended duration)*

1. Not recommended for patients with Q80K polymorphism

	2. *Treatment should be stopped at week 4 of treatment if HCV RNA is 25 IU/ml or more and stopped at week 12 or 24 if HCV RNA is detectable.* 3. *Peg-IFN and ribavirin treatment should continue for 36 weeks if patient is a partial or null responder to previous treatment or has HIV co-infection* There is emergent evidence of efficacy in relation to patients with cirrhosis and infected with genotypes 2, 5 or 6. However, as these cohorts are very small in number, the evidence base remains limited. For these and other patients with cirrhosis who do not meet the commissioning criteria above but are at risk of serious deterioration prior to NICE technology appraisal guidance implementation, an application to the national expert clinical panel can be made to the following address: kch-tr.EAPpanelreview@nhs.net <u>Starting / stopping criteria</u> Patients meeting the criteria for treatment will be started on treatment. The patient's viral load will be measured at week 2, 4 and 8 (three measurements) during treatment. An increase in viral load from on-treatment nadir of greater than 1 log is indicative of poor adherence and virological breakthrough and treatment will be discontinued. Discontinuation avoids futile therapy and minimises the development of drug resistance. At the end of 12 weeks treatment, viral load is measured to determine that SVR has been achieved. For patients who breakthrough on therapy or do not respond to current therapies there are currently no proven therapeutic options but trials of 'rescue' medications are on-going and likely to report shortly. <u>Operating Arrangements</u> The provision of care under this policy will be overseen within formalised Operational Delivery Networks (ODNs) which will be in place by August 2015. The ODNs will provide clinical leadership over a given geography, co-ordinating high quality patient care through a specialist multidisciplinary team (MDT) and delivering oral therapies in line with this policy in largely outpatient (including outreach) settings.

	Ahead of the ODNs being formally established, treatment decisions will be overseen by providers currently commissioned by NHS England to provide specialised Infectious Diseases and Hepatobiliary Services, with reference to the providers currently operating the Early Access Scheme for patients with decompensated cirrhosis. This ensures that the policy can be implemented from the date of publication whilst maintaining access to MDT expertise and experience in oral therapies during the interim period.
Effective from:	June 2015
Evidence summary:	**Sofosbuvir/ledipasvir +/- ribavirin** Based on clinical trial data from over 3,000 patients in 12 Phase II and III studies, LDV/SOF provides efficacy across a spectrum of HCV patients including those who are obese, methadone users, those with low platelets, different ethnicity and cirrhosis. SVR rates reported in trials are therefore expected to be reflective of those that will be achieved in clinical practice. LDV/SOF offers an improvement on the high cure rates achieved by SOF+Peg-IFN and ribavirin. For treatment-naïve patients without cirrhosis, short treatment duration of only 8 weeks gives SVR rates of 94%. The LDV/SOF clinical trial programme assessed efficacy as defined by HCV RNA below the lower limit of quantification at 12 or 24 weeks post-treatment (SVR12 and SVR24, respectively). Many studies also investigated safety, tolerability, virological failure and viral resistance. In phase 3 clinical trials, LDV/SOF has shown very high efficacy along with low rates of AEs (Table 1). Emerging data from AASLD reviewed by the hepatitis C sub group demonstrated that the most difficult to treat patients with compensated liver disease, namely treatment experienced patients with cirrhosis, GT1 patients, including those who have previously failed a protease inhibitor (PI) regimen, could successfully be treated with LDV/SOF and ribavirin for 12 weeks with an SVR rate of 96% or LDV/SOF for 24 weeks with an SVR rate of 97% (Bourliere, M. et al.). In patients with advanced liver disease (Child Pugh scores 7-12), emerging data (SOLAR-1) from AASLD reviewed by the hepatitis C sub group demonstrated that, when treated with LDV/SOF and ribavirin, this population achieves similar SVR12 rates with 12 versus 24 weeks: 87% (45/52) v. 89% (42/47). In the post-transplant arm of

