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Horizon scanning report

Molecular adsorbents recirculating system (MARS®): A haemo-dialysis and haemo-filtration device for acute liver failure.

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Enquiries about the content of the report should be directed to:

HealthPACT Secretariat
Department of Health and Ageing
MDP 106
GPO Box 9848
Canberra ACT 2606
AUSTRALIA

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The production of this *Horizon scanning report* was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

This *Horizon scanning report* was prepared by Ms Linda Mundy, Ms Tracy Merlin, Dr Annette Braunack-Mayer and Professor Janet Hiller from the National Horizon Scanning Unit, Adelaide Health Technology Assessment, Department of Public Health, Mail Drop 511, University of Adelaide, Adelaide, South Australia, 5005.

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Executive Summary

MARS® is intended to treat acute liver failure (ALF) or acute-on-chronic liver failure (AoCLF). In ALF and AoCLF, metabolites such as bilirubin, aromatic amino acids and bile acids, are accumulated and are toxic if not cleared effectively by the liver. MARS® is intended to selectively remove these excess metabolites and in so doing, stabilise liver function by decreasing circulating levels of toxins.

MARS® is registered by the Therapeutic Goods Administration and is in limited use in Australia.

There are few treatment options available for patients with ALF or AoCLF and liver transplant is widely accepted as the only effective therapy once supportive measures have failed. However due to the scarcity of organ availability, mortality rates in liver failure patients are high at approximately 80 per cent. Many AoCLF patients are not suitable transplant recipients and ALF patients may not be transplanted in time. In January 2005 there were 116 patients on the liver transplant waiting list. MARS® may provide bridging therapy until a suitable organ becomes available.

Of the considerable amount of literature describing the use of MARS® for the treatment of liver failure, the majority are small, uncontrolled case series studies. This poorer quality evidence (level IV intervention evidence) was not assessed for effectiveness outcomes in this report. There was *considerable variation* in the characteristics of patients enrolled in these studies (patients with cardiogenic shock, AoCLF, ALF, hepatorenal syndrome) and in the *stage of illness* when patients commenced treatment with MARS®. This has implications for the generalisability of these results and for patient selection. In addition, timing of treatment may be a critical issue as patients may already be too critically ill to benefit from MARS® therapy.

Mortality or increased survival was the main effectiveness outcome reported in the high quality evidence assessed. There was no statistically significant difference in the risk of death between the intervention and control groups in the highest level of evidence (level I intervention evidence). This meta-analysis, however, reported a 44% reduction in the risk of death for all MARS® treated patients (RR=0.56 95% CI 0.28, 1.14) relative to patients receiving usual care. This analysis was under powered due to the small numbers of patients enrolled in the trials included in the meta-analysis. The Evaluators calculated that *only 19* patients would be needed to be treated with MARS®, as opposed to usual care, to *prevent one death*. A stratified analysis demonstrated no effect modification by type of liver failure as there was no statistically significant difference in mortality between AoCLF (RR= 0.50) and ALF patients (RR= 0.50) (treated with MARS® compared to controls).

Two studies were halted prematurely by the ethics committee after interim analysis revealed a greater mortality in the control group when compared to MARS® treated patients.

Many of the surrogate outcomes were characterised by large standard deviations or ranges. However, most studies were able to demonstrate statistically significant differences between baseline and post-MARS® treatment values.

Only one study reported on adverse events associated with MARS® therapy, although it is difficult to differentiate between adverse events normally associated with liver failure and those exclusively attributable to treatment with MARS®. However, there were numerically fewer adverse events for most morbidity, excluding coagulopathy, with MARS® treatment than with patients undergoing standard medical therapy.

A cost-effectiveness study by Hassanein et al (2003) analysed the difference in costs for liver failure patients randomised to either treatment with MARS® or standard medical care. The total cost incurred by the MARS® treatment group was $US 352,396 (cost of hospitalisation plus the cost of MARS® therapy). This translated to an expenditure of $US 32,036 per survivor in the MARS® therapy group compared to $US 35,904 per survivor in the standard medical care group, a saving of $US 4,000 per survivor (length of survival not stated).

In Australia, the cost of the MARS® device and a single treatment respectively is approximately $AUD 30,000 and $AUD 5,000. Patients currently average three to five treatments and are being treated at a later stage of disease than ideal (personal communication Teraklin AG company representative, May 2005). A conservative estimate of the number of patients who may benefit from MARS® therapy in Australia and New Zealand is approximately ten per cent of patients on the liver transplant waiting, or 20 patients annually (personal communication, New Zealand liver transplant surgeon). If all of these patients received 3-5 treatments with MARS® therapy, the estimated cost to the health care system would range from $300-500,000 per year, not including the cost of the MARS® apparatus. However, if treatment with the MARS® device was effective in improving morbidity and mortality, it is likely that the high costs of treatment would be offset by a reduction in patients requiring liver transplant and hospitalisation in intensive care and thus be cost-saving compared to current supportive therapy and transplantation.

In conclusion, the highest level of evidence suggests that MARS® therapy may increase the survival of patients with liver failure. However, the analysis was under-powered to determine with assurance whether this result was statistically significant relative to therapy with standard medical management. High quality evidence also suggests that MARS® has a beneficial impact on several surrogate physiological outcomes.

HealthPACT Advisory

MARS® therapy may offer survival benefit for patients with acute or acute on chronic liver disease, however there is currently insufficient evidence to support this hypothesis for either condition. Acute on chronic liver failure patients may be more likely to benefit from treatment with MARS® due to the nature of their disease, which is episodic, precipitated by an event such as a bleed or infection. MARS® treatment may assist these patients to recover sufficiently to then benefit from a liver transplantation. In addition, costs are likely to be high for the few patients likely to benefit. More robust evidence will be available in March 2008 when the results of two large ongoing trials should be published.

Introduction

The National Horizon Scanning Unit, Discipline of Public Health, University of Adelaide, on behalf of the Medical Services Advisory Committee (MSAC), has undertaken an Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the state of play of the introduction and use of the molecular adsorbents recirculating system (MARS®) (Horizon Scanning register number: 00171).

Teraklin AG (Rostock, Germany) manufactures the molecular adsorbents recirculating system (MARS®), a haemo-dialysis and haemo-filtration device, for the treatment of patients with liver failure. It is offered through specialist tertiary hospitals and has been in limited use in Australia since 2002. The MARS® device is registered with the Australian Therapeutic Goods Administration (ARTG number 81638). In addition, the MARS® device was granted 510K pre-market approval from the FDA in June 2005 for the management of drug overdose and poisoning treatment.

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of the molecular adsorbents recirculating system (MARS®), its present use, the potential future application of the technology, and its likely impact on the Australian health care system.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with molecular adsorbents recirculating system (MARS®).

Background

Description of the Technology

The procedure

The molecular adsorbents recirculating system (MARS®) (Figure 1) is designed to support excretory liver function. The MARS® system consists of three compartments – a blood circuit, an albumin circuit and an open-loop single-pass dialysate circuit. The MARS® device is piggybacked onto standard haemo-dialysis or haemo-filtration equipment to control the blood and dialysate circuits. The patient is connected to the blood circuit containing the MARS® membrane. One pump drives blood from the venous access site (double-lumen catheter) to the MARS® cartridge at a rate of 150-250 ml/min, where it is dialysed across an albumin-impregnated membrane (Kapoor 2002).

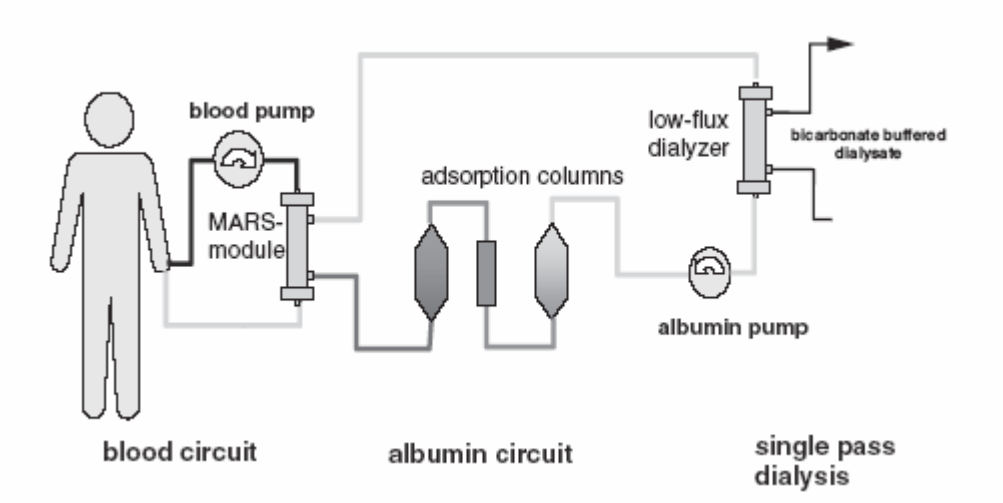

Figure 1 The MARS® albumin treatment method (Printed with permission Teraklin AG, 2005)

Albumin bound to the polymers of the MARS® membrane has a greater affinity for the plasma albumin-bound toxins (Figure 2). Albumin is pumped through the MARS® membrane compartment counter current to the blood flow. The passage of albumin-bound toxins from the patient's blood is facilitated by active competition from the MARS® membrane bound albumin. Toxins bound by albumin in the plasma detach and then reattach to the binding sites of the albumin impregnated on the MARS® membrane. Subsequently these toxins permeate into the dialysate solution, containing 20% human albumin (Kapoor 2002; Mitzner et al 2001b; Sen & Jalan 2004).

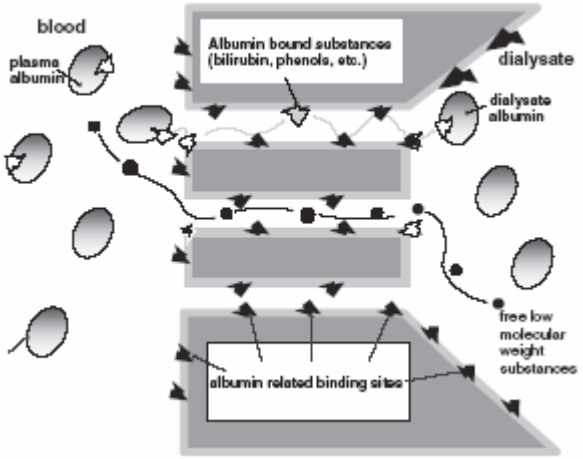

Figure 2 Schematic representation of the MARS® membrane (Printed with permission (Stange et al 1999))

The albumin dialysate (with bound toxins) is then passed through an additional low-flux dialysis membrane, counter-current to a standard dialysis solution, and subsequently regenerated against a bicarbonate-buffered dialysate. The solution is

then cleared of its albumin-bound toxins by passage through an activated carbon adsorption column and an anion exchanger. Treatment duration ranges from 6 to 24 hours (Kapoor 2002; Mitzner et al 2001b; Sen & Jalan 2004). Substances with a molecular weight greater than 50 kDa, such as hormones bound to carrier proteins, growth factors or endogenous albumin (65 kDa) are not removed from the perfused plasma due to the small pore size of the MARS® membrane (Kapoor 2002; Sen & Jalan 2004).

The efficacy of the system may decrease over the treatment time as the concentration of albumin coating the dialysate side of the MARS® membrane decreases. Patients may be treated every day, however it is common for patients to be treated every alternate day (Kapoor 2002). In clinical trials to date, the number of treatment days have ranged between 1 and 24, with an average of 5-6 treatment days per patient (Mitzner et al 2001b).

Intended purpose

MARS® is intended to treat patients with acute liver failure (ALF) or acute-on-chronic liver failure (AoCLF). ALF develops *de novo*, in the absence of any pre-existing liver disease. AoCLF results from an acute deterioration in liver function in patients with previously well-compensated chronic liver disease, precipitated by events such a bacterial or viral infection, sepsis, intoxication or gastrointestinal bleeding. Both AoCLF and ALF are characterised by hepatic encephalopathy, renal dysfunction and circulatory changes and both are considered to be reversible (Jalan & Williams 2002; Mitzner et al 2001b; Sen & Jalan 2004). Failure of the liver to clear toxic metabolites may seriously affect regulatory pathways and the functioning of other organ systems, resulting in multiorgan failure. Metabolites found to accumulate in ALF and AoCLF include: aromatic amino acids, bile acids, bilirubin, copper (Wilson's disease), digoxin-like substances, endogenous benzodiazepines, indols, phenols, mercaptans, short and medium chain fatty acids, tryptophan, nitric oxide and prostaglandins (Jalan & Williams 2002; Kapoor 2002; Mitzner et al 2001b). The majority of these metabolites are strongly bound to the protein human serum albumin. Failure by the liver to clear these albumin-bound metabolites results in elevated tissue levels of toxic metabolites.

Conventional haemo-dialysis or haemo-filtration can remove only *water soluble,* non protein-bound toxins. MARS® is intended to selectively remove the albumin-bound metabolites, decreasing the plasma and tissue concentrations of these toxic metabolites, resulting in the stabilisation of liver function. The aim of MARS® therapy is to support the liver until it recovers or as a bridge to liver transplantation (Jalan & Williams 2002; Kapoor 2002; Mitzner et al 2001b; Sen & Jalan 2004).

MARS® has been used in the treatment of primary graft dysfunction following liver transplantation, with some success (Hommann et al 2002; Kapoor 2002; Sen & Jalan 2004). In addition, MARS® has been used successfully in patients with Wilson's disease, an autosomal recessive hereditary disease which affects copper

metabolism (Kapoor 2002; Sen et al 2002). Other indications for MARS® therapy include the treatment of liver failure after hepatic resection (Kellersmann et al 2002), the treatment of intractable pruritus in patients with cholestasis (abnormal flow of bile leading to elevated levels of bilirubin) (Macia et al 2003), toxicity resulting from the accumulation of phenytoin, a common antiepileptic drug (Sen et al 2003), ALF due to paracetamol overdose (Siewert-Delle et al 2001), cardiogenic shock (El Banayosy et al 2004a) and the treatment of Amanita phalloides (mushroom) poisoning (Sein Anand et al 2005; Shi et al 2002; Wu & Wang 2004). MARS® was recently used to treat a patient who had deteriorated into multiorgan failure after being diagnosed with severe acute respiratory syndrome (SARS) (Luo et al 2003).

Clinical need and burden of disease

In Australia ALF (43% of all cases) is most commonly cryptogenic (of indeterminate aetiology) with patients sero-negative for hepatitis A, B or C. Drug-induced ALF, including paracetamol overdose, is less common in Australia (21% of all cases) than in countries like the United States (32% of all cases). Hepatitis and Wilson's Disease may account for a large proportion of ALF cases (Holt 1999).

Cirrhosis is one of the most common causes of liver failure and may be caused by hepatitis infection or excessive alcohol intake. Chronic active hepatitis can progress to both cirrhosis and liver cancer. Cirrhosis contributes significantly to the burden of disease in Australia, both in terms of premature mortality and health system costs (AIHW 2000). Alcohol consumption patterns have remained relatively unchanged with approximately 50 per cent of the Australian population aged over 14 years drinking regularly. Of these regular drinkers, however, 7 per cent and 4 per cent of males and females, respectively, drink to hazardous or harmful levels. A lower proportion of Aboriginal and Torres Strait Islander peoples consume alcohol compared to non-indigenous Australians. Of concern, however, is that of those who do consume, a higher proportion will drink at hazardous levels (12% of Indigenous males and 3% of Indigenous females). In 1996 it was estimated that 4 and 2 per cent of all deaths in Australia for males and females respectively, were attributable to 'alcohol harm'. Of these deaths, 16 per cent were due to cirrhosis of the liver (AIHW 2002).

The number of people living with hepatitis infection is increasing in Australia. In 2002, there were 390 newly acquired cases of hepatitis B infection diagnosed in Australia with an annual incidence rate of 2 per 100,000. During the same period there were 225,000 people living with hepatitis C with approximately 16,000 new notifications in that year alone. Chronic hepatitis infection may lead to cirrhosis of the liver over a prolonged period of time. During the year 2002, hepatitis C was the primary cause of liver disease for which 41 people received a liver transplant (AIHW 2004). It has been estimated that in Australia during 2001 there were 6,500 people living with hepatitis C related cirrhosis and 175 individuals who developed hepatitis C related liver failure. It has also been estimated that 22,500

quality adjusted life years were lost to chronic hepatitis C related liver disease during this same period. Modelling has suggested that the prevalence of hepatitis C related cirrhosis and the incidence of hepatitis C related liver failure will more than treble by 2020 in Australia (Law et al 2003). Modelling in New Zealand suggests that approximately 0.7 per cent of the total population had hepatitis C antibodies in the year 2000 and that this number will increase by 50 per cent by 2010. In the year 2000 it was estimated that there were 1200 people with hepatitis C related cirrhosis and 21 incident cases of hepatitis C related liver failure in New Zealand. Modelling suggests that by 2010 there will be 1,930 individuals with hepatitis C related cirrhosis and 35 cases of hepatitis C related liver failure in New Zealand (Ministry of Health 2000).

In Australia during the period 2003-04 there were 10,837 hospital separations, representing 73,659 patient days, for the principal diagnoses K70 -76 liver diseases. The AR-DRG for alcoholic liver disease (K70) represents 41 per cent of the total number of separations; 64 per cent (6,911) of these separations occurred in males (AIHW 2005). In addition, liver disease ranked as the 17th leading underlying cause of death for males in the year 2002 with 918 male deaths (1.3% of all male deaths) being directly attributable to liver disease (AIHW 2004). Liver disease is predominantly a disease that occurs in older individuals, with 86 per cent of hospital separations being for patients aged 40 years and above (AIHW 2005).

In New Zealand during the year 2001 there were 1,284 public hospital separations for the principal diagnoses K70 -77 liver diseases. As in Australia, diseases of the liver affect mainly older individuals, however in New Zealand the distribution between the sexes is more even with 56 per cent of those affected being male (NZHIS 2005b). A small number of patients (14 separations) were reported in private hospitals for the treatment of liver disease and cirrhosis. There were 6 separations for the sequelae of chronic liver disease, with a mean stay of 9.8 days. Other disorders of the liver (not stated) accounted for a total of 106 private hospital separations, with a mean stay of 10.1 days (NZHIS 2005a).

The Australia and New Zealand Organ Donation (ANZOD) registry reported that in 2004 there were 177 and 36 liver transplants performed in Australia and New Zealand respectively. Seven livers were donated from Australia and transplanted into New Zealand recipients and seven livers were donated and transplanted in the opposite direction. These transplants involved 164 Australian and 35 New Zealand donors, with 28 transplants being performed using the split liver system (one liver transplanted into two recipients). In January 2005 there were 104 Australian and 12 New Zealand patients on the waiting list for a liver transplant (ANZOD 2005). A conservative estimate of the number of patients who may benefit from MARS® therapy would be ten per cent of patients on the liver transplantation waiting list (approximately 20), as this figure represents the number of critically ill patients transplanted out of intensive care units in a calendar year (personal communication, New Zealand liver transplant surgeon).

Stage of development

The MARS® system became available for clinical use in Australia in 2002 and to date approximately 20 patients have been treated. The MARS® system has been used in the Royal Prince Alfred Hospital and the Prince of Wales Hospital in Sydney, and the Austin and Repatriation Hospital and Alfred Hospital in Melbourne. More than 4,500 patients had been treated worldwide as of June 2004 (personal communication, Teraklin AG). Other centres likely to use the MARS® system include those that already perform liver transplants: the New Children's Hospital in New South Wales, Princess Alexandra Hospital in Queensland, the Royal Children's Hospital in Victoria, Flinders Medical Centre and Queen Elizabeth Hospital in South Australia and Auckland Hospital in New Zealand (ANZOD 2005).

Treatment Alternatives

Existing comparators

There are few treatment options available for patients with ALF or AoCLF. Transplantation is widely accepted as the only effective therapy for liver failure once supportive measures have failed. Liver transplantation is capable of curing approximately 90 per cent of patients from a terminal or pre-terminal state of liver failure. However, due to the shortage of suitable donor organs and long waiting lists, mortality rates associated with ALF approach 80 per cent (Liu et al 2004). In addition, liver transplantation is an expensive procedure and patients experience a lifetime risk of graft rejection and immunosuppression, with its associated risk of malignancy (Court et al 2003). Contraindications to liver transplantation include extrahepatic malignancy, severe cardiopulmonary disease, systemic sepsis, active alcoholism and an inability to comply with regular drug treatment (Prasad & Lodge 2001). AoCLF patients may not be eligible for liver transplantation due to the chronic nature of their disease, while ALF patients often cannot be transplanted in time. These patients may be candidates for other types of artificial liver support (Hassanein et al 2003).

Other surgical techniques which may be performed whilst patients await a liver transplant include total hepatectomy with portocaval drainage or auxiliary orthotopic liver transplantation (using the donor's left or right hepatic lobe with the removal of the corresponding lobe from the recipient) (Cao et al 1998).

Non-biological techniques

Charcoal haemoperfusion was developed for liver failure in the 1960s. Rates of clinical improvement were statistically significant with this technique, however there was no significant improvement in patient survival. Filtering whole blood results in complement and platelet activation, leukopaenia, removal of coagulation factors, hormones and growth factors which play a vital role in the regeneration of

the liver. Plasma separation, such as that used in the MARS® system, was deemed to be more favourable than whole blood filtration (Court et al 2003).

Hybrid bioartificial liver support systems

Hybrid biological artificial support systems (BAL) are based on the premise that liver function can be replaced by hepatocytes in an exogenous environment (a synthetic framework consisting of a plastic housing and semipermeable membrane) (Court et al 2003). Human hepatocytes are the ideal cellular component to be used in BAL systems, however as supply is limited porcine hepatocytes tend to be used. Approximately 150-450g of cells (10^{10} hepatocytes) are required to provide the function of 10-30 per cent of normal liver mass. A genetically engineered human hepatocyte cell line is currently under investigation (Jalan et al 2004). The artificial component of the BAL device consists of a column containing hollow fibre capillaries through which the patient's blood or plasma is circulated. The hepatocytes are located in the extracapillary space. Plasma is separated, warmed and oxygenated in a secondary circuit and is then perfused through the capillaries. The semipermeable membrane separates the two compartments and allows passage of substances in both directions. Toxins and transport proteins such as albumin can pass through from the plasma into the extracapillary space, however large molecules such as immunoglobulins, complement, viruses and cells cannot. Several BAL systems are being trialled, including the extracorporeal liver assist device (ELAD), HepatAssist BAL and the modular extracorporeal liver support (MELS) system. Concerns with the use of porcine hepatocytes include immune reactions to foreign antigens and cross species infection with the porcine endogenous retrovirus (Jalan et al 2004). An additional problem is the maintenance of hepatocyte viability, however this may be improved by the addition of specific growth and adhesion factors (Court et al 2003).

Clinical Outcomes

There is a considerable amount of literature describing the use of MARS® treatment for patients with liver failure. The majority of this literature is case series evidence (level IV Intervention evidence) and is therefore of poor quality. Only high quality evidence is presented and analysed in the effectiveness section of this report, however a list of the case series and their abbreviated results are presented in Appendix C. This list is by no means exhaustive. Most case series reported high rates of mortality despite treatment with MARS®, however this was dependent on the initial diagnosis of liver failure (whether ALF, AoCLF or drug induced toxaemia) and the MELD (Mayo end-stage liver disease) score of patients prior to treatment. The majority of case series reported significant reductions in serum bilirubin, ammonia, urea and creatinine levels (surrogate outcomes) after MARS® treatment. Improvements in the grade of encephalopathy were also noted along with improvements in mean arterial pressure and cardiac index. In addition

changes in coagulation factors were reported including a decrease in the platelet count and an increase in antithrombin and prothrombin. All case series reported a variation in the number of MARS® treatments each patient received, which tended to depend on how ill particular patients were at the time. The characteristics of patients differed widely with patients suffering a variety of conditions including alcoholic hepatitis, ALF, AoCLF, Wilson's Disease, intractable pruritus, hepatitis C cirrhosis, hepatic failure due to chemotherapy, post-surgical multiple organ failure and hepatorenal syndrome (see Appendix C).

A Cochrane Systematic Review was published in 2004 which described the use of artificial and bio-artificial support systems versus standard medical therapy for the treatment of liver failure (Liu et al 2004) (level I Intervention evidence). This review could not be included in this report as it included all forms of support systems and did not provide a sub-group analysis of MARS® therapy versus standard medical therapy alone. However this review did note that mortality in severe liver failure will depend on the degree of liver damage and therefore the liver's ability to regenerate. Systems such as MARS® may provide support during episodes of bleeding or infection, which are common causes of AoCLF. Causative factors in ALF such as toxicity and viral hepatitis are difficult to treat. This review reported that support systems such as MARS® were more effective treating AoCLF than ALF patients, which may have implications for patient selection (Liu et al 2004). The same conclusion was reached by another systematic review of artificial and bio-artificial support systems versus standard medical therapy conducted by Kjaergard et al (2003) (level I Intervention evidence). Support systems had no effect on overall mortality when compared to standard medical therapy alone (RR=0.86, 95%CI [0.65, 1.12]). However, when stratified by type of liver failure, support systems could reduce mortality by 33 per cent in AoCLF patients (RR=0.67, 95%CI [0.51, 0.90]) but not in ALF patients (RR=0.95, 95%CI [0.71, 1.29]) (Kjaergard et al 2003).

In addition, the National Institute for Clinical Excellence in the United Kingdom published an interventional overview on the use of MARS®. (NICE 2003). This overview included two of the randomised trials included in this assessment, as well as several uncontrolled studies. The overview informed the development of an Interventional Procedure Guidance (NICE 2004). NICE advised that current evidence on the safety and efficacy of treatment with MARS® for AoCLF was inadequate for the procedure to be used without special arrangements for consent and for audit or research. The Specialist Advisors commented that although MARS® treatment reduces bilirubin levels, it is unclear whether this results in increased survival of patients.

Safety

Only one of the good quality studies reported on adverse events associated with the treatment of patients with MARS® (Table 1). Heeman et al (2002) reported 17 adverse events in 12 patients after 91 MARS® treatment sessions. There were numerically fewer adverse events for most morbidity, excluding coagulopathy with MARS® treatment when compared to patients treated with standard medical care. Although case series evidence (level IV intervention evidence) was not considered for effectiveness outcomes, they are included for assessment in the safety section of this report. Two case series studies reported adverse events related to the treatment of patients with MARS®.

In this extremely ill population it may be difficult to differentiate between normal adverse events associated with liver failure and those associated with MARS® treatment.

Table 1 Adverse events

Study	Level of Intervention Evidence	Study Design	Population	Outcomes
Heeman et al (2002) * RCT was included in meta-analysis by Khuroo et al (2004)	II	Randomised controlled trial	24 patients with liver cirrhosis and a super-imposed acute liver injury. 12 patients randomised to MARS® treatment. 12 patients randomised to standard medical therapy.	**Adverse events associated with MARS®** Only 4/12 (33.3%) of control patients underwent routine dialysis. 6 adverse events in 4 control patients receiving 11 dialysis treatments 17 adverse events in 12 patients receiving 91 MARS® treatments. Event — MARS® (%) — Control (%) Deterioration in clinical condition: 1/12 (8.3) — 0/4 (0) anaemia: 6/12 (50) — 3/4 (75) haemorrhage: 1/12 (8.3) — 1/4 (25) hypotension: 0/12 (0) — 2/4 (50) coagulopathy: 3/12 (25) — 0/4 (0) disorientation: 1/12 (8.3) — 0/4 (0) dyspnea: 1/12 (8.3) — 0/4 (0) arterial puncture: 1/12 (8.3) — 0/4 (0) fever/sepsis: 2/12 (16.6) — 0/4 (0) parathesia: 1/12 (8.3) — 0/4 (0) **Adverse events associated with end stage liver disease** Event — MARS® (%) — Control (%) Deterioration in HE: 0/12 (0) — 3/12 (25) hypotension: 2/12 (16.6) — 3/12 (25) worsening renal function: 1/12 (8.3) — 7/12 (58.3) electrolyte disorders: 4/12 (33.3) — 10/12 (83) coagulopathy: 4/12 (33.3) — 3/12 (25) ascites formation: 0/12 (0) — 1/12 (8.3)

Adverse events reported from case series				
Mullhaupt et al (2002)	IV	Case series	6 patients with severe liver insufficiency	3/6 (50%) suffered kidney failure and required kidney replacement therapy 2/6 (33.3%) MARS® treatment precipitated a disseminated intravascular coagulation
Jalan et al (2003)	IV	Case series	8 patients with hepatorenal syndrome (Type 1 n=5, Type 2 n=3), all encephalopathic	Thrombocytopenia was reported as an adverse event of MARS®

* Study by Heeman et al 2002 supported in part by Teralkin AG, manufacturer of MARS® system, HE = hepatic encephalopathy

Effectiveness

Only higher quality evidence is presented in this assessment of effectiveness. This includes one meta-analysis (level I Intervention evidence), four randomised controlled trials (level II Intervention evidence), one non-randomised study (level III-2 Intervention evidence) and one study from an International Register of case series (Level IV Intervention evidence). In the trials large differences were noted between groups for baseline values for some variables. However, all studies adjusted for baseline differences between the groups when conducting statistical analysis.

All studies included for assessment reported on survival (Table 2) or mortality (Table 3) after treatment with MARS®. The high quality study by Khuroo et al (2004) (level I Intervention evidence) reported that of the four randomised controlled trials (RCT) included in the meta-analysis[1], only one demonstrated a *statistically significant* reduction in mortality following treatment with MARS®, in comparison to a control group. However, the risk (RR) of death for all MARS® treated patients included in the meta-analysis was 0.56, [95%CI 0.28, 1.14] relative to patients receiving medical management, which indicates a potentially large reduction in mortality. Due to the small numbers of patients included in the trials, the meta-analysis was under powered (power = 40% to detect a 10% reduction in mortality in the intervention group). Therefore the lack of a statistically significant difference in the risk of death between the intervention group and controls may be a result of a lack of statistical power, rather than a lack of treatment effect. The absolute risk difference is 5.3 per cent. An estimate of the number of patients with ALF or AoCLF that would be needed to be treated with MARS® therapy as opposed to standard medical management, *to prevent one*

[1] The meta-analysis by Khuroo et al (2004) included 3 RCTs presented separately in this report: El Banayosy (2004), Heeman (2002) and Mitzner (2000). It also included the study by Schmidt et al (2003) as an RCT, which was included in this report as a quasi-randomised, comparative study. Patients in this study were not randomised to treatment: consecutive patients were assigned to the intervention group followed by the control group.

death, is the inverse of the absolute risk difference. Therefore the number needed to treat with MARS® to *benefit (prevent one death)* is 19 patients. This figure does, however, have a wide confidence interval with the minimum number needed to treat to benefit being as low as four patients, and including no effect or a harmful effect for one patient for every six patients treated with MARS®.

Khuroo et al (2004) suggest that an RCT should be conducted with a large number of enrolled patients, to enable sufficient power (80%) to detect a statistically significant difference between the MARS® intervention and control groups.

There was considerable variation in the characteristics of patients enrolled in these trials (patients with cardiogenic shock, AoCLF, ALF, hepatorenal syndrome) and in the stage of illness when patients commenced treatment with MARS®. This is likely to have impacted on the results as approximately 40 per cent of patients with ALF may survive the acute episode with medical therapy alone, whilst there are few effective treatment options, apart from transplantation, available for patients with AoCLF. It has been suggested that treatment with MARS® may give sufficient benefit to this patient group with ALF to allow time to regenerate the native liver and also to allow patients with AoCLF to remain well enough until a suitable organ became available for transplantation (Barshes et al 2005). A stratified analysis by Khuroo et al (2004) demonstrated no difference in the mortality risk of patients (treated with MARS® compared to controls) with AoCLF (RR=0.50, 95%CI [0.12, 2.17], p=0.35) and ALF patients (RR=0.50, 95%CI [0.15, 1.58], p=0.23), but again the wide confidence intervals suggest that the sub-group analysis was underpowered.

Table 2 Mortality

Study	Level of Intervention Evidence	Study Design	Population	Outcomes
Khuroo et al (2004)	I	Systematic review of RCTs	Study included data from 4 RCTs (n=67 patients) and 2 non-randomised trials (n=61 patients).	**RCTs** Control group mortality rate in meta-analysis 12/31 (38.7%) MARS® group mortality rate in meta-analysis 12/36 (33.3%) **Pooled RR=0.56, 95%CI [0.28, 1.14]** **Absolute risk difference = 5.3%** **NNTB = 19 [NNTB 4 to ∞ to NNTH 6]** Cochran Q test for heterogeneity NS (p=0.39) therefore trials for this endpoint were homogenous. No publication bias (p=0.17) **Effect of MARS® on mortality of AoCLF patients** RR=0.50, 95%CI [0.12, 2.17], *p*=0.35 (NS) **Effect of MARS® on mortality of ALF patients** RR=0.50, 95%CI [0.15, 1.58], *p*=0.23 (NS) **Non-Randomised studies** * **AoCLF patients** MARS® treatment group compared to controls RR=0.36, 95%CI [0.17, 0.76], *p*=0.007 Cochran Q test for heterogeneity NS (p=0.46) therefore studies for this endpoint were homogenous. No publication bias (p=0.17) The estimated effect of MARS® on mortality did not differ significantly between the randomised and non-randomised studies (p value for heterogeneity = 0.39).

* The non-randomised studies included one with historic controls of patients with alcoholic liver disease and another which used patients who dropped out after only one treatment of MARS® and so became "controls", RCT = randomised controlled trial, RR= relative risk, ALF = acute liver failure, AoCLF = acute on chronic liver failure
NNTB = number needed to benefit, NNTH = number needed to harm

Table 3 summarises the mortality data reported by the four RCTs included in this assessment. Only the study by Mitzner et al (2000) reported a statistically significant improvement in the prolongation of survival ($p<0.05$) and in survival ($p<0.01$) of patients treated with MARS® compared to patients treated with standard medical therapy. It should be noted that the studies by Heeman et al (2002) and Mitzner (2000) were halted prematurely by the ethics committee after interim analysis revealed a greater mortality in the control group when compared to MARS® treated patients. This would also have the effect of limiting the power of these studies in the final analysis.

Table 3 Survival

El Banayosy et al (2004) RCT was included in meta-analysis by Khuroo et al (2004)	II	Randomised controlled trial	27 patients with hypoxic liver failure caused by cardiogenic shock bought on as a result of cardiac surgery. 14 patients randomised to MARS® treatment. 13 patients randomised to standard medical therapy.	**MARS® group** 7/14 (50%) survival (time point not stated) **Control group** 4/13 (31%) survival (time point not stated) MARS® vs Control survival NS
Heeman et al (2002) * RCT was included in meta-analysis by Khuroo et al (2004)	II	Randomised controlled trial	24 patients with liver cirrhosis and a super-imposed acute liver injury. 12 patients randomised to MARS® treatment. 12 patients randomised to standard medical therapy.	**MARS® group** 11/12 (91.7%) 30-day survival 6/12 (50%) 6-month survival, of these 1/6 (16.7%) received LTX **Control group** 6/12 (50%) 30-day survival Death occurred on day 5,6,8,8,10,23 Of these survivors 4/6 (66.7%) 6-month survival, of these 1/4 (25%) received LTX ITT analysis MARS® vs Control 30-day survival *p*=0.069 (NS) Note: Original protocol was designed to study 48 patients, however this study was halted by the Ethics Committee after interim 30-day survival analysis revealed greater mortality in the Control group. The Ethics Committee advised that a new protocol be designed which would allow patients who deteriorate a chance to cross-over to MARS® therapy.

Mitzner et al (2000) * RCT was included in meta-analysis by Khuroo et al (2004)	II	Randomised controlled trial	13 patients with hepatorenal syndrome. 8 patients assigned to MARS® treatment in conjunction with standard medical therapy and HDF. 5 patients assigned to standard medical therapy and HDF.	**Prolongation of survival** **MARS® group** 25.2 ± 34.6 days Mortality at day 7 5/8 (62.5%) Mortality at day 30 6/8 (75%) **HDF group (Control)** 4.6 ± 1.8 days Mortality at day 7 5/5 (100%) MARS® vs Control prolongation of survival *p*<0.05 MARS® vs Control survival *p*<0.01
Sen et al 2004)	II	Randomised controlled trial	18 patients with AoCLF and alcoholic aetiology. 9 patients assigned to MARS® treatment + standard medical care. 9 patients assigned to standard medical care alone.	**MARS® group** 4/9 (44.4%) survival at 3 months follow-up 2/9 (22.2%) died due to variceal bleeding 3/9 (33.3%) died from multi-organ failure, 2 of which were associated with sepsis **Control group** 4/9 (44.4%) survival at 3 months follow-up 1/9 (11.1%) died due to variceal bleeding 4/9 (44.4%) died from multi-organ failure, 2 of which were associated with sepsis
Schmidt et al (2003)	III-2	Non-randomised	13 patients with hyper-acute liver failure. 8 consecutive patients assigned to MARS® treatment. 5 consecutive patients assigned as temperature ** matched controls treated with standard medical care.	**MARS® group** 5/8 (62.5%) survival, of these 2/5 (40%) received LTX **Control group** 3/5 (60%) survival

<table>
<tr>
<td>Steiner & Mitzner ** (2002)</td>
<td>IV</td>
<td>International Register (case series)</td>
<td>176 patients
99/176 (56.3%) AoCLF
38/176 (21.6%) ALF
27/176 (15.3%) primary graft dysfunction (PGD) after LTX
7/176 (4.0%) liver failure/ dysfunction after liver surgery and 5/176 (2.8%) miscellaneous</td>
<td>AoCLF patients
56/99 (56.6%) discharged with fully re-compensated liver from hospital
Of these 6/56 (10.7%) received LTX
<table>
<tr><th>CPS</th><th>n</th><th>% survival</th></tr>
<tr><td>10</td><td>1</td><td>100</td></tr>
<tr><td>11</td><td>7</td><td>86</td></tr>
<tr><td>12</td><td>17</td><td>71</td></tr>
<tr><td>13</td><td>20</td><td>60</td></tr>
<tr><td>14</td><td>11</td><td>55</td></tr>
<tr><td>15</td><td>5</td><td>0</td></tr>
</table>
<table>
<tr><th>MELD</th><th>n</th><th>% survival</th></tr>
<tr><td><9</td><td>0</td><td>-</td></tr>
<tr><td>10-19</td><td>9</td><td>89</td></tr>
<tr><td>20-29</td><td>14</td><td>64</td></tr>
<tr><td>30-39</td><td>19</td><td>42</td></tr>
<tr><td>>40</td><td>9</td><td>33</td></tr>
</table>
ALF patients
19/38 (50%) survived
(follow-up time period not stated)
Of these 6/19 (31.6%) received LTX (average bridging time 8 days, range 1-20 days).
4/19 (21%) patients listed for LTX survived without one
PGD patients
15/27 (55.6%) survival without re-LTX
(follow-up time period not stated)
Remaining patients groups could not be analysed</td>
</tr>
</table>

* Study by Mitzner et al 2000 and Heeman et al 2002 supported in part by Teralkin AG, manufacturer of MARS® system
** Temperature matched controls were used as treatment with MARS® has a cooling effect on the body
ITT = intention-to-treat analysis, LTX = liver transplant, INR= international normalized ratio, HE = hepatic encephalopathy
CPS= Child-Pugh Score employs 5 clinical measures of liver disease (levels of bilirubin, serum albumin, INR, ascites and HE): Class A = 5-6 points, life expectancy of 15-20 years; Class B =7-9 indicated for LTX evaluation; Class C =life expectancy 1-3 months.
MELD = Mayo end-stage liver disease score assesses the patient's risk of dying from liver disease within 3 months. Scores incorporate levels of bilirubin, creatinine and INR. Scores range from 6 (least ill patient) to >40 (extremely ill patient requiring LTX)
NS = non-significant, HDF = haemo-diofiltration, ALF = acute liver failure, AoCLF = acute on chronic liver failure

Mayo end-stage liver disease (MELD) scores or Child-Pugh/ Child-Turcotte-Pugh (CPS) scores are established tools for assessing the prognosis of patients with liver failure. Two high quality studies (level II intervention evidence) and one poorer quality study (level IV) reported on MELD and CPS scores before and after treatment with MARS® Results are presented in Table 4.

Heeman et al (2002) reported no significant difference in absolute CPS scores at four weeks between the MARS® and control group. However when changes from baseline were accounted for in both groups at four weeks there was a significant difference between the MARS® and control group ($p<0.05$) and there was a statistically significant improvement in CPS scores from baseline for patients treated with MARS® ($p<0.05$). Sen at al (2004) reported a similar improvement in MARS® treated patients for both CPS and MELD scores ($p<0.01$). However, a significant improvement in MELD scores was also observed in control patients

(p<0.05). It should be noted that there was a great variation in MELD scores in both the MARS® and control groups.

Table 4 Prognostic scores

Study	Level of Intervention Evidence	Study Design	Population	Outcomes
Heeman et al (2002) ** RCT was included in meta-analysis by Khuroo et al (2004)	II	Randomised controlled trial	24 patients with liver cirrhosis and a super-imposed acute liver injury. 12 patients randomised to MARS® treatment. 12 patients randomised to standard medical therapy.	CPS NS difference between MARS® and control groups in absolute values, at 4 weeks. There was a significant difference between the MARS® and control groups taking into account *changes from baseline values* at 4 weeks , p<0.05 There was a significant improvement in MARS® group from baseline to 30-days MARS® pre 11.5 post 10 p<0.05 range (7-15) (6-15)
Sen et al (2004)	II	Randomised controlled trial	18 patients with AoCLF and alcoholic aetiology. 9 patients assigned to MARS® treatment + standard medical care. 9 patients assigned to standard medical care alone.	Follow-up Day7 MELD MARS® / Control pre 16.5 / 19.4 range (13.1-31.2) / (4.3-25.2) post 14.1 / 14.5 range (4.8-41.9) / (2.9-18.4) p<0.01 / p<0.05 CPS MARS® / Control pre 13 / 12 range (11-14) / (10-13) post 11 / 12 range (10-14) / (8-14) p<0.01 / NS

Steiner & Mitzner * (2002)	IV	International Register (case series)	176 patients 99/176 (56.3%) AoCLF 38/176 (21.6%) ALF 27/176 (15.3%) primary graft dysfunction (PGD) after LTX 7/176 (4.0%) liver failure/ dysfunction after liver surgery and 5/176 (2.8%) miscellaneous	**AoCLF patients** MELD n 51 Pre 30.4 ± 9.3 (12.3-50.7) Post 22.1 ± 8.6 (4.7-42.8) p<0.0001 MELD score 10-19 / 20-29 / 30-39 / >40 **Predicted survival (%)** 7-day 94 / 87 / 69 / 44 30-day 77 / 55 / 20 / 3 90-day 61 / 28 / 4 / 0 **Observed Survival (%)** 89 / 64 / 42 / 33

* Study by Heeman et al 2002 supported in part by Teralkin AG, manufacturer of MARS® system
CPS = Child-Pugh Scores, MELD = Mayo end-stage liver disease, AoCLF = acute on chronic liver failure

Five studies included in this assessment reported on haemodynamic and clinical parameters after treatment with MARS® (Table 5). One of the most common complications of liver failure is the development of hepatic encephalopathy (HE). HE results from portal blood being diverted into the systemic circulation, carrying with it neurotoxins, which pass through the blood-brain barrier. HE is graded from 0 to 4. Patients graded 0 have a clinically normal mental status with minimal changes in concentration, co-ordination and memory. Patients graded 4 are seriously ill, are in a coma and may or may not respond to external stimuli (Wolf 2005). Patients with liver failure and grade III/IV HE may be at risk of cerebral oedema. This is associated with increased pressure resulting in cerebral herniation, a common cause of death in these patients (Harry & Wendon 2001). In addition liver failure results in cardiovascular changes. It is characterised by peripheral vasodilation, leading to a decrease in cardiac afterload and an increase in cardiac output. A decrease in the circulating volume, reflected by a decrease in mean arterial pressure (MAP), is often the end result. Cerebral blood flow correlates highly with MAP and therefore maintaining cerebral oxygenation, and by extension improving MAP, is important in the treatment of HE (Harry & Wendon 2001). Treatment with MARS® aims to increase MAP and to decrease the grade of HE. Improvements in the HE grade indicate an improvement in neurological status of the patient due to the removal of toxins.

Three of the high quality studies (level II Intervention evidence) included in this assessment reported before and after values of MAP, in both MARS® and control patients. The study by Heeman et al (2002) reported a statistically significant increase in MAP in the MARS® treated group and a decrease in the control group, however data for this analysis were not supplied. In the two remaining RCTs there was no significant increase or decrease reported for either the MARS® or control treated groups, but again this may be due to small patient numbers. The good quality study (level III-2 Intervention evidence) by Schmidt et al (2003) reported a

statistically significant improvement in MAP in MARS® treated patients, however there was no statistically significant difference when the MARS® and control groups were compared. The poorer quality study (level IV intervention evidence) by Steiner and Mitzner (2002) reported on outcomes of the international register of MARS® patients and stratified their results according to patients with ALF or AoCLF. A statistically significant improvement in MAP was observed in AoCLF patients (p=0.0001) but not in ALF patients.

Only two of the high quality studies (level II intervention evidence) reported before and after values of HE, in MARS® and control patients. Both of these studies reported a statistically significant improvement in HE (ie a decrease in the grade of HE), although Heeman et al (2002) did not report the data. Steiner and Mitzner (2002) found a statistically significant decrease in HE in AoCLF (p<0.0001) and ALF (p=0.0006) patients, and those with primary graft dysfunction following liver transplantation (p=0.034).

The poorer quality study by Schmidt et al (2003) identified increased vascular resistance and decreased cardiac index in patients treated with a single six hour episode of MARS®. These changes occurred in conjunction with a decrease in both oxygen delivery and oxygen consumption, although the latter is not generally viewed as being beneficial to seriously ill patients.

Table 5 Clinical and haemodynamic parameters (surrogate outcomes)

Study	Level of Intervention Evidence	Study Design	Population	Outcomes
Heeman et al (2002) * RCT was included in meta-analysis by Khuroo et al (2004)	II	Randomised controlled trial	24 patients with liver cirrhosis and a super-imposed acute liver injury. 12 patients randomised to MARS® treatment. 12 patients randomised to standard medical therapy.	MAP (mmHg) Increased significantly in MARS® treatment group but decreased in control group (no data given) Renal function Worsened in 1/12 (8.3%) MARS® group and in 7/12 (58.3%) of control group, $p<0.05$ HE grade Improved significantly in MARS® treatment group but worsened in control group (no data given)
Mitzner et al (2000) * RCT was included in meta-analysis by Khuroo et al (2004)	II	Randomised controlled trial	13 patients with hepatorenal syndrome. 8 patients assigned to MARS® treatment in conjunction with standard medical therapy and HDF. 5 patients assigned to standard medical therapy and HDF	MAP (mmHg) (mean ± SD) MARS® / Control pre 67 ± 13 / 66 ± 11 post 82 ± 17 / 61 ± 10 NS / NS No between group analysis Urine volume (mL/day) (mean ± SD) MARS® / Control pre 82 ± 76 / 214 ± 143 post 482 ± 724 / 51 ± 87 NS / NS No between group analysis
Sen et al (2004)	II	Randomised controlled trial	18 patients with AoCLF and alcoholic aetiology. 9 patients assigned to MARS® treatment + standard medical care. 9 patients assigned to standard medical care alone.	Follow-up Day 7 MAP (mmHg) (mean) MARS® / Control pre 85 / 77 range (60-130) / (57-100) post 75 / 80.5 range (55-105) / (66-97) NS / NS HE grade (mean) MARS® / Control pre 2.5 / 2 range (2-4) / (2-4) post 1 / 2 range (0-4) / (0-4) $p<0.01$ / NS

Schmidt et al (2003)	III-2	Non-randomised	13 patients with hyper-acute liver failure. 8 consecutive patients assigned to MARS® treatment. 5 consecutive patients assigned as temperature ** matched controls treated with standard medical care.	Patients received a single 6-hour MARS® treatment. SVRI (dynes · s · cm^{-5} · m^{-2}) (mean ± SD) MARS® Control pre 1215 ± 437 1166 ± 373 post 1778 ± 710 1233 ± 403 *p*<0.0001 *p*=0.004 MARS® vs Controls *p*=0.006 MAP (mmHg) (mean ± SD) MARS® Control pre 69 ± 5 70 ± 8 post 83 ± 11 69 ± 4 *p*<0.0001 NS MARS® vs Controls *NS* Cardiac index (L/min · m^{-2}) (mean ± SD) MARS® Control pre 4.6± 1.8 4.5 ± 1.4 post 3.7 ± 11 4.2 ± 1.3 *p*=0.0007 *p*<0.03 MARS® vs Controls *NS* Heart rate (beats/min) (mean ± SD) MARS® Control pre 105 ± 21 100 ± 14 post 85 ± 15 101 ± 17 *p*<0.0001 NS MARS® vs Controls *NS* DO_2 (ml/min · m^{-2}) (mean ± SD) MARS® Control pre 621 ± 198 701 ± 206 post 486 ± 141 645 ± 173 *p*<0.0001 NS MARS® vs Controls *NS* VO_2 (ml/min · m^{-2}) (mean ± SD) MARS® Control pre 142 ± 31 136 ± 34 post 112 ± 21 131 ± 49 *p*<0.05 NS MARS® vs Controls *NS* No significant changes before and after treatment in both control and MARS® groups, or between groups for: central venous pressure, pulmonary artery mean pressure, pulmonary artery wedge pressure, stroke volume, pulmonary vascular resistance index, oxygen extraction ratio, lactate, arterial pH, $PaCO_2$

Steiner & Mitzner (2002)	IV	International Register (case series)	176 patients 99/176 (56.3%) AoCLF 38/176 (21.6%) ALF 27/176 (15.3%) primary graft dysfunction (PGD) after LTX 7/176 (4.0%) liver failure/ dysfunction after liver surgery and 5/176 (2.8%) miscellaneous	**AoCLF patients** HE grade (mean ± SD) n: 60/99 Range; Pre: 2.2 ± 0.9 (1-4); Post: 0.9 ± 1.2 (0-4); *p*<0.0001 MAP mmHg (mean ± SD) n: 44/99 Range; Pre: 76.6 ± 13.9 (52-120); Post: 85.5 ± 14.2 (42-130); *p*=0.0001 **ALF patients** HE grade (mean ± SD) n: 14/38; Pre: 2.86 ± 1.1; Post: 1.71 ± 1.6; *p*=0.0006 MAP mmHg (mean ± SD) n: 12/38; Pre: 78.7 ± 12.8; Post: 77.3 ± 11.5; NS **PGD patients** HE grade (mean ± SD) n: 13/27; Pre: 2.7 ± 1.0; Post: 1.75 ± 1.6; *p*=0.034

* Study by Mitzner et al 2000 and Heeman et al 2002 supported in part by Teralkin AG, manufacturer of MARS® system

** Temperature matched controls were used as treatment with MARS® has a cooling effect on the body

SD= standard deviation, HE= hepatic encephalopathy, MAP = mean arterial pressure, NS = not significant, SVRI = systemic vascular resistance index, DO_2, = oxygen delivery, VO_2 = oxygen consumption, LTX = liver transplantation, HDF = haemo-diofiltration, ALF = acute liver failure, AoCLF = acute on chronic liver failure

Note: Treatment with MARS® aims to increase MAP and to decrease the grade of HE

Liver failure may result in the disruption of the coagulation cascade. Blood clotting factors, with the exception of factor VIII, are made in hepatocytes. These factors have a rapid turnover, with half-lives ranging from six hours to five days, therefore measurement of clotting factors is an accurate measure of hepatic synthetic function. Serum prothrombin time, which collectively is a measure of factors II, V, VII and X, is a useful measure to evaluate liver function. Normal prothrombin time is approximately 11-15 seconds. A prolonged prothrombin time may be indicative of hepatitis, cirrhosis or vitamin K deficiency. A prothrombin time greater than 30 seconds is grounds for concern, as abnormal bleeding may occur. Prothrombin times may vary from laboratory to laboratory and so the international normalised ratio (INR) was developed. Corresponding normal values for INR are 1.0-1.4. In addition, platelet numbers may be affected by liver disease. In liver disease, blood flow is reduced through the liver and the spleen becomes enlarged, leading to platelets being sequestered in the spleen and therefore a fall in circulating platelet numbers. A normal platelet count ranges from approximately 150 to 400 $x10^6$/ml blood (Pratt & Kaplan 2001).

El Banayosy et al (2004) reported no statistically significant difference between the MARS® and control groups for platelet numbers, prothrombin time or INR (Table 6). No analysis was presented for these outcomes within each group and it is interesting to note that platelet numbers rose from baseline to day-14 in both

groups and prothrombin time was extended, albeit with large variation at day-14 in both groups. Mitzner et al (2000) did report a significant change from baseline in MARS® treated patients for prothrombin activity ($p<0.01$), but this was a significant *increase*, rather than the expected *decrease*. A similar discrepancy was observed in the poorer quality study by Schmidt et al (2003) (level III-2 Intervention evidence), who reported a significant *decrease* ($p<0.05$) in the number of platelets in the MARS® treated group, rather than an increase. This perhaps indicates the impact of study quality on the results or alternatively the difficulty with using surrogate outcomes to estimate patient relevant clinical effects.

Table 6 Coagulation variables

Study	Level of Intervention Evidence	Study Design	Population	Outcomes
El Banayosy et al (2004) RCT was included in meta-analysis by Khuroo et al (2004)	II	Randomised controlled trial	27 patients with hypoxic liver failure caused by cardiogenic shock bought on as a result of cardiac surgery. 14 patients randomised to MARS® treatment. 13 patients randomised to standard medical therapy.	Platelets (10^6/L) (mean ± SD) MARS® