NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of ex-vivo machine perfusion for extracorporeal preservation of livers for transplantation

A donor's liver for a transplant is usually stored with cold fluid and ice until it is put into the patient. In this procedure, a special machine is used to deliver oxygenated blood to the donor liver. The aim is to reduce damage to the liver after it has been removed from the donor, and to improve how it works once it has been transplanted. The machine also allows the liver's function to be assessed before it is transplanted, and may increase how long the liver can be stored before a transplant.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in January 2018.

Procedure name

- Ex-vivo machine perfusion for extracorporeal preservation of livers for transplantation

Specialist societies

- British transplantation society (BTS)
- NHS Blood and Transplant
- British Association for the Study of the Liver (BASL)
- British Liver Transplant Group (BLTG)
- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland
- British Society of Gastroenterology
- Royal College of Surgeons.

Description of the procedure

Indications and current treatment

Liver transplantation is the treatment of choice for patients with end-stage liver disease. It may also be indicated in patients with some types of primary liver cancer. End‑stage liver failure can be either acute (for example, from poisoning) or chronic (for example, because of cirrhosis from alcohol-related liver disease,

metabolic, autoimmune or infectious conditions). In children, the most common cause of end‑stage liver failure is congenital biliary atresia.

Limited availability of deceased donor livers for transplantation led to the development of techniques that increase the number of recipients who can benefit from 1 available organ. These include split liver grafts (the larger right lobe is usually grafted into an adult and the left lobe into a child) and reduced (segmental) liver grafts.

Living‑donor liver transplantation is also an option for patients who are deteriorating clinically while waiting for a deceased donor transplant.

What the procedure involves

Ex-vivo machine perfusion preserve the donor liver outside the body under normothermic or hypothermic conditions using a perfusion machine that delivers oxygenated blood supplemented with nutrients and metabolic substrates. The intention is to:

- reduce the rate of tissue deterioration that occurs after the liver has been removed from the donor compared with that seen with conventional static cold storage (SCS)
- allow for better assessment of donor liver function pretransplantation
- extend how long the liver can be stored to allow more flexibility in the timing of the transplant operation.

The aim is to improve clinical outcomes for the recipient and to enable otherwise marginal organs (such as those donated after circulatory death, steatotic livers and livers from older people) to be transplanted safely so increasing the number of livers available for transplantation.

In this procedure, the donor liver is placed in a perfusion machine. The perfusion machine comprises a blood reservoir, a pump, blood oxygenator, blood warming unit and monitoring equipment. Both the hepatic artery and portal vein of the liver are perfused, and effluent blood is collected and recirculated through the liver. This procedure has been used to store a donor liver for up to 24 hours, after which it can be implanted into a recipient in the conventional way.

Outcome measures

Early allograft dysfunction was defined as the occurrence of: bilirubin over 170 micromol/litre on day 7 after transplant, or international normalised ratio (INR) over 1.6 on day 7 after liver transplantation, or peak alanine aminotransferase (ALT) over 2000 U/litre within the first 7 days after liver transplantation.

Primary non-function: retransplantation or death within 7 days of transplantation.

Model for End-Stage Liver Disease (MELD) score: MELD is calculated using bilirubin, INR and creatinine. A higher score indicates a higher risk of perioperative mortality.

Efficacy summary

Patient survival

In a matched case-control study of 61 patients comparing 31 liver grafts preserved with hypothermic machine perfusion (HMP) with 30 liver grafts preserved with SCS, patient survival rate at 1 year was similar in both groups: 84% (26/31) in the group using HMP and 80% (24/30) in the group using SCS (p=0.761).[1]

In a matched case-control study of 40 patients comparing 20 liver grafts preserved with HMP with 20 liver grafts preserved with cold storage (CS), patient survival rate at 1 year was 90% (18/20) in both groups.[3]

In a matched case-control study of 30 patients comparing 10 liver grafts preserved with dual hypothermic oxygenated machine perfusion (DHOPE) with 30 liver grafts preserved with SCS, patient survival rate at 1 year was similar in both groups: 100% (10/10) in the group using DHOPE and 85% (17/20) in the group using SCS (p=0.209).[4]

In a matched case-control study of 112 patients comparing 6 liver grafts preserved with controlled oxygenated rewarming (COR) with 106 liver grafts preserved with CS, patient survival rate at 6 months was 100% in the COR group and 85% in the CS group (p=0.28).[5]

In a randomised controlled trial (RCT) of 222 patients comparing 121 livers preserved with normothermic machine perfusion (NMP) with 101 livers preserved with SCS, there was no statistically significant difference in patient survival rate at 1 year between the groups (96% compared with 97%, p=0.671).[6]

In a matched case-control study of 60 patients comparing 20 liver grafts preserved with NMP with 40 liver grafts preserved with CS, patient survival rate at 6 months was 100% (20/20) in the NMP group and 98% (39/40) in the CS group (risk ratio [RR] 1.03, 95% confidence interval [CI] 0.98 to 1.08; p=1.000). In the NMP group, 1-year patient survival was 95% (19/20) (1-year patient survival was not reported in the CS group).[7]

In a non-randomised comparative study of 36 patients comparing 12 declined liver grafts preserved with NMP with 24 non-declined liver grafts not preserved with NMP, patient survival rate at a median of 1 year was 92% (11/12) in the NMP group compared with 96% (23/24) in the non-NMP group (p value not reported).[8]

In a matched case-control study of 40 patients comparing 10 liver grafts preserved with NMP with 30 liver grafts preserved with CS, 30-day patient survival rate per protocol was 100% in both groups (9/9 and 27/27 respectively) and 6-month patient survival rate per protocol was 89% (8/9) for NMP and 100% (27/27) for CS (p=0.25).[9]

In a second matched case-control study of 40 patients comparing 10 liver grafts preserved with NMP with 30 liver grafts preserved with CS, patient survival at 3 months was 100% in both groups.[10]

Graft survival

In the matched case-control study of 61 patients, graft survival rates at 1 year were statistically significantly similar in both groups: 81% in the group using HMP and 80% in the group using SCS.[1]

In a matched case-control study of 125 patients comparing 25 liver grafts from donation after cardiac death (DCD) preserved with hypothermic oxygenated perfusion (HOPE) with 50 liver grafts from DCD preserved with CS and 50 liver grafts from donation after brain death preserved using CS, graft survival rate at 1 year was statistically significantly higher (90%) in the HOPE DCD group than in the CS DCD group (69%) (p=0.035).[2]

In the matched case-control study of 40 patients comparing HMP and CS, graft survival rate at 1 year was 90% (18/20) in both groups.[3]

In the matched case-control study of 30 patients, graft survival rates at 1 year were similar in both groups: 100% (10/10) in the group using DHOPE and 67% in the group using SCS (p=0.052).[4]

In the matched case-control study of 112 patients, graft survival rate at 6 months was 100% in the COR group and 81% in the CS group (p=0.24).[5]

In the RCT of 222 patients comparing 121 livers preserved with NMP with 101 livers preserved with SCS, there was no statistically significant difference in graft survival rate at 1 year between groups (95% compared with 96%, p=0.707).[6]

In the matched case-control study of 60 patients, graft survival rate at 30 days was 100% (20/20) in the NMP group and 98% (39/40) in the CS group (RR 1.03, 95% CI 0.98 to 1.08; p=1.000).[7]

In the non-randomised comparative study of 36 patients, graft survival rate at median 1 year was 83% (10/12) in the NMP group and 88% (21/24) in the non-NMP group (p value not reported).[8]

In the first matched case-control study of 40 patients comparing NMP with CS, there was no statistically significant difference between groups for 30-day and 6-month graft survival in the intention-to-treat (ITT) population. Thirty-day graft survival rate was 90% (9/10) for NMP and 100% (30/30) for CS (p=0.25) and 6-month graft survival was 80% (8/10) for NMP and 100% (30/30) for CS (p=0.06).[9]

In the second matched case-control study of 40 patients comparing NMP with CS, graft survival at 3 months was 100% in both groups.[10]

Hospital length of stay and intensive care unit (ICU) length of stay

In the matched case-control study of 61 patients, hospital length of stay (mean ± standard deviation [SD]) was statistically significantly shorter in the HMP group (13.6±10.9 days) than in the SCS group (20.1±11.1 days) (p=0.001).[1]

In the matched case-control study of 125 patients, there was no statistically significant difference between the groups in hospital length of stay (median interquartile range [IQR]; HOPE DCD group – 20 days [14 to 23], CS DCD group – 18 days [15 to 29]).The ICU length of stay was also similar between groups (median 3 days).[2]

In the matched case-control study of 40 patients comparing HMP and CS, hospital length of stay (mean ± SD) was statistically significantly lower in the HMP group (10.9±4.7 days) than in the CS group (15.3±4.9 days; p=0.006).[3]

In the matched case-control study of 30 patients, duration of hospital stay and ICU stay were similar in both groups (DHOPE and SCS): median 22 days compared with median 23 days (p=0.880) for hospital stay and median 2 days of ICU stay in each group (p=0.475).[4]

In the matched case-control study of 112 patients, duration of hospital stay and duration of ICU stay were similar between groups (DHOPE and SCS): median 22 days compared with median 19 days respectively (p=0.60) for hospital stay, and median 3 days of ICU stay in each group (p=0.89).[5]

In the RCT of 222 patients, there was no statistically significant difference in the length of hospital stay and ICU stay between NMP and SCS (median 15 days in

both groups for hospital stay, p=0.926; median 4 days in both groups for ICU stay, p=0.339).[6]

In the matched case-control study of 60 patients, duration of hospital stay and ICU stay (median) were similar between groups: 12 days for NMP compared with 14 days for CS (effect size [ES] -0.44, 95% CI -0.98 to 0.11, p=0.100) and 3 days in both groups for ICU (ES -0.42, 95% CI -0.96 to 0.13, p=0.459).[7]

In the first matched case-control study of 40 patients comparing NMP with CS, hospital stay and ICU stay were statistically significantly longer in the NMP group in the per protocol population. Hospital stay (median [range]) was 45 days (13 to 114) for NMP and 25 days (9 to 89) for CS (p=0.01), and ICU stay was 16 days (2 to 65) for NMP and 4 days (1 to 29) for CS (p=0.004).[9]

In the second matched case-control study of 40 patients comparing NMP with CS, hospital stay after the transplant and ICU stay were similar between groups. Hospital stay (median) was 11 days (8 to 17) for NMP and 13 days (7 to 89) for CS (p=0.23), and ICU stay was 1 day (0 to 8) for NMP and 2 days (0 to 23) for CS (p=0.54).[10]

In a case series of 6 recipients of declined livers preserved with NMP, median hospital length of stay was 10 days (range 6 to 15 days) and median intensive therapy unit length of stay was 3 days (range 2 to 6 days).[11]

Primary non-function

In the matched case-control study of 61 patients, the primary non-function rates were not statistically significantly different between groups: 3% (1/31) in the HMP group and 7% (2/30) in the SCS group (p=0.612).[1]

In the matched case-control study of 125 patients, primary non-function rates were similar in both groups: 0% (0/25) in the HOPE DCD group and 6% (3/50) in the CS DCD group, p=NS.[2]

In the matched case-control study of 40 patients comparing HMP and CS, there was no primary non-function in either group.[3]

In the matched case-control study of 30 patients, primary non-function (determined as retransplantation or death within 7 days of transplantation) was reported in none of the patients in either group (DS and SCS).[4]

In the matched case-control study of 112 patients, primary non-function rates were similar in both groups: 0% in the COR group and 3% (3/106) in the CS group (p=0.68).[5]

In the RCT of 222 patients comparing NMP with SCS, primary non-function was reported in 1 patient in the NMP group and in none of the patients in the SCS group.[6]

In the matched case-control study of 60 patients comparing NMP with CS, there was no primary non-function in either group.[7]

In the first matched case-control study of 40 patients comparing NMP with CS, there was no primary non-function in either group.[9]

Early allograft dysfunction

In the matched case-control study of 61 patients, the early allograft dysfunction rates were not statistically significantly different between groups: 19% (6/31) in the HMP group and 30% (9/30) in the SCS group (p=0.384).[1]

In the matched case-control study of 125 patients, the early allograft dysfunction rate was statistically significantly lower in the HOPE DCD group (20% [5/25]) than in the CS DCD group (44% [22/50]), p=0.046.[2]

In the matched case-control study of 40 patients comparing HMP and CS, the early allograft dysfunction rate was 5% (1/20) and 25% (5/20) respectively (p=0.08).[3]

In the matched case-control study of 112 patients, early allograft dysfunction rates were similar in both groups: 0% (0/6) in the COR group and 36% (38/106) in the CS group (p=0.07).[5]

In the RCT of 222 patients comparing NMP with SCS, the early allograft dysfunction rates were statistically significantly lower in the NMP group (10% [12/119]) than in the SCS group (30% [29/97]; odds ratio 0.63, 95% CI 0.126 to 0.550; p=0.0002).[6]

In the matched case-control study of 60 patients, early allograft dysfunction rates were similar in both groups: 15% (3/20) in the NMP group and 23% (9/40) in the CS group (RR 0.67, 95% CI 0.20 to 2.19, p=0.734).[7]

In the first matched case-control study of 40 patients comparing NMP with CS, early allograft dysfunction rates per protocol were similar in both groups: 56% (5/9) in the NMP group and 30% (8/27) in the CS group (p=0.23).[9]

In the case series of 6 recipients of declined livers preserved with NMP, no (0/5) early allograft dysfunctions were reported (5/6 livers met the viability criteria and were used for transplantation).[11]

Liver function

In the matched case-control study of 61 patients, aspartate aminotransferase (AST), ALT, total bilirubin, and serum creatinine levels were lower in the HMP group than the SCS group. The ALT levels in the HMP group at 1 day and the serum creatinine levels at 5 days were statistically significantly lower than in the SCS group (p=0.049 and p=0.020 respectively). The post-transplant recovery of liver and renal markers to normal laboratory reference ranges was faster in the HMP group than in the SCS group, with serum creatinine recovery to normal being statistically significantly faster in the HMP group (p=0.031).[1]

In the matched case-control study of 125 patients, alkaline phosphatase (ALP) levels, peak bilirubin levels, peak AST levels, peak ALT levels and INR (median IQR) were all statistically significantly lower in the HOPE DCD group than in the CS DCD group (p<0.05).[2]

In the matched case-control study of 40 patients comparing HMP and CS, peak serum levels of markers of liver injury were statistically significantly reduced after HMP compared with after CS. Peak levels were measured at 48 hours post-reperfusion for AST (p=0.011) and ALT (p=0.044), and at 5 days post-reperfusion for total bilirubin (p=0.042). Serum markers of liver damage were lower in the HMP group over the 14 days after surgery and total bilirubin normalised statistically significantly faster compared with the CS group (p=0.023).[3]

In the matched case-control study of 30 patients, peak serum ALT at 7 days, serum bilirubin at 7 days, median ALT at 30 days, median γ-glutamyl transferase at 30 days, median ALP and median bilirubin levels at 30 days were all statistically significantly lower in the DHOPE group than in the SCS group (p<0.05).[4]

In the matched case-control study of 112 patients, peak total bilirubin levels (day 1 to day 7) and maximal INR levels were similar in both groups (p=0.18 and p=0.07 respectively) but peak serum AST levels (day 1 to day 7) were statistically significantly lower in the COR group (563.5 units/litre) than in the CS group (1,204 units/litre; p=0.023).[5]

In the RCT of 222 patients comparing NMP with SCS, the geometric mean peak AST levels (ITT analysis adjusted for donor type and transplant centre) were statistically significantly lower in the NMP group (488.1 IU/litre) than in the SCS group (964.9 IU/litre; 50% reduction, p=0.000). Median bilirubin levels between days 1 and 7, AST levels between days 1 and 7, and creatinine levels at 30 days were also statistically significantly lower in the NMP group (p<0.05).[6]

In the matched case-control study of 60 patients, peak AST levels within 7 days (IU/litre, median range)) were statistically significantly lower for NMP (417 [84 to

4,681]) than for CS (902 [218 to 8,786]; p=0.034). There was no statistically significant difference between groups for bilirubin levels, INR and ALP levels at 7 days (p=0.203, p=0.922 and p=0.798 respectively).[7]

In the non-randomised comparative study of 36 patients, the peak ALT levels in the first 7 days were 1,069 IU/litre (median; range 187 to 4991) in the NMP group and 787 IU/litre (155 to 2238) in the non-NMP group (p value not reported).[8]

In the first matched case-control study of 40 patients comparing NMP with CS, there was no statistically significant difference between groups for peak AST (days 1 to 7; p=0.52), bilirubin at day 7 (p=0.35) and INR at day 7 (p=0.44).[9]

In the second matched case-control study of 40 patients comparing NMP with CS, there was no statistically significant difference between groups for peak ALT at 48 hours (p=0.55), INR at 3 months (p=0.91), bilirubin at 3 months (p=0.21) and ALP at 3 months (p=0.33).[10]

In the case series of 6 recipients of declined livers preserved with NMP, the results of the liver function tests (range) after transplantation were: peak ALT (1,188 to 1,879 IU/litre); peak bilirubin (87 to 167 micromol/litre); ALT at 3 months (8 to 29 IU/litre); bilirubin at 3 months (5 to 21 micromol/litre); ALP at 3 months (63 to 135 IU/litre); and creatinine at 3 months (77 to 147 micromol/litre).[11]

Acute rejection

In the matched case-control study of 125 patients, acute rejection rate (rejection activity index over 4) was similar in both groups: 12% (3/25) in the HOPE DCD group compared with 16% (8/50) in the CS DCD group (p=NS).[2]

Discard rates

In the RCT of 222 patients comparing NMP with, the discard rates were statistically significantly lower in the NMP group (12% [16/137]) than in the SCS group (24% [32/133]; p=0.008; denominators for the discard rates were the total number of livers retrieved, n=270). One NMP discard was the result of a device malfunction in an already marginal organ.[6]

Retransplantation

In the matched case-control study of 125 patients, retransplantation for ischaemic cholangiopathy or primary non-function was statistically significantly lower (0%) in the HOPE DCD group than in the CS DCD group (18%) (p=0.025).[2]

Safety summary

Death

Death was reported in 10% (2/20) of patients in each group in the matched case-control study of 40 patients comparing HMP with CS. The causes of the deaths in the HMP group were cardiovascular death at 1 month, and pneumonia and sepsis at 3 months. In the CS group, the causes of the deaths were 1 recurrent cancer at 5 months, and 1 recurrent hepatitis C virus infection and sepsis at 7 months.[3]

Death of 1 patient from alcohol recidivism was reported in the NMP group at 9 months in the matched case-control study of 60 patients (the complications were not reported for the CS group).[7]

Death of 1 patient 2 days after the procedure from a difficult hepatectomy complicated by coagulopathy and severe haemorrhage, with 28 litres of blood loss before implantation was reported in the NMP group in the non-randomised comparative study of 36 patients. The liver suffered primary non-function, and the patient died despite urgent retransplantation.[8]

Hepatic complications

Hepatic complications represented 24% (44/128) of all adverse events in the NMP group compared with 29% (48/164) of all adverse events the SCS group in the RCT of 222 patients.[6]

Postoperative hepatic parenchymal infarcts were reported in 5% (1/20) of patients in the NMP group in the matched case-control study of 60 patients; they resolved without treatment (the complications were not reported for the CS group).[7]

Biliary complications

Biliary complications were reported in 13% (4/31) of patients in the HMP group and in 43% (13/30) of patients in the SCS group in the matched case-control study of 61 patients (p=0.001). They consisted of bile leaks (3% [1/31] in the HMP group compared with 10% [3/30] in the SCS group, p=0.354) and biliary strictures (10% [3/31] compared with 33% [10/30] respectively, p=0.031).[1]

Biliary complications were reported in 20% (5/25) of patients in the HOPE DCD group and in 46% (23/50) of patients in the CS DCD group in the matched case-control study of 125 patients (p=0.042). In the same study, anastomotic strictures or leaks were reported in 20% (5/25) of patients in the HOPE DCD group and in

24% (12/50) of patients in the CS DCD group (no statistically significance difference between groups).[2]

Biliary complications were reported in 10% (2/20) of patient in the HMP group and in 20% (4/20) of patients in the CS group in the matched case-control study of 40 patients comparing HMP with CS. Early bile leakage was reported in 5% (1/20) of patients in each group, and biliary stricture was reported in 5% (1/20) of patients in the HMP group and in 15% (3/20) of patients in the CS group.[3]

Anastomotic biliary stricture was reported in 20% (2/10) of patients in the DHOPE group and in 15% (3/20) patients in the SCS group in the matched case-control study of 30 patients (p=1). In the same study, biliary cast formation was reported in 30% (3/10) of patients in the DHOPE group and in 15% (3/20) patients in the SCS group (p=0.372); ischaemic cholangiopathy was reported in 10% (1/10) of patients in the DHOPE group (1 non-anastomotic biliary stricture treated successfully with endoscopic stenting) and in 45% (9/20) of patients in the SCS group (7 non-anastomotic biliary strictures and 2 cases of massive biliary necrosis) (p=0.101). There were no retransplantations for biliary complications in the DHOPE group compared with 25% (5/20) in the SCS group (p=0.140).[4]

Clinically relevant ischaemic cholangiopathy was reported in 1 patient in each group in the RCT of 222 patients comparing NMP with SCS. Both patients had retransplantations.[6]

Anastomotic biliary stricture was reported in 20% (4/20) of patients in the NMP group in the matched case-control study of 60 patients; this was treated by stenting (the complications were not reported for the CS group).[7]

Cholangiopathy was reported in 27% (3/11) of patients in the NMP group and in 29% (7/24) of patients in the non-NMP group in the non-randomised comparative study of 36 patients.[8]

Six-month biliary complications rate was 0% (0/8) in the NMP group and 15% (4/27) in the CS group (per protocol population) in the first matched case-control study of 40 patients comparing NMP with CS (p=0.55).[9]

Non-cirrhotic portal hypertension with ascites

Non-cirrhotic portal hypertension with ascites was reported in 5% (1/20) of patients in the NMP group in the matched case-control study of 60 patients (the complications were not reported for the CS group).[7]

Vascular complications

Hepatic artery thrombosis

Hepatic artery thrombosis was reported in 3% (1/31) of patients in the HMP group and in 7% (2/30) of patients in the SCS group in the matched case-control study of 61 patients (p=0.612). The patient with hepatic artery thrombosis reported in the HMP group needed retransplantation. This was because of kinking in the donor artery and was deemed unrelated to the HMP procedure.[1]

Hepatic artery thrombosis was reported in 4% (1/25) of patients in the HOPE DCD group and in 6% (3/50) of patients in the CS DCD group in the matched case-control study of 125 patients (no statistically significant difference between groups).[2]

Hepatic artery thrombosis was reported in none of the patients in the DHOPE group and in 2 patients in the SCS group in the matched case-control study of 30 patients (p=0.54).[4]

No vascular complication was reported in the NMP group in the matched case-control study of 60 patients (the complications were not reported for the CS group).[7]

Portal vein thrombosis

Portal vein thrombosis was reported in 6% (2/31) of patients in the HMP group and in none of the patients in the SCS group in the matched case-control study of 61 patients (p=0.492). They had thrombectomy.[1]

Cardiovascular complications

Cardiovascular complications represented 4% (5/128) of all adverse events in the NMP group compared with 3% (5/164) of all adverse events in the SCS group in the RCT of 222 patients.[6]

Acute coronary syndrome was reported in 1 patient 8 days after transplantation in the case series of 6 patients with liver grafts preserved using NMP. It was treated with percutaneous coronary intervention with stent insertion.[11]

Reoperation

Reoperation for bleeding was reported in 6% (2/31) of patients in the HMP group and in 23% (7/30) of patients in the SCS group in the matched case-control study of 61 patients (p=0.081).[1]

Relaparotomy was reported in 3 patients in the DHOPE group and in 7 patients in the SCS group in the matched case-control study of 30 patients. The indications for relaparotomy in the DHOPE group were: intra-abdominal blood loss because

of diffuse oozing (1); removal of surgical gauzes used for packing to control diffuse oozing during transplantation (1); and biliary anastomotic leakage (1).[4]

Reoperation for intra-abdominal bleeding was reported in 1 patient in the NMP group in the first matched case-control study of 40 patients comparing NMP with CS.[9]

Kidney complications

Acute kidney injury was reported in 10% (3/31) of patients in the HMP group and in 27% (8/30) of patients in the SCS group in the matched case-control study of 61 patients (p=0.106).[1]

Renal failure needing haemodialysis was reported in 1 patient in the DHOPE group and in 2 patients in the SCS group in the matched case-control study of 30 patients.[4]

Need for renal replacement therapy was reported in 22% (27/121) of patients in the NMP group and in 21% (21/101) of patients in the SCS group within 6 months of the procedure in the RCT of 222 patients (p=0.784).[6]

Renal insufficiency was reported in 1 patient in the NMP group in the first matched case-control study of 40 patients comparing NMP with CS; it was treated with transient haemodialysis.[9]

Need for renal replacement therapy was reported in 20% (1/5) of patients in the case series of 6 patients with liver grafts preserved using NMP (5/6 livers met the viability criteria and were used for transplantation).[11]

Post-reperfusion complications

Post-reperfusion syndrome (defined as more than a 30% drop in mean arterial pressure lasting for more than 1 minute within 5 minutes of reperfusion) was reported in 12% (15/121) of patients in the NMP group compared with 33% (32/101) of patients in the SCS group in the RCT of 222 patients (p=0.0002).[6]

Post-reperfusion syndrome (defined as a fall in mean arterial pressure within 5 minutes of reperfusion in the recipient to less than 70% of the baseline value in the last 5 minutes of the anhepatic period) was reported in 42% (5/12) of patients in the NMP group and in 25% (6/24) of patients in the non-NMP group in the non-randomised comparative study of 36 patients.[8]

Vasoplegia

Vasoplegia (defined as a fall in mean arterial pressure on reperfusion to less than 50 mmHg either sustained longer than 30 minutes or needing greater than 0.15 microgram/kg per minute norepinephrine, greater than 2 U/h argipressin, or infusion of epinephrine) was reported in 33% (4/12) of patients in the NMP group and in 21% (5/24) of patients in the non-NMP group in the non-randomised comparative study of 36 patients.[8]

Hypokalaemia

Hypokalaemia (less than 3.5mEq/litre) was reported in 3 patients after reperfusion in the DHOPE group and in none of the patients in the SCS group in the matched case-control study of 30 patients (p=0.03).[4]

Bleeding complications

Bleeding complications represented 7% (9/128) of all adverse events in the NMP group compared with 4% (6/164) of all adverse events the SCS group in the RCT of 222 patients.[6]

Infection

Sepsis

Infection represented 20% (25/128) of all adverse events in the NMP group compared with 10% (17/164) of all adverse events the SCS group in the RCT of 222 patients.[6]

Sepsis was reported in 20% (4/20) of patients in the NMP group in the matched case-control study of 60 patients (the complications were not reported for the CS group).[7]

Technical complications with the perfusion system

Two different technical problems were reported during perfusion in the NMP group in the non-randomised comparative study of 36 patients. One related to occlusion of the biliary catheter in 3 patients, preventing assessment of bile production (but without long-term biliary sequelae). The second related to occlusion of the hepatic vein catheter shortly after beginning the perfusion in 1 patient (it was not used in the first 6 patients).[8]

Device error

Device error was reported once in the NMP group in the RCT of 222 patients.[6]

Device user error

Device user error was reported twice in the NMP group in the RCT of 222 patients.[6]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed the following anecdotal adverse events: marginal liver discarded because of a period of hypoperfusion during preservation. They considered that the following were theoretical adverse events: perfusion at the wrong temperature and pressure, microbiological contamination, blood borne virus transmission, inadvertent perfusion with wrong blood type, device malfunction or operator error, warm ischaemic injury when the organ comes off normothermic perfusion until circulation is established in the recipient, and damage to artery or vein during cannulation or perfusion.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to ex-vivo machine perfusion for extracorporeal preservation of livers for transplantation. The following databases were searched, covering the period from their start to 29/01/2018: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients needing liver transplantation.
Intervention/test	Ex-vivo machine perfusion for extracorporeal preservation of livers.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 772 patients from 1 randomised controlled trial[6], 7 matched case-control studies[1-4, 7, 9, 10], 2 non-randomised control studies[5, 8], and 1 case series[11].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in the appendix.

Table 2a Summary of key efficacy and safety findings on ex-vivo hypothermic machine perfusion for extracorporeal preservation of livers for transplantation

Study 1 Guarrera J V (2015)

Details

Study type	**Matched case-control study**
Country	USA
Recruitment period	2007-12
Study population and number	n=**61 (31 hypothermic machine preservation [HMP] versus 30 static cold storage [SCS])** adult patients who had extended criteria donor (ECD) livers
Age and sex (recipient)	Mean 58 years; gender not reported
Patient selection criteria	HMP inclusion criteria: adult patients between 18 and 75 years of age having isolated primary liver transplantation who met the centre's defined allocation and ECD criteria (defined as at least 1 of the following criteria: (1) donor age >65 years; (2) hepatitis C virus (HCV) positive with 15% macrosteatosis; (3) >25% macrovesicular steatosis by biopsy; or (4) evidence of significant donor ischemic injury (donor serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1000 IU/litre at the time of organ offer). In addition, livers must had been deemed ''orphan'' livers as defined by being declined by the entire originating United Network for Organ Sharing (UNOS) region or all other centres in UNOS Region. HMP exclusion criteria: dual organ recipients and patients with a Model for End-Stage Liver Disease (MELD) score of ≥35.
Technique	HMP: a modified Medtronic PBS perfusion machine and Vasosol solution were used. HMP was done for 3 to 7 hours at 4 to 8 ºC. The timing of machine perfusion initiation and removal was determined by the attending surgeon.
Follow-up	**1 year**
Conflict of interest/source of funding	JVG has received travel grants to attend scientific symposia and post-study research sponsorship from Organ Recovery Systems. All other authors have no conflicts to report.

Analysis

Follow-up issues: All patients enrolled in the trial completed the study protocol. There were no withdrawals or patients who were lost to follow-up.

Study design issues:

- Clinical data from patients in the HMP group were collected prospectively.
- The primary end points of this study were the mean incidences of primary non-function, early allograft dysfunction and vascular complications, graft and patient survival at 1 year.

Study population issues: The HMP group was compared with a 1:1 control group of 30 patients transplanted during the same time period who had SCS livers. Control subjects were matched for donor and recipient age, MELD score, donor risk index and cold ischemia times.

Other issues: The authors said: ''One limitation of our study is that in the HMP group about 40% of the total cold time was static ice time for transportation to our centre. Delayed initiation of HMP means that we may not be achieving the full potential of the technique.''

Key efficacy and safety findings

Efficacy

Number of patients analysed: **61 (31 HMP versus 30 SCS)**

Machine perfusion data

There were no technical failures or interruption of HMP in any patient.

Portal vein and hepatic artery pressures were maintained at a stable rate throughout the HMP procedure in 29/31 allografts.

Patient outcomes

Primary non-function

- HMP: 3% (1/31)
- SCS: 7% (2/30)

p=0.612

Early allograft dysfunction

- HMP: 19% (6/31)
- SCS: 30% (9/30)

p=0.384

1-year patient survival

- HMP: 84% (26/31)
- SCS: 80% (24/30)

p=0.761

1-year graft survival

- HMP: 81%
- SCS: 80%

p=NS

Hospital length of stay (days; mean±SD)

- HMP: 13.6 ± 10.9
- SCS: 20.1±11.1

p=0.001

Serum markers of liver damage and renal function (within 10 days of the surgery)

- AST, ALT, TBili and SCr were lower in HMP patients compared with SCS patients.
- HMP ALT levels at 1 day and SCr levels at 5 days were statistically significantly lower when compared with the SCS group ALT and SCr at the same time point (p=0.049 and 0.020, respectively).
- More rapid post-transplant recovery of liver and renal markers to normal laboratory reference ranges was seen in the HMP group compared with the SCS group, with SCr recovery to normal being statistically significantly faster in the HMP group (p=0.031).

Safety

No serious adverse events were deemed ‘‘probably’’ or ‘‘possibly’’ related to the HMP technique.

Postoperative complications within 1 year of the surgery

	HMP	SCS	p value
Hepatic artery thrombosis	3% (1/31)*	7% (2/30)	0.612
Portal vein thrombosis	6% (2/31)**	0	0.492
Biliary complications	13% (4/31)	43% (13/30)	**0.001**
Bile leak	3% (1/31)***	10% (3/30)	0.354
Biliary stricture	10% (3/31)	33% (10/30)	**0.031**
Reoperation for bleeding	6% (2/31)	23% (7/30)	0.081
Acute kidney injury	10% (3/31)	27% (8/30)	0.106
Incisional hernia	13% (4/31)	17% (5/30)	0.732

* It needed retransplant. This was a result of kinking in the donor artery and was deemed unrelated to the HMP procedure.

** These were treated by thrombectomy.

***The leak was treated with drainage and endoscopic retrograde cholangiopancreatography.

Abbreviations used: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NS, not statistically significant; SCr, serum creatinine; SD, standard deviation; TBili, total bilirubin.

Study 2 Dutkowski P (2015)

Details

Study type	**Matched case-control study**
Country	Hypothermic oxygenated perfusion (HOPE) DCD group: Switzerland Cold storage (CS) DCD group: The Netherlands and UK CS DBD group: Switzerland and UK
Recruitment period	HOPE DCD group: 2012-14 CS DCD group: 2005-14 CS DBD group: 2004-14
Study population and number	n=**125 (25 hypothermic oxygenated perfusion (HOPE) DCD grafts versus 50 cold storage [CS] DCD grafts versus 50 CS DBD grafts)** adult patients who had liver transplantation
Age and sex (recipient)	HOPE: Mean 60 years; 80% (20/25) male CS DCD: Mean 56 years; 70% (35/50) male CS DBD: Mean 54 years; 74% (37/50) male
Patient selection criteria	All HOPE-treated DCD livers from Zurich were matched to CS DCD livers according to the following criteria: donor warm ischemia and key confounders summarised in the balance of risk (BAR) score (donor age, recipient age, model of end-stage liver disease (MELD) score, cold storage, retransplantation, preoperative recipient life support). The liver grafts from standard brain dead donors were also matched according to the BAR score.
Technique	Hypothermic oxygenated perfusion was done after cold flush and cold storage during recipient hepatectomy, exclusively through the portal vein for 1 to 2 hours. The perfusate, used was recirculated University of Wisconsin gluconate solution which was oxygenated and cooled (10ºC) by an ECOPS device (Organ Assist). The transplant procedure was done by classic liver implantation technique in HOPE-treated livers, and by cava preserving technique (piggyback) in unperfused DCD livers.
Follow-up	**Median 448 days (HOPE DCD livers), 528 days (unperfused DCD livers) and 1530 days (DBD livers)**
Conflict of interest/source of funding	The authors declared no conflicts of interest. P.D. was supported by the Swiss National Science Foundation grant no 32003B-140776/1 and 32003B-153012/1. P.A.C. was supported by grant no 32003B-109906 of the Swiss National Science Foundation, the Clinical Research Priority Program of the University of Zurich, and the Liver and Gastrointestinal (LGID) foundation.

Analysis

Study design issues:

- Matching was done retrospectively and anonymously using SPSS software. Matching criteria limits were extended in the unperfused DCD group for 2 cases with shorter asystolic warm ischemia, in 9 cases for cold storage >8 hours, and in 3 of those cases for BAR 10, because of the lack of suitable matches.
- The primary endpoint was the incidence and severity of biliary complications within 1 year after transplantation.

Study population issues: There were statistically significant variations between groups for the following parameters: cold storage was generally shorter in HOPE-treated compared with unperfused livers; recipient age was higher in HOPE-treated DCD livers; unperfused DCD livers exhibited a shorter period of relevant hypotension before cardiac arrest, resulting in significant shorter functional donor warm ischemia in unperfused DCD livers, as compared with HOPE-treated DCD livers.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **125 (25 HOPE DCD grafts versus 50 CS DCD grafts versus 50 CS DBD grafts)**

Efficacy outcomes (median [IQR])

	HOPE DCD, (n=25)	CS DCD, (n=50)	p value
Intraoperative RBC	2 U (0–4)	2 U (0.8–6.3)	NS
Intraoperative FFP	0 U (0)	6 U (2–12)	**0.0001**
INR day 1	1.3 (1.6–2.1)	1.9 (1.1–1.6)	**0.0001**
Peak ALT	1239 U/litre (689–2126)	2065 U/litre (1331–3596)	**0.02**
Peak AST	1808 U (1133–3547)	2848 U (1485–6724)	**0.04**
Peak creatinine	154 micromol/litre (105–313)	158 micromol/litre (108–218)	NS
Renal replacement	7/25 (28%)	5/50 (10%)	NS
Peak bilirubin	44 micromol/litre (21–106)	109 micromol/litre (60–183)	**0.016**
Early graft dysfunction*	5/25 (20%)	22/50 (44%)	**0.046**
PNF	0/25	3/50 (6%)	NS
Acute rejection (>RAI 4)	3/25 (12%)	8/50 (16%)	NS
ICU stay	3 days (1.3–5.7)	3 days (2–6)	NS
Hospital stay	20 days (14–23)	18 days (15–29)	NS
3-month alkaline phosphatase	109.5 U/litre (63–740)	178 U/litre (77–415)	**0.04**
6-month alkaline phosphatase	92 U/litre (71–220)	172.5 U/litre (97–327)	**0.02**
Retransplant for IC or PNF	0/25	9/50 (18%)	**0.025**
Graft loss total	2/25 (8%)	15/50 (30%)	**0.041**
1-year graft survival**	90%	69%	**0.035**

*Early allograft dysfunction was defined by the occurrence of the following: bilirubin>170micromol/litre on day 7 after OLT, or INR>1.6 on day 7 after liver transplantation, or peak ALT>2000 U/litre within the first 7 days after liver transplantation.

**The effect of HOPE was independent from the length of cold storage as tested by regression analysis (hazard ratio 4.19; 95% CI, 0.96–18.2).

No statistically significant differences were seen in all analysed endpoints between HOPE-treated DCD livers and matched DBD livers.

Safety

Safety outcomes

	HOPE DCD, (n=25)	CS DCD, (n=50)	p value
Ischemic cholangiopathy	0/25	11/50 (22%)	0.013
Anastomotic strictures or leaks	5/25 (20%)	12/50 (24%)	**NS**
Total biliary complication	5/25 (20%)	23/50 (46%)	**0.042**
Hepatic artery thrombosis	1/25 (4%)	3/50 (6%)	NS

No statistically significant differences were seen in all analysed endpoints between HOPE-treated DCD livers and matched DBD livers.

Abbreviations used: ALT indicates alanine-aminotransferase; AST, aspartate-aminotransferase; CS, cold storage; DBD, donation after brain death; DCD, donation after cardiac death; EAD, early allograft dysfunction; FFP, fresh frozen plasma; HOPE, hypothermic oxygenated perfusion; ; IC, ischemic cholangiopathy; ICU, intensive care unit; INR, international normalised ratio; IQR, interquartile range; NS, not statistically significant; PNF, primary non-function; RAI, rejection activity index; RBC, red blood cells; U, unit.

Study 3 Guarrera J V (2010)

Details

Study type	**Matched case-control study**
Country	USA
Recruitment period	2004-08
Study population and number	n=**40 (20 hypothermic machine preservation [HMP] versus 20 cold storage [CS])** adult patients who had liver transplantation from donation after brain death
Age and sex (recipients)	HMP: Mean 55 years CS: Mean 53 years Gender not reported.
Patient selection criteria	Inclusion criteria: Adult patients between 18 and 65 years of age having isolated primary orthotopic liver transplantation with Model for End-Stage Liver Disease (MELD) scores not greater than 35 who were not in the ICU at the time of organ offer. Exclusion criteria: patients were excluded if the expected cold ischemia time was less than 4 h or if the estimated total travel time from the donor hospital was greater than 3 h. Recipients of grafts from donation after circulatory death or donors older than 65 years, or those with greater than 25% macrovesicular steatosis on biopsy, or significant liver dysfunction or ischemic injury were also excluded. Patients who met all criteria but declined to participate as HMP patients or were ruled out because of logistical reasons were identified as potential control subjects.
Technique	HMP was done for 3–7 h using centrifugal perfusion with Vasosol solution at 4–6◦C and a modified Medtronic PBS perfusion machine.
Follow-up	**1 year**
Conflict of interest/source of funding	This study was supported by Grant no. R38OT01301 from the Department of Health and Human Services (HHS), Health Resources and Services Administration (HRSA), Division of Transplantation (DoT).

Analysis

Follow-up issues: not reported.

Study design issues:

- At times logistics of the operating room ruled out enrolment as an HMP patient.
- The primary end points of this study were the mean incidences of primary non-function, early allograft dysfunction and graft and patient survival at 1 month and at 1 year.
-

Study population issues: Control subjects were matched for donor and recipient age, Model for End-Stage Liver Disease (MELD) score, and cold and warm ischemia times.

Other issues: Within the study, all livers had a certain amount of CS cold ischemic time, regardless of whether they were used for the HMP or CS groups because of transport from donor centres.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 40 (20 HMP versus 20 CS)

All 20 HMP grafts functioned immediately, with intraoperative bile production

Primary non-function: none in either group.
Early allograft dysfunction
• HMP: 5% (1/20)
• CS: 25% (5/20)
p=0.08
1-year patient and graft survival
• HMP: 90% (18/20)
• CS: 90% (18/20)
Hospital length of stay (days; mean ± SD)
• HMP: 10.9 ± 4.7
• CS: 15.3±4.9
p=0.006
Peak serum levels of markers of liver injury and renal function were statistically significantly reduced after HMP as compared with CS. Peak levels were measured at 48 h post-reperfusion for AST, ALT and INR, whereas at 5 days post-reperfusion for SCr and TBili. AST (p=0.011), ALT (p=0.044), TBili (p=0.042), SCr (p=0.013) and INR (p=0.133).

Serum markers of liver damage and renal function were lower in the HMP group over 14 days after surgery with both SCr and TBili achieving statistically significantly lower time to normalisation (days) in the HMP group (p=0.041, p=0.023, respectively) when compared with the CS group.</td><td>Postoperative complications within 1 year of the surgery
<table>
<tr><th></th><th>HMP</th><th>CS</th></tr>
<tr><td>Death with functional graft</td><td>10% (2/20)
1 cardiovascular death at 1 month and 1 pneumonia and sepsis at 3 months</td><td>10% (2/20)
1 recurrent cancer at 5 months and 1 recurrent HCV and sepsis at 7 months</td></tr>
<tr><td>Vascular complications</td><td>0</td><td>5% (1/20)
Hepatic artery stenosis</td></tr>
<tr><td>Biliary complications (total)</td><td>10% (2/20)</td><td>20% (4/20)</td></tr>
<tr><td>Early bile leak</td><td>5% (1/20)*</td><td>5% (1/20)</td></tr>
<tr><td>Biliary stricture</td><td>5% (1/20)**</td><td>15% (3/20)</td></tr>
</table>
*This was treated with drainage.
**One mild anastomotic stricture in a patient with a Roux-en-Y hepaticojejunostomy that was serially dilated and resolved.</td></tr>
<tr><td colspan="2">Abbreviations used: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CS, cold storage; HCV, hepatitis C virus; HMP, hypothermic machine preservation; INR, international normalised ratio; SCr, serum creatinine; SD, standard deviation; TBili, total bilirubin.</td></tr>
</table>

Study 4 van Rijn R (2017)

Details

Study type	**Matched case-control study**
Country	The Netherlands
Recruitment period	Intervention group: 2014 Control group: 2008-14
Study population and number	n=**30 (10 dual hypothermic oxygenated machine perfusion [DHOPE] versus 20 SCS)** adult patients who had liver transplantation from donation after circulatory death
Age and sex (recipient)	Intervention group: Median 53 years; 50% (5/10) male Control group: Median 53 years; 65% (13/20) male
Patient selection criteria	Inclusion criteria: consecutive patients (aged at least 18 years) having DCD liver transplantation with DHOPE at the authors' centre. Exclusion criteria: inability to give informed consent; high urgency status; human immunodeficiency virus positivity; pregnant or nursing; donor positive for hepatitis B or C; or an expected cold ischaemia time greater than 8 h. In the control group, for each recipient of a DHOPE-preserved graft 2 control patients were identified within a cohort of patients who had primary DCD liver transplantation between 2008 and 2014 at the authors' centre. Matching criteria were based on known risk factors for graft survival: recipient age (±5 years), donor warm ischaemia time (±5min) and MELD score (less than 22 or at least 23).
Technique	Intervention group: All livers had at least 2 h of DHOPE (active oxygenation and perfusion via both the portal vein and the hepatic artery) using the Liver Assist device (Organ Assist). Machine perfusion was done simultaneously with the recipient hepatectomy. Four litres of UW MPS, supplemented with 3 mmol/litre glutathione, were used as perfusion fluid at a temperature of 10°C. Control group: The DCD livers were preserved with conventional SCS only. Implantations were done using the piggy-back technique without use of venovenous bypass.
Follow-up	**1 year**
Conflict of interest/source of funding	The authors declared no conflict of interest.

Analysis
Study design issues:
- The twenty control patients were identified from a cohort of 64.
- All livers were allocated according to the regular Eurotransplant rules based on blood type compatibility and MELD score.
- The primary endpoint was graft survival at 6 months after transplantation.
- Graft survival was defined as the time interval between transplantation and retransplantation or death from graft failure.
- All recipients of a DHOPE-preserved liver had MR cholangiopancreatography 6 months after transplantation.

Study population issues: Donors in the DHOPE group had a statistically significantly lower BMI than donors in the control group (median 23 versus median 25, p=0.044).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **30 (10 DHOPE versus 20 SCS)**

Graft and patient survival

	DHOPE	Control	p value*
Graft survival at 6 months	100% (10/10)	80% (16/20)	0.052
Graft survival at 1 year	100% (10/10)	67%	0.052
Patient survival at 1 year	100% (10/10)	85% (17/20)	0.209

*Log rank test

Graft loss in the control group was because of hepatic artery thrombosis (1 patient), necrotic bile ducts (2) and NAS (3). Patient death in the control group was because of angiosarcoma (1 patient), pneumonia as a complication of treatment for haemophagocytic syndrome (1) and haemorrhagic shock because of intrathoracic bleeding after thoracentesis for pleural effusion.

Post-transplant hepatobiliary injury and function (median [IQR])

	DHOPE	Control	p value
Peak serum ALT at 7 days	966 units/l	1858 units/l	**0.006**
Serum bilirubin at 7 days	1.0 (0.7–1.4) mg/dl	2.6 (0.9–5.1) mg/dl	**0.044**
Median ALT at 30 days	17 units/l	51 units/l	**0.015**
Median GGT at 30 days	74 units/l	176 units/l	**0.049**
Median ALP at 30 days	115 units/l	182 units/l	**0.019**
Median bilirubin at 30 days	0.5 mg/dl	1.0mg/dl	**0.019**

Post-transplant outcomes (median [IQR])

	DHOPE	Control	p value**
Peak serum creatinine at ≤ 1week	1.4 (1.0–2.8) mg/day	1.3 (0.8–1.8) mg/day	0.373
Duration of ICU stay (days)	2 (2–6)	2 (1–5)	0.475
Duration of hospital stay (days)	22 (16–33)	23 (15–32)	0.880

**Mann–Whitney U test

Machine perfusion data

No technical problems or device malfunction occurred during machine perfusion.

Safety

Complications

	DHOPE	Control	p value***
Hypokalaemia (<3.5mEq/l) after reperfusion	3	0	0.030
Initial poor function§	0	2	1.000
Primary non-function¶	0	0	-
Relaparotomy#	3	7	1.000
Renal failure needing haemodialysis	1	2	1.000
Hepatic artery thrombosis	0	2	0.5402
Biliary complications			
Anastomotic biliary stricture	2[a]	3[b]	1.000
Biliary cast formation	3[a]	3[b]	0.372
Ischaemic cholangiopathy	1	9	0.101
Non-anastomotic biliary stricture	1[a] This was treated successfully with endoscopic stenting	7[b] Treated successfully in 4 patients; needed retransplantation in 3	0.210
Massive biliary necrosis	0	2 Both patients needed retransplantation	1.000
Retransplantation for biliary complications	0	5	0.140

***χ^2 or Fisher's exact test

§Defined based on a modification of the Olthoff criteria: international normalised ratio above 1.6 and/or serum total bilirubin level greater than 10 mg/dl on postoperative day 7.

¶Determined as retransplantation or death within 7 days of transplantation.

#Indications for relaparotomy in DHOPE group: intra-abdominal blood loss because of diffuse oozing (1); removal of surgical gauzes used for packing to control diffuse oozing during transplantation (1); and biliary anastomotic leakage (1). Indications for relaparotomy in control group: intra-abdominal blood loss because of diffuse oozing (1); removal of surgical gauzes used for packing to control diffuse oozing during transplantation (4); and biliary anastomotic leakage (2).

[a] 1 patient had a combination of anastomotic biliary stricture and biliary cast formation; 1 patient had biliary cast formation as well as non-anastomotic biliary stricture.

b 1 patient had non-anastomotic biliary stricture and later also developed an anastomotic biliary stricture; 1 patient had biliary cast formation as well as non-anastomotic biliary stricture; 2 patients had a combination of non-anastomotic biliary stricture and biliary cast formation.

Abbreviations used: ALP, alkaline phosphatase; ALT, alanine aminotransferase; DCD, donation after cardiac death; DHOPE, dual hypothermic oxygenated machine perfusion; GTT, γ-glutamyl transferase; IQR, interquartile range; MELD, model for end-stage liver disease; NAS, non-anastomotic biliary strictures; SCS, static cold storage.

Study 5 Hoyer D P (2016)

Details

Study type	**Comparative case series**
Country	Germany
Recruitment period	Intervention group: 2014 Control group: 2010-12
Study population and number	n=**112 (6 controlled oxygenated rewarming [COR] versus 106 control)** patients who had liver transplantation from DBD (marginal donors)
Age and sex	Intervention group: Median 53 years; 100% (6/6) male Control group: Median 55 years; 64% (68/106) male
Patient selection criteria	COR: Recipients with little chance of having a graft in acceptable times because of a MELD score deviant from the clinical status and not granted exceptional MELD scores. Control: historical control cohort of constant and similar transplant policies and conditions at the same centre. All consecutive adult recipients with a rescue offer organ that had cold storage and had a macrovesicular steatosis of less than 10% to match the treatment group.
Technique	COR: controlled oxygenated rewarming (10ºC increased to 20ºC) for 90 minutes before engrafting. The COR was carried out only if the planned application time of 90 minutes did not prolong the overall cold ischemic time and was conducted during anaesthesia induction and during hepatectomy of the recipient. The system used was the LiverAssist device. After COR, all livers were flushed with cold (4°C) histidine-tryptophan-ketoglutarate solution before immediate transplantation that likely reduced the temperature of the graft to approximately 14 to 16°C. The perfusate used was Custodiol-N.
Follow-up	**6 months**
Conflict of interest/source of funding	The study was supported by a local grant of the University Hospital Essen. The authors declare no conflicts of interest.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **112 (6 COR versus 106 control)** All 6 livers in the COR group had controlled rewarming without any complication, and all livers were successfully transplanted.	No treatment-associated complications leading to deviations from a typical postoperative course were witnessed in the COR group. One patient suffered from a fall (without evidence of encephalopathy or liver dysfunction) with subsequent subdural haematoma and prolonged intensive care unit and hospital stay.

Post-transplant outcomes (median [range])

	COR	Control	p value
Peak serum AST (Day 1 to Day 7)	563.5 units/litre	1204 units/litre	**0.023**
Maximal INR levels	1.48	1.87	0.07
Peak total bilirubin levels (Day 1 to Day 7)	34.2 (32.5-51.3) micromol/litre	50.5 (10.3-201.8) micromol/litre	0.18
EAD	0%	36% (38/106)	0.07
PNF	0%	3% (3/106)	0.68
ICU stay (days)	3 (2-26)	3 (0-161)	0.89
Hospital stay (days)	21.5 (14-103)	19 (0-168)	0.60

Graft and patient survival

	COR	Control	p value (logRank)
Graft survival after 6 months	100%	81%	0.24
Patient survival at 6 months	100%	85%	0.28

Abbreviations used: AST, aspartate aminotransferase; COR, controlled oxygenated rewarming; DBD, donation after brain death; EAD, early allograft dysfunction; ICU, intensive care unit; INR, international normalised ratio; MELD, model for end-stage liver disease; PNF primary non-function

Table 2b Summary of key efficacy and safety findings on ex-vivo normothermic machine perfusion for extracorporeal preservation of livers for transplantation

Study 6 Nasralla D (2018)

Details

Study type	**RCT**
Country	7 centres from the UK, Spain and Germany
Recruitment period	2014-16
Study population and number	n=**222 (121 NMP versus 101 SCS)** patients who had liver transplantation from DBD or DCD donors
Age and sex	NMP group: Median 55 years; 71% (86/121) male SCS group: Median 55 years; 73% (74/101) male
Patient selection criteria	Donors: whole livers from DBD and DCD donors at least 16 years of age. No organs were procured from prisoners. Recipients: at least 18 years of age, listed for a liver-only transplant. Patients with fulminant liver failure were excluded.
Technique	SCS group: livers were retrieved, preserved, transported and transplanted according to local standard practice. NMP: The OrganOx metra normothermic liver perfusion device was used. The perfusate contained heparinised blood, bicarbonate, antibiotics, insulin, prostacyclin, bile salts, fat-free parenteral nutrition and Gelofusine. The temperature was maintained at 37ºC. NMP duration was between 4 hours and 24 hours.
Follow-up	**1 year**
Conflict of interest/source of funding	The study was done by the consortium for organ preservation in Europe (COPE). PJF is a co-founder, CMO and consultant to OrganOx Limited and also holds shares in the company. CCC is a co-founder, chief technical officer and consultant to OrganOx Limited and also holds shares in the company.

Analysis
Follow-up issues: Daily during the first postoperative week, and at 10 days, 30 days, 6 months and 12 months, biochemical results were recorded as well as graft and patient survival data. An MRI scan of the biliary tree was done to assess evidence of biliary injury at 6 months.
Study design issues:

- 334 livers were originally randomised with 64 livers subsequently excluded. Following organ retrieval, there were 120 NMP livers (12% [16/137] had been discarded) and 100 SCS livers (24% [32/133] had been discarded) available for primary outcome reporting with 121 NMP livers and 101 SCS livers available for secondary outcome analysis. This discrepancy in group size reduced the

study power to 90%. The difference in discard rates was statistically significantly different between groups: -12.4% (95% CI -21.4 to -3.3%, p=0.008).

- 1 NMP liver was cold stored and 8 NMP livers had machine perfusion for less than 4 hours. For the per protocol sensitivity analysis, the 8 livers perfused for less than 4 hours were excluded and the single NMP liver that was preserved using SCS was reassigned to the SCS group.
- The primary endpoint was defined as the difference between the 2 treatment arms in the peak level of serum AST within 7 days after transplant.
- The study was powered to detect a 33% reduction in peak AST with 90% power at a 5% significance level, needing 110 transplanted livers per arm.
- Once an eligible donor organ was allocated to a consented recipient and the availability of the NMP device and team was confirmed, the liver was randomised with 1:1 allocation ratio as per a computer-generated randomisation schedule, using variable block size, stratified by transplant centre and donor type.

Study population issues:

- The median functional warm ischaemia time (applies to DCD livers) was longer for NMP than for SCS livers (21 minutes compared with 16 minutes, p=0.003).
- The median total preservation time was longer for NMP than SCS livers (11h54 min compared with 7h45 min, p<0.001).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **222 (121 NMP versus 101 SCS)**

Trial outcomes

	NMP (n=121)[a]	Control (n=101)[a]	Effect (95% CI)	p-value
Peak AST (primary outcome, IU/l)				
ITT				
Adjusted	488.1 (408.9-582.8)	964.9 (794.5-1,172.0)	0.5 (0.4-0.7)[c]	**0.0000**
Unadjusted	484.5 (406.4-577.6)	973.7 (795.2-1,192.3)	0.5 (0.4-0.6)[c]	**0.0000**
Test for interaction by donor type				**0.012**
Subgroup analysis by donor type				
DBD	526.2 (427.3-647.9)	880.2 (708.5-1,093.5)	40.2% (19.3-55.7%)[c]	**0.0009**
DCD	389.7 (278.0-546.4)	1,458.1 (944.7-2,250.5)	73.3% (53.7-84.6%)[c]	**0.0000**
Per protocol analysis	498.6 (414.8-599.4)	982.9 (810.4-1,192.2)	0.5 (0.4-0.7)[c]	**0.0000**
Secondary outcomes				
Discard rates[d]	11.7% (16)	24.1% (32)	Difference in proportions: -12.4 % (-21.4 to -3.3%)	**0.008**
Primary non-function[e]	0.8% (1)	0%	NA	NA

Safety

One NMP discard was the result of a **device malfunction** in an already marginal organ.

	NMP (n=121)[a]	Control (n=101)[a]	Effect (95% CI)	p-value
Need for RRT				
Day 1-7 after transplant	21% (26)	19% (19)	Difference in proportions: 2.7% (-7.9 to 13.2%)	0.621
30 days	22% (27)	20% (20)	Difference in proportions: 2.5% (-8.2 to 13.3%)	0.648
6 months	22% (27)	21% (21)	Difference in proportions: 1.5% (-9.3 to 12.4%)	0.784
Duration of RRT (day 1-7)*	4 (2-6) days	5 (4-6) days	–	0.346
Non-anastomotic biliary strictures on MRCP				
DBD	7% (4/54)	5% (3/55)		0.678
DCD	11% (3/27)	26% (5/19)		0.180
Ischemic cholangiopathy clinically relevant within 1 year**	1% (1/121)**	1% (1/101)**		
Anastomotic biliary strictures on MRCP				

Post-reperfusion syndrome	12.4% (15)	33.0% (32)	Difference in proportions: -20.6 % (-31.6 to –9.6%)	**0.0002**
Post-reperfusion lactate*	3.6 (2.6-4.2)	4.1 (3.2-5.0)	NR	**0.018**
Early allograft dysfunction	10.1% (12/119)	29.9% (29/97)	Odds ratio: 0.63 (0.126-0.550)	**0.0002**
Biochemical liver tests (median [IQR] value over day 1-7)				
Bilirubin (micromol/litre)				
Days 1-7	38.5 (21.0-73.2)	49.1 (26.0-85.5)	_	**0.029**
30 days	13.0 (8.0-22.1)	13.0 (9.1-21.0)	_	0.479
6 months	9.1 (6.0-15.1)	9.1 (6.0-13.0)	_	0.671
AST				
Days 1-7	167.5 (98.0-320.7)	318.5 (152-611.5)	_	**0.000**
30 days	20 (14-35)	22 (15-40)	_	0.707
6 months	23 (18-33)	23 (18-37)	_	0.931
ɣGT				
Days 1-7	268.1 (156.3-408.3)	301 (201.1-443.9)	_	0.157
30 days	178 (109.5-410.0)	200 (96.0-397.5)	_	0.949
6 months	47 (28-144)	47 (26-128)	_	0.452
INR				
Days 1-7	1.2 (1.2-1.4)	1.2 (1.2-1.4)	_	0.644
30 days	1.1 (1.0-1.2)	1.1 (1.0-1.2)	_	0.735
6 months	1.1 (1.0-1.2)	1.1 (1.0-1.1)	_	0.167
Creatinine (micromol/litre)				
Days 1-7	92.8 (60.1-121.1)	97.2 (67.2-143.2)	_	0.139
30 days	82.2 (66.3-104.3)	90.2 (72.5-121.1)	_	**0.019**
6 months	99.9 (81.3-117.6)	99.9 (83.1-134.4)	_	0.265
Lactate (mmol/l)				
Days 1-7	1.3 (1.0-1.7)	1.1 (0.9-1.6)	_	0.130
Other outcomes				
Length of hospital stay*	15 (10-24) days	15 (11-24) days	-	0.926
Length of ICU stay*	4 (2-7) days	4 (3-7) days	-	0.339
Graft survival at 1 year	0.950 (0.893-0.977)	0.960 (0.897-0.985)	-	0.707
DBD	41% (22/54)	42% (23/55)		0.909
DCD	48% (13/27)	58% (11/19)		0.515

**Both patients were retransplanted.

Detailed breakdown of adverse events

Event category	NMP	SCS
Infection	20% (25/128)	10% (17/164)
Hepatic	24% (44/128)	29% (48/164)
Cardiovascular	4% (5/128)	3% (5/164)
Dermatologic	1% (1/128) (Seroma)	0%
Gastrointestinal	4% (5/128)	4% (6/164)
Genitourinary	6% (8/128)	10% (17/164)
Respiratory	3% (4/128) (Pneumonia)	5% (9/164)
Bleeding complications	7% (9/128)	4% (6/164)
Fluid collection	5% (7/128)	11% (18/164)
Device error	1% (1/128)	-
Device user error	2% (2/128)	-
Other systemic diseases	13% (17/128)	23% (38/164)
Total	**128**	**164**

Patient survival at 1 year[#]	0.958 (0.902-0.982)	0.970 (0.909-0.990)	_	0.671

[a]Total number of livers transplanted and analysed overall. Primary outcome analysed on n=220 because of unavailability of AST values during the first 7 days after transplant. Specific outcomes may have different denominators because of some missing data.

[b]ITT analysis was adjusted for donor type and transplant centre.

[c]Percentage reduction from geometric mean ratio.

[d]Denominators for the discard rates were the total number of livers retrieved (n=270 [NMP, n=137; SCS, n=133])

[e]Test not done because of few events and no events in 1 arm.

*Median and IQR are reported, a non-parametric Mann-Whitney U-test was used.

[#]3 deaths in the NMP group and 2 deaths in the SCS group were because of graft failure.

Abbreviations used: AST, aspartate transaminase; DBD, donation after brain death; DCD, donation after cardiac death; ICU, intensive care unit; INR, international normalised ratio; IQR, interquartile ratio; ITT, intention to treat; MRCP, magnetic resonance cholangiopancreatography; NA, not available; NMP, normothermic machine perfusion; NR, not reported; RRT, renal replacement therapy; SCS, static cold storage

Study 7 Ravikumar R (2016)

Details

Study type	**Matched case-control study**
Country	UK (Oxford)
Recruitment period	Intervention group: 2013 Control group: 2011-13
Study population and number	n=**60 (20 consecutive normothermic machine perfusion [NMP] versus 40 CS)** adult patients who had liver transplantation from DBD or DCD
Age and sex (recipient)	Intervention group: Median 54 years Control group: Median 55 years Gender not reported
Patient selection criteria	Patients and donors in the NMP group: All adult donor organs, aged over 18 years, including DBD and DCD were potentially eligible, except those having splitting for 2 recipients. All adult recipients, aged over 18 years, were potentially eligible, except those having transplantation for fulminant liver failure or transplantation of more than 1 organ. Matched cohort (CS group): patients having transplantation of conventional CS livers at the same centres Criteria for matching: (i) graft type (DBD, DCD); (ii) donor age (within 5 years); (iii) recipient MELD score (within 2 points); (iv) recipient age (within 10 years). Matching criteria limits were extended when no suitable matches were identified.
Technique	NMP group: organs were retrieved using standard techniques, attached to the OrganOx metra liver perfusion device at the donor hospital, and transported to the implanting centre in a functioning. The livers were stored at 37ºC. The perfusate contained heparinised blood, bicarbonate, calcium gluconate, cefuroxime and Gelofusine. Before implantation, perfusion was stopped and the liver was cooled by rapid perfusion of 2 L of cold HTK solution. Postoperative management was conducted according to standard local protocols, which included tacrolimus-based immunosuppression. Control group: conventional cold storage.
Follow-up	**1 year**
Conflict of interest/source of funding	The funder for this study, OrganOx Ltd, is also the Sponsor. The members of the research team who were responsible for the organ perfusions all have associations with the device manufacturer (P.F. and C.C.) in addition to being full-time academics at the University of Oxford, receive consultancy payments as non-executive medical and technical directors of OrganOx, and are shareholders. R.R., D.H., and T.V. received consultancy income from OrganOx for assisting with the design and testing of the normothermic liver perfusion device and for carrying out normothermic organ preservation out-of-hours. All clinical data were acquired as part of an MHRA-regulated Phase-1 clinical study, and none of the clinicians who were responsible for organ selection, transplantation, and patient management (W.J., H.M., T.P., D.M., N.H., A.Q.) have any conflicts of interest to disclose.

Analysis
Study design issues: The primary end-point was 30-day graft survival.
Study population issues:

- NMP group: 10 donor livers were within standard criteria and the other 10 donor livers were specifically selected as high-risk, using criteria based on the Eurotransplant Donor Risk Index. Sixteen livers (80%) were from DBD and 4 (20%) were from DCD donors. The indication for transplantation was chronic liver failure except in 1 recipient who had retransplantation for hepatic artery thrombosis.
- Control group: matching criteria were extended in 4 patients.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **60 (20 NMP versus 40 CS)**

There were no device failures leading to organs not being transplanted.

Median NMP time: 9.3 hours

Clinical outcomes

	NMP (n=20)	Control (n=40)	Risk ratio/effect size (95% CI)	p-value
30-day graft survival	100% (20/20)	98% (39/40)	1.03 (0.98–1.08) RR	1.00
PNF	0	0	_	1.00
EAD*	15% (3/20)	23% (9/40)	0.67 (0.20–2.19) RR	0.734
Peak AST within 7 days (IU/L), median (range)	417 (84–4681)	902** (218–8786)	-0.44 (-0.98 to 0.11) ES	**0.034**
Bilirubin on day 7 (micromol/litre), median (range)	25 (8–211)	30** (9–221)	-0.23 (-0.77 to 0.32) ES	0.203
INR on day 7, median (range)	1.05 (0.88–1.40)	1.03 (0.90–2.22)**	-0.16 (-0.70 to 0.38) ES	0.922
ALP on day 7 (U/L)	245 (81–568)	243 (76–743)**	-0.11 (-0.65 to 0.43) ES	0.798
ITU stay (days), median (range)	3 (1–8)	3 (1–41)**	-0.42 (-0.96 to 0.13) ES	0.459
Hospital stay (days), median (range)	12 (6–34)	14 (8–88)**	-0.44 (-0.98 to 0.11) ES	0.100
30-day mortality (%)	0	3% (1/40)		1.000
6-month survival	100% (20/20)	98% (39/40)	1.03 (0.98–1.08) RR	1.000
1-year survival	95% (19/20)***	_	_	_

* EAD was defined by the occurrence of 1 or more of: bilirubin >170 micromol/litre on day 7 post-transplant; INR >1.6 on day 7 post-transplant; peak AST >2000 IU/litre within the first 7 days post-transplant.

** n=39 as there was 1 death on day 0 from a cardiovascular event.

*** The death was from alcohol recidivism at 9 months.

Safety

Complications in the NMP group

	Number of patients	Treatment
Anastomotic biliary stricture	20% (4/20)	Stent
Vascular complications	0	
Postoperative hepatic parenchymal infarcts	5% (1/20)	They resolved spontaneously
Non-cirrhotic portal hypertension with ascites	5% (1/20)	_
Sepsis	20% (4/20)	_
Diabetes	5% (1/20)	_
Death	5% (1/20)	_
CMV contamination by donor	5% (1/20)	_

Abbreviations used: ALP, alkaline phosphatase; AST, aspartate aminotransferase; CI, confidence interval; CMV, cytomegalovirus; CS, cold storage; DBD, donation after brain death; DCD, donation after cardiac death; EAD, early graft dysfunction; ES, effect size; INR, international normalised ratio; ITU, intensive therapy unit; MELD, model for end-stage liver disease; NMP, normothermic machine perfusion; RR, relative risk; PNF, primary non-function.

Study 8 Watson C J E (2017)

Details

Study type	**Non-randomised comparative study**
Country	UK (Cambridge)
Recruitment period	Not reported
Study population and number	n=**36 (12 normothermic ex situ machine perfusion [NMP] recipients of declined livers versus 24 non-NMP recipients of non-declined livers)** who had livers from DBD or DCD
Age and sex	Intervention group: Median 57 years Control group: Median 54 years Gender not reported
Patient selection criteria (recipient)	NMP group: Routine national and zonal liver offers, and those offered through the UK fast-track liver offering scheme, were considered. Livers that had been offered directly for research were also considered. NMP was considered where there was uncertainty about the liver such that the recipient hepatectomy could not start before visualising the liver, and the prolongation of cold ischemic time that this imposed would have deleterious consequences on the liver. Livers were offered to the highest priority patient of suitable size and blood group match who had previously consented for a liver of that type and separately consented for it to have NMP. Non-NMP group: all other fast-track recipients in the study period along with livers transplanted immediately before and after each NMP case of similar type (DBD/DCD).
Technique	NMP group: NMP was done after a cold storage period, using a Liver Assist device (Organ Assist). The perfusate comprised red cells with either succinylated gelatin or Steen solution (Xvivo Perfusion) supplemented with sodium bicarbonate, heparin, antibiotics, calcium chloride, magnesium sulphate, and amino acids (Aminoven-25, Fresenius Kabi Ltd). NMP was commenced at 20°C, and the circuit warmed to 37°C over 20 to 30 minutes.
Follow-up	**1 year**
Conflict of interest/source of funding	The research was funded in part by Addenbrooke's Charitable Trust and in part by the National Institute for Health Research Blood and Transplant Research Unit (NIHR BTRU) in Organ Donation and Transplantation at the University of Cambridge in collaboration with Newcastle University and in partnership with NHS Blood and Transplant (NHSBT). One of the authors is a joint holder of a patent on the design of the perfusion circuit used by the OrganOx metra liver perfusion device. Another author is now an employee of OrganOx. The other authors declare no other conflicts of interest.

Analysis

Study population issues:

- In the NMP group, there were 9 donations after circulatory death and 3 from brain-dead donors.
- The first 6 livers were perfused at high perfusate oxygen tensions, and the subsequent 6 at near-physiologic oxygen tensions as the perfusion technique used in the first 6 livers was associated with damage from reactive oxygen species.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **36 (12 NMP declined livers versus 24 non-NMP non-declined livers)**

Median NMP time: 4.7 hours

Efficacy outcomes

	NMP	Non-NMP
Peak ALT in first 7 days: median (range), IU/L	1069 (187-4991)	787 (155-2238)
Actual graft survival (median follow up 12 months; range, 9-24)	83% (10/12)	88% (21/24)
Actual patient survival (median follow-up 12 months; range, 9-24)	92% (11/12)	96% (23/24)

Safety

Technical outcomes

There were 2 technical problems during perfusions. One related to occlusion of the biliary catheter in 3 patients, preventing assessment of bile production (but without long term biliary sequelae). The second related to occlusion of the hepatic vein catheter shortly after beginning the perfusion in 1 patient; it was not used in the first 6 patients.

Complications

	NMP	Non-NMP
Post-reperfusion syndrome* incidence	83% (5/6) hyperoxic NMP 0% (0/6) normoxic NMP	25% (6/24)
Vasoplegia incidence**	67% (4/6) hyperoxic NMP 0% (0/6) normoxic NMP	21% (5/24)
Cholangiopathy (ignoring patient who died day 2)	27% (3/11)	29% (7/24)

* Post-reperfusion syndrome was defined as a fall in mean arterial pressure within 5 minutes of reperfusion in the recipient to less than 70% of the baseline value in the last 5 minutes of the anhepatic period.

** Vasoplegia was defined as a fall in mean arterial pressure on reperfusion to less than 50 mm Hg either sustained longer than 30 minutes and/or needing greater than 0.15 microgram/kg per minute norepinephrine, greater than 2 U/h argipressin, or infusion of epinephrine.

One patient in the NMP group **died** at 2 days from a difficult hepatectomy complicated by coagulopathy and severe haemorrhage, with a 28-L blood loss before implantation. The liver suffered **primary non-function**, and the patient died despite urgent retransplantation.

Abbreviations used: ALT, alanine aminotransferase; DBD, donation after brain death; DCD, donation after cardiac death; ; NMP, normothermic machine perfusion;

Study 9 Bral M (2017)

Details

Study type	**Matched case-control study**
Country	Canada
Recruitment period	Intervention group: 2015 Control group: over 36 months before 2015
Study population and number	n=**40 (10 normothermic machine perfusion [NMP] versus 30 static cold storage [SCS])** patients who had liver transplantation from DCD or DBD
Age and sex (recipients)	Intervention group: Median 53 years Control group: Median 59 years Gender not reported
Patient selection criteria	Deceased donors (≥40 kg in weight) were included in both groups. All DCD livers were procured with <30 min of warm ischemia. Living donors and livers intended for split transplant were excluded. Recipient participants with end-stage chronic non-fulminant liver disease were included. Patients having retransplantation or transplantation of other organs were excluded. SCS: patients were selected from a pool of 150 adult deceased donor liver transplants at the University of Alberta over the previous 36 months based on closest matching for (i) recipient Model for End-Stage Liver Disease (MELD) score, (ii) donor risk index (DRI), (iii) donor age, (iv) recipient age, and (v) graft type (DBD versus DCD).
Technique	NMP: the livers were preserved using he OrganOx metra system. Machine perfusate consisted of 500 mL of Gelofusine (B. Braun) and 3 U of type O packed red blood cells. All livers were procured in standard fashion, flushed in situ with histidine–tryptophan–ketoglutarate solution (HTK; Custodiol HTK; Methapharm), prepared, and cannulated on a “back table” at the donor hospital. Surgical implantation techniques were identical between NMP and SCS groups.
Follow-up	**6 months**
Conflict of interest/source of funding	None of the clinicians responsible for organ selection, organ perfusion, transplantation, and patient care had any conflicts of interest to disclose. Collaborative members of the OrganOx Ltd. team (L.R., C.C., P.F.) held relevant patents, were involved with device manufacture, or received consultancy support from OrganOx Ltd.

Analysis

Follow-up issues:

- All participants who had DCD liver grafts underwent magnetic resonance cholangiopancreatography (MRCP) at 6 months to rule out the presence of non-anastomotic biliary strictures secondary to ischemic cholangiopathy.
- In the NMP group, 10 liver grafts were procured, 9 of which were successfully perfused using NMP and transplanted. One liver from a 60-year-old DCD donor was procured and cannulated for NMP but was promptly discarded because of an occult portal venous twist that retracted into the liver hilum, preventing perfusion.

Study design issues:

- The primary objective was to assess safety of NMP in continuous liver preservation, with the primary outcome measure being graft survival at day 30 after transplant.
- NMP duration was determined by the recipient surgeon based on logistics surrounding the transplant

Study population issues: In the NMP group, 4 grafts (40%) were from DCD donors (Maastricht category III), and 6 (60%) were from DBD donors. In the SCS group, 27% (8/30) of grafts were from DCD donors.

Other issues: The authors noted: ‘’ The cold ischemic times taken to complete back-table preparation, cannulation, and complex arterial reconstructions were considerable (median 2 h 47 min) and likely offset the potential benefit of NMP technology in the present study.’’

Key efficacy and safety findings

Efficacy

Number of patients analysed: **40 (10 NMP versus 30 SCS)**

For the 9 livers perfused successfully, there were no technical complications during NMP.

Median NMP time: 11.5h (1 DCD liver was perfused for 22.5 h)

Efficacy outcomes

	NMP	SCS	p value
Intent-to-treat graft survival, n	10	30	_
30-day graft survival, intent to treat	90% (9/10)	100% (30/30)	0.25
6-month graft survival, intent to treat	80% (8/10)	100% (30/30)	0.06
Recipient outcomes for transplanted grafts per protocol, n	9	27	_
Peak AST, days 1–7, U/L, median (range)	1252 (383 to >2600)	839 (153 to >2600)	0.52
Bilirubin day 7, median (range)	79 (17–344)	53 (8–340)	0.35
INR day 7, median (range)	1.1 (1.1–1.6)	1.1 (0.9–1.5)	0.44
PNF	0% (0/9)	0% (0/27)	_
EAD	56% (5/9)	30% (8/27)	0.23
ICU stay, days, median (range)	16 (2–65)	4 (1–29)	**0.004**
Hospital stay, days, median (range)	45 (13–114)	25 (9–89)	**0.01**
30-day patient survival per protocol	100% (9/9)	100% (27/27)	_
6-month patient survival per protocol	89% (8/9)	100% (27/27)	0.25

Safety

Safety outcomes for transplanted grafts per protocol, n

	NMP	SCS	p value
Major complications (Clavien-Dindo ≥3)	22% (2/9)	37% (10/27)	0.69
6-month biliary complications	0% (0/8)	15% (4/27)	0.55

In the NMP group, complications included:

- 1 **reoperation for intra-abdominal bleeding**
- 1 **patient with renal insufficiency** needing transient haemodialysis.
- 1 NMP graft developed **early aggressive cholestatic hepatitis secondary to uncontrolled recurrent hepatitis C infection**; the recipient was unable to access pre-emptive sofosbuvir and ledipasvir and died at 3 months after transplant.

Abbreviations used: AST, aspartate aminotransferase; DBD, donation after brain death; DCD, donation after cardiac death; EAD, early allograft dysfunction; ICU, intensive care unit; INR, international normalised ratio; MELD, Model for End-stage Liver Disease; NMP, normothermic machine perfusion; PNF, primary non-function; SCS, static cold storage

Study 10 Selzner M (2016)

Details

Study type	**Matched case-control study**
Country	Canada
Recruitment period	Intervention group: 2015 Control group: 2005-15
Study population and number	n=**40 (10 normothermic machine perfusion [NMP] versus 30 cold storage [CS])** patients who had liver transplantation from DCD or DBD
Age and sex (recipient)	Intervention group: Median 56 years Control group: Median 54 years Gender not reported
Patient selection criteria	NMP group: all deceased donor full-size grafts (from heart-beating donation [HBD] or DCD) that were within a 2-hour drive to the institution were eligible for inclusion in this study. Recipients participating in the study had to be 18 years of age or older and had provided written informed consent before the organ offer. Recipient candidates waiting for multiple organ transplants, patients with fulminant liver failure, or retransplantation were excluded from the study. Control group: retrospectively matched 3:1 based on stepwise matching for 30-day survival, donor age, recipient medical Model for End-Stage Liver Disease (MELD) score, and donor type (DCD versus DBD). Recipients with retransplantation, multiorgan transplants, or fulminant hepatic failure were excluded.
Technique	NMP was done with Steen solution and red blood cells, using the Metra device. The perfusion temperature was maintained at 37 ºC during the entire perfusion. The donor liver was procured in the usual technique and flushed in situ with cold HTK solution. Static CS was done with HTK or University of Wisconsin solution.
Follow-up	**3 months**
Conflict of interest/source of funding	None reported

Analysis

Follow-up issues: In the NMP group, 12 livers were procured and 10 underwent transplantation.

Study population issues: In the NMP group, 2 grafts (20%) were from DCD donors, and 8 (80%) were from DBD donors. In the SCS group, 20% (6/30) of grafts were from DCD donors

Key efficacy and safety findings

Efficacy

Number of patients analysed: **40 (10 NMP versus 30 CS)**

Median NMP time: 8 hours

No problems occurred during machine perfusion and transport.

Graft function and injury after transplantation (median [range])

	NMP (n=10)	CS (n=30)	p value
ALT peak 48 hours, U/L	619 (55-2858)	949 (233-3073)	0.55
INR peak	2.6 (2-4.4)	2.7 (1.7-5.8)	0.61
INR 1 week	1.1 (1-1.56)	1.1 (1-1.3)	0.47
INR 3 months	1 (1-2)	1 (1-2)	0.91
Bilirubin 1 week, mg/dL	1.5 (1.0-7.7)	2.78 (0.4-15)	0.49
Bilirubin 3 month, mg/dL	0.4 (0.2-0.8)	0.6 (0.2-18)	0.21
ALP 1 week, U/L	202 (96-452)	147 (87-456)	0.21
ALP 3 months, U/L	111 (101-136)	132 (54-657)	0.33
Creatinine 1 week, mg/dL	1.0 (0.5-2.0)	0.9 (0.5-2.3)	0.76
Creatinine 3 months, mg/dL	1.1 (0.9-2.4)	1.1 (0.3-1.8)	0.53

Efficacy outcomes (median [range])

	NMP (n=10)	CS (n=30)	p value
ICU stay, days	1 (0-8)	2 (0-23)	0.54
Stepdown unit stay, days	3 (1-8)	3 (1-32)	0.3
LOH after LT, days	11 (8-17)	13 (7-89)	0.23
Fast-tracked patients (no ICU after transplantation)	3 (30)	5 (17)	0.5

Safety

Complications

	NMP (n=10)	CS (n=30)	p value
Minor complications (Dindo-Clavien<3b)	60% (6/10)	53% (16/30)	0.8
Major complications (Dindo-Clavien≥3b)	10% (1/10)*	23% (7/30)**	0.5
Graft loss at 3 months	0	0	–
Patient death at 3 months	0	0	–

*The patient developed a severe **pneumonia** post-transplant needing reintubation and ventilation for 3 days. Following extubation the patient recovered without further problems.

**The complications included gastrointestinal bleeding, intra-abdominal abscess, bile duct stricture, and intra-abdominal bleeding.

Abbreviations used: ALP, alkaline phosphatase; ALT, alanine aminotransferase; CS, cold storage; DBD, donation after brain death; DCD, donation after cardiac death; HTK, histidine tryptophan ketoglutarate; INR, international normalised ratio; LOH, length of hospital stay; NMP, normothermic machine perfusion.

Study 11 Mergental (2016)

Details

Study type	**Case series**
Country	UK (Birmingham)
Recruitment period	2014 (?)
Study population and number	n=**6 consecutive NMP** recipients of declined livers who had liver transplantation from DCD or DBD
Age and sex (recipient)	Median 56 years; gender not reported
Patient selection criteria	Graft inclusion criteria: Cold ischemic times less than 16 h for livers from DBD, or less than 10 h from DCD, donor warm ischemic time in DCD organs less than 60 min, absence of hepatitis B, hepatitis C, or human immunodeficiency virus infection, a macroscopic appearance without fibrosis or cirrhosis, and maximum donor age of 65 years.
Technique	The rejected livers were assessed for viability by NMP within 3 h of perfusion. The evaluation protocol consisted of perfusate lactate level, bile production, vascular flows, and liver appearance. The perfusate included packed red blood cells with 5% albumin solution. All livers were exposed to a variable period of static cold storage before commencing NMP. 2 systems were used for NMP: Liver Assist (n=5) and OrganOx metra (n=1). Recipients considered for this study had low surgical perioperative risk. Patients with hepatocellular carcinoma, with a high risk of waiting list dropout because of tumour progression, were regarded as favourable recipients.
Follow-up	**Mean 6 months**
Conflict of interest/source of funding	None reported

Analysis

Follow-up issues:

- Following discharge from the hospital, patients were reviewed in the outpatient clinic weekly (first month) and then every 2 weeks (second to third month).

Study population issues:

- Four livers were recovered from DCD and 2 from DBD donors.
- This small group of livers did not include any organs with moderate or severe macrosteatosis, a key risk factor for initial graft dysfunction/primary non-function.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 6 NMP

Five out of 6 livers met the viability criteria and were used for transplantation.

The transplant procedure was uneventful in every recipient, with immediate function in all grafts.

Patient outcomes
<table>
<tr><th></th><th>NMP (n=5)</th></tr>
<tr><td>Median intensive therapy unit stay</td><td>3 (range 2–6) days</td></tr>
<tr><td>Median in-hospital stay</td><td>10 (range 6–15) days</td></tr>
<tr><td>EAD</td><td>0/5</td></tr>
<tr><td>Liver function tests</td><td></td></tr>
<tr><td>Peak ALT (IU/L)</td><td>Range (1188 to 1879)</td></tr>
<tr><td>Peak bilirubin (micromol/litre)</td><td>Range (87 to 167)</td></tr>
<tr><td>ALT (IU/L) at 3 months</td><td>Range (8 to 29)</td></tr>
<tr><td>Bilirubin (micromol/litre) at 3 months</td><td>Range (5 to 21)</td></tr>
<tr><td>ALP (IU/L) at 3 months</td><td>Range (63 to 135)</td></tr>
<tr><td>Creatinine (micromol/litre) at 3 months</td><td>Range (77 to 147)</td></tr>
</table></td><td>1 patient developed acute coronary syndrome 8 days following surgery. It was treated with percutaneous coronary intervention with stent insertion.

Renal replacement therapy: 20% (1/5)</td></tr>
<tr><td colspan="2">Abbreviations used: ALT, ALT, alanine aminotransferase; ALP, alkaline phosphatase; DBD, donation after brain death; DCD, donation after cardiac death; EAD, early allograft dysfunction; NMP, normothermic machine perfusion.</td></tr>
</table>

Validity and generalisability of the studies

- One recently published European RCT6 was included in Table 2. Most of the other studies were matched case-control studies.
- The longest follow-up was 448 days (in study 2).
- The studies were grouped according to the type of machine preservation used (hypothermic or normothermic).
- The liver grafts transplanted were from donors who were braindead or from donation after cardiac death. In some of the studies, the liver grafts transplanted had previously been declined for transplantation.
- In the hypothermic machine preservation studies, single oxygenated perfusion or dual hypothermic oxygenation were used in some of the studies.
- The machine preservation devices were used for preservation or evaluation of the graft before transplantation.
- Four of the studies included were from the UK.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Living-donor liver transplantation. NICE interventional procedures guidance 535 (2015). Available from http://www.nice.org.uk/guidance/ipg535

Technology appraisals

- Everolimus for preventing organ rejection in liver transplantation. NICE technology appraisal 348 (2015). Available from http://www.nice.org.uk/guidance/ta348

NICE guidelines

- Organ donation for transplantation: improving donor identification and consent rates for deceased organ donation. NICE clinical guideline 135 (2011). Available from http://www.nice.org.uk/guidance/cg135

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. 9 Specialist Advisor Questionnaires for ex-vivo machine perfusion for extracorporeal preservation of livers for transplantation were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 4 companies who manufacture a potentially relevant device for use in this procedure. NICE received 3 completed submissions. These were considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing trials

- A Multicentre, Single-arm, Prospective Clinical Trial to Investigate the Safety and Feasibility of Cold Storage Prior to Normothermic Machine Perfusion in Adult Human Liver Transplantation NCT03176433 – Device: OrganOx Metra. Estimated completion date: 31/07/2018. Sponsor: University of Oxford. Estimated enrolment: 30.

- Assessing the Safety and Efficacy of a Portable Ex Vivo Oxygenated, Normothermic Liver Perfusion System (OrganOx Metra™) Prior to Liver Transplantation. NCT03089840 - Device: OrganOx Metra. Estimated completion date: January 2020. Sponsor: University of Alberta. Estimated enrolment: 50.

- An Open Label, Non-randomised, Prospective, Single Arm, 2-part Trial, Using Normothermic Machine Liver Perfusion NMLP to Test Viability and Transplantation of Marginal Livers. VITTAL study. NCT02740608 – Device: OrganOx Metra. Estimated completion date: January 2020. Sponsor: University of Birmingham. Estimated enrolment: 50.

- A Single Centre Study of the Feasibility and Safety of Using Ex-vivo Normothermic Machine Perfusion With the Organox Metra™ Device to Store Human Livers for Transplantation. NCT02478151 – Device: OrganOx Metra. Estimated completion date: April 2019. Sponsor: University Health Network, Toronto. Estimated enrolment: 40.

- Controlled oxygenated rewarming of liver grafts by ex-situ machine perfusion prior to transplantation. (CORAL) ISRCTN15686690. Ongoing. Single-center randomized controlled clinical pilot study with two parallel arms. Estimated completion date: October 2019. Sponsor: University of Duisburg-Essen (Germany).

- A Multicenter Randomized Controlled Trial to Compare the Efficacy of End-ischemic Dual Hypothermic Oxygenated Perfusion With Standard Static Cold Storage of Liver Grafts Donated After Circulatory Death in Preventing Biliary Complications. NCT02584283. Device: Liver Assist. Estimated completion date: October 2019. Sponsor: University Medical Center Groningen. Estimated enrolment: 156.

- Pilot, Open, Monocentric, Randomized, Prospective Trial for the Evaluation of the Efficacy of Normothermic Perfusion Machine for Organ Preservation in Liver Transplantation Using Brain Death Donors Older or Equal Than 70 Years. NCT02940600. Device: Liver Assist. Estimated completion date: April 2018. Sponsor: Azienda Ospedaliero, Universitaria Pisana. Estimated enrolment: 30.

- A Phase I Pilot Study to Assess Safety and Feasibility of Normothermic Machine Preservation In Human Liver Transplantation NCT02515708. Device: Normothermic Liver perfusion Device. Estimated completion date: September 2019. USA. Estimated enrolment: 25

- Hypothermic Oxygenated Machine Perfusion (HOPE) for Liver Transplantation of Human Liver Allografts From Extended Criteria Donors (ECD) in Donation After Brain Death (DBD); a Prospective Multicenter Randomized Controlled Trial (HOPE ECD-DBD) NCT03124641. Estimated completion date: June 2019. University Hospital, Aachen. Estimated enrolment: 46

- A Multicenter Randomized Controlled Trial to Compare the Efficacy of Ex-vivo Normothermic Machine Perfusion With Static Cold Storage in Human Liver Transplantation NCT02775162. Estimated primary completion date: March 2018. Sponsor: OrganOx. USA. Estimated enrolment: 266

- A Double Blinded Randomized Study on the Effects of Hypothermic Oxygenated Perfusion (HOPE) on Human Liver Grafts Before Transplantation NCT01317342. Estimated completion date: April 2019. Sponsor: University of Zurich. Estimated enrolment: 70

- Post-Static Cold Storage Hypothermic Oxygenated Perfusion in Bergamo Liver Transplant Program: a Prospective Observational Study NCT03098043. Estimated completion date: April 2020. Italy. Estimated enrolment: 20

- TransMedics (OCS) Liver Trial: Preserving and Assessing Donor Livers for Transplantation (Liver PROTECT) NCT02522871. RCT. Estimated completion date: December 2020. USA. Estimated enrolment: 300

References

1. Guarrera J V, Henry S D, Samstein B et al. (2015) Hypothermic machine preservation facilitates successful transplantation of "orphan" extended criteria donor livers. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 15(1), 161-9
2. Dutkowski P, Polak W G, Muiesan P et al. (2015) First Comparison of Hypothermic Oxygenated PErfusion Versus Static Cold Storage of Human Donation After Cardiac Death Liver Transplants: An International-matched Case Analysis. Annals of surgery 262(5), 764-1
3. Guarrera J V, Henry S D, Samstein B et al. (2010) Hypothermic machine preservation in human liver transplantation: the first clinical series. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 10(2), 372-81
4. van Rijn R, Karimian N, Matton A P. M et al. (2017) Dual hypothermic oxygenated machine perfusion in liver transplants donated after circulatory death. The British journal of surgery 104(7), 907-917
5. Hoyer D P, Mathe Z, Gallinat A et al. (2016) Controlled oxygenated rewarming of cold storer livers prior to transplantation: first clinical application of a new concept. Transplantation 100: 147–152
6. Nasralla D, Coussios C, Mergental H et al. (2018) A randomized trial of normothermic preservation in liver transplantation. Nature doi:10.1038/s41586-018-0047-9 [Epub ahead of print]
7. Ravikumar R, Jassem W, Mergental H et al. (2016) Liver transplantation after ex vivo normothermic machine preservation: a phase 1 (first-in-man) clinical trial. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 16(6), 1779-87
8. Watson C J E, Kosmoliaptsis V, Randle L V et al. (2017) Normothermic perfusion in the assessment and preservation of declined livers before transplantation: hyperoxia and vasoplegia—important lessons from the first 12 cases. Transplantation 101: 1084–1098
9. Bral M, Gala-Lopez B, Bigam D et al. (2017) Preliminary single-center Canadian experience of human normothermic ex vivo liver perfusion: results of a clinical trial. American Journal of Transplantation 17(4), 1071-1080
10. Selzner M, Goldaracena N, Echeverri J et al. (2016) Normothermic ex vivo liver perfusion using steen solution as perfusate for human liver

transplantation: First North American results. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 22(11), 1501-1508

11. Mergental H, Perera M T. P. R, Laing R W et al. (2016) Transplantation of declined liver allografts following normothermic ex-situ evaluation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 16(11), 3235-3245

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	29/01/2018	Issue 1 of 12, January 2018
HTA database (Cochrane)	29/01/2018	Issue 4 of 4, October 2016
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane)	29/01/2018	Issue 12 of 12, December 2017
MEDLINE (Ovid)	29/01/2018	1946 to Present with Daily Update
MEDLINE In-Process (Ovid)	29/01/2018	January 26, 2018
MEDLINE Epubs ahead of print (Ovid)	29/01/2018	January 26, 2018
EMBASE (Ovid)	29/01/2018	1974 to 2018 January 26
BLIC (British Library)	29/01/2018	n/a

Trial sources searched 19th October 2017

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched 19th October 2017

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan

General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Liver Transplantation/
2 ((hepat* or liver*) adj4 (transplant* or graft* or allograft* or donor* or donat*)).tw.
3 or/1-2
4 exp Liver Diseases/

5 liver/
6 (Liver* adj4 (disease* or failure* or cirrhosis* or neoplasm* or cancer* or dysplas* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or blastoma* or sarcoma*)).tw.
7 Hepatiti*.tw.
8 (Hep adj4 (B or C)).tw.
9 exp Cholangitis, Sclerosing/
10 (Primary* adj4 scleros* adj4 cholangit*).tw.
11 (PSC or PBC).tw.
12 Biliary Atresia/
13 (Biliar* adj4 atresia*).tw.
14 or/4-13
15 organ preservation/
16 perfusion/
17 ((Subnormotherm* or normotherm* or hypotherm* or subhypotherm* or oxygen*) adj4 perfus* adj4 (machine* or device* or preserv*)).tw.
18 (HMP or NMP or NELP).tw.
19 (("ex vivo" or ex-vivo or "ex situ" or ex-situ or extracorp*) adj4 perfus* adj4 (machine* or device* or preserv*)).tw.
20 ((hepat* or portal* or venous* or arterial*) adj4 perfus* adj4 (machine* or device*)).tw.
21 or/15-20
22 3 and 14 and 21
23 (organox or lifeport or "OCS liver protect" or "organ care system").tw.
24 22 or 23
25 animals/ not humans/
26 24 not 25

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Hypothermic machine perfusion			
De Carlis R, Di Sandro S , Lauterio A et al (2017) Successful donation after cardiac death liver transplants with prolonged warm ischemia time using normothermic regional perfusion. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 23(2), 166-173	Case series n=7 normothermic regional perfusion (NRP) + HMP in 5 selected patients Mean FU=6 months	DCD liver transplantation is feasible in Italy despite the protracted no-touch period. The use of NRP and HMP seems to earn good graft function and proves safe in these organs.	Studies with more patients or longer follow-up are included.
Dutkowski P, Schlegel A, de Oliveira M et al. (2014) HOPE for human liver grafts obtained from donors after cardiac death. Journal of hepatology 60(4), 765-72	Case series n=8 HOPE Median FU=8.5 months	This is the first report on cold machine perfusion of human liver grafts obtained after cardiac arrest and subsequent transplantation. Application of HOPE appears well tolerated, easy-to-use, and protective against early and later injuries.	The patients included in this study had most likely also been included in the Dutbowski (2015) paper which is in Table 2.
Normothermic machine perfusion			
Angelico R, Perera MT, Ravikumar R et al. (2016) Normothermic Machine Perfusion of Deceased Donor Liver Grafts Is Associated With Improved Postreperfusion Hemodynamics. Transplant Direct. 5;2(9):e97.	Matched case-control study n=18 (6NMP versus 12 CS) FU=intraoperative	Normothermic machine perfusion is associated with a stable intraoperative hemodynamic profile post-reperfusion, needing significantly less vasopressor infusions and blood product transfusion after graft reperfusion and may have benefit to alleviate ischemia-reperfusion injury in liver transplantation.	Studies with more patients or longer follow-up are included.
Pezzati D, Ghinolfi D, Balzano E et al. (2017) Salvage of an Octogenarian Liver Graft Using Normothermic Perfusion: A Case Report. Transplant Proc. 49(4):726-728.	Case report n=1 NMP FU=4 months	During machine perfusion lactates decreased, vascular flow was stable, and bile production restored, and the graft was considered suitable for transplantation. The postoperative course was	Studies with more patients or longer follow-up are included.

doi:10.1016/j.transproceed.2017.02.014.		uneventful and 4 months after surgery the patient is in good clinical condition with normal liver function. To date, few liver transplants have been done with NMP in humans, but its preliminary results are promising. NMP allows functional evaluation of the graft and possibly reduction of post-transplantation complications when extended-criteria donor grafts are used.	
Watson CJ, Kosmoliaptsis V, Randle LV et al. (2016) Preimplant Normothermic Liver Perfusion of a Suboptimal Liver Donated After Circulatory Death. Am J Transplant. 2016 Jan;16(1):353-7. doi: 10.1111/ajt.13448. Epub 2015 Sep 22.	Case report n=1 NMP FU=6 months	After transplantation, the patient made an uneventful recovery and was discharged on day 8; liver biochemistry was normal by day 19 and has remained normal thereafter. Preimplant ex situ normothermic perfusion of the liver appears to be a promising way to evaluate a marginal liver before transplantation and may modify the response to ischemia.	Studies with more patients or longer follow-up are included.