	this study, similar SVR12 rates were observed with 12 versus 24 weeks LDV/SOF and ribavirin for each patient group: those without cirrhosis: 96% (53/55) v. 98% (55/56); compensated cirrhosis: 96% (25/26) v. 96% (24/25); Child Pugh score 7-9: 85% (22/26) v. 83% (15/18); Child Pugh score 10-12: 60% (3/5) v. 67% (2/3). The evidence to support the use of LDV/SOF in GT3 patients are limited, and the relative efficacy of a 12-week regimen consisting of LDV/SOF and ribavirin, compared to 12 weeks of SOF plus PEG-IFN + RBV or a 24-week regimen of SOF and ribavirin has not been investigated. This led to the EMA recommending a conservative 24 weeks of LDV/SOF + RBV therapy in all treatment-experienced genotype 3 patients and those treatment-naïve genotype 3 patients with cirrhosis. This data follows the earlier publication of the safety and efficacy of LDV/SOF with or without ribavirin in 51 treatment-naïve patients with genotype 3 HCV infection, with or without cirrhosis. Patients were treated with LDV/SOF (n=25) or LDV/SOF and ribavirin (n=26) for 12 weeks. SVR12 rates were 64% (16/25) and 100% (26/26) in the LDV/SOF and LDV/SOF and ribavirin treatment groups, respectively. Since this recommendation, a 12 week regimen of LDV/SOF + ribavirin used for the treatment of GT3 treatment-experienced patients demonstrated an SVR rate of 89% (25/28) in patients without cirrhosis, whilst the treatment-experienced patients GT3 patients with cirrhosis achieved an SVR rate of 73% (16/22). **Ombitasvir/paritaprevir/ritonavir +/- dasabuvir +/- ribavirin** These regimens represent treatment options for patients with GT1 and GT4 chronic hepatitis C infection whilst satisfying current unmet need associated with interferon-based therapies. They represent predominantly 12-week all-oral DAA regimens, with or without ribavirin, which deliver SVR rates of 92-100%, low discontinuation rates, and favourable safety and tolerability profiles when compared to Peg-INF and ribavirin-based therapies. The data presented relates to the efficacy, safety and tolerability of these regimens in the treatment of patients with chronic hepatitis C (genotypes 1 and 4) and comes from the Phase II and III clinical development programme, including six Phase III studies and three relevant Phase II studies, namely: • **SAPPHIRE-I;** (GT1a/b treatment-naïve, no cirrhosis; *N* = 631) • **SAPPHIRE-II;** (GT1a/b treatment-experienced, no cirrhosis; *N* = 394)

	• **PEARL-II;** (GT1b treatment-experienced, no cirrhosis; *N* = 179) • **PEARL-III;** (GT1b treatment-naïve, no cirrhosis; *N* = 149) • **PEARL-IV;** (GT1a treatment naïve, no cirrhosis; *N* = 305) • **TURQUOISE-II;** (GT1a/b treatment-naïve and treatment-experienced, specifically and exclusively patients with cirrhosis only; *N* = 380) • **TURQUOISE-I;** (Phase II/III clinical trial) (GT1a/b HCV/HIV-1 co-infected treatment-naïve and treatment-experienced, with and without cirrhosis; *N* = 63) • **CORAL-I;** (Phase II clinical trial) [GT1 post-liver transplant patients only (treatment-naïve post-transplant); *N* = 34] • **PEARL-I;** (Phase II clinical trial) (GT4 patients only, treatment-naïve and treatment-experienced patients, no cirrhosis; *N* = 135 These studies demonstrate that ombitasvir/paritaprevir/ritonavir + dasabuvir +/- ribavirin (GT1 regimen), and ombitasvir/paritaprevir/ritonavir and ribavirin (GT4 regimen), are effective and generally well-tolerated by patients (with discontinuation rates of generally <1%), and with overall safety profiles that are favourable compared to those of Peg-INF based regimens **Sofosbuvir / daclatasvir +/- ribavirin** In an open label of GT3 patients, a regimen containing sofosbuvir and daclatasvir given for 12 weeks achieved SVR rates of at least 86%. In a phase 2 study (AI444-040), daclatasvir was evaluated in 211 HCV genotype 1, 2 and 3 infected patients without cirrhosis, in combination with sofosbuvir with or without ribavirin. The study resulted in overall SVR12 rates of 98% (n=167) in patients with HCV genotype 1 and 89% (n=18) in patients with HCV genotype 3 (Sulkowski). 100% of patients with ≥F3 fibrosis achieved SVR12 (BMS Data on File. DACL002). The ALLY 3 phase 3 study enrolled 152 patients with genotype 3 infection (101 treatment naive and 51 treatment experienced). All patients received a 12 week course of the oral regimen of daclatasvir plus sofosbuvir. Overall SVR12 was achieved in 90% of the treatment-naive patients and in 86% of the treatment experienced patients (Nelson).
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Responsible CRG:	Infectious Diseases & Hepato-Pancreas-Biliary Clinical Reference Groups
Mechanism for Funding:	Through NHS England standard contract arrangements
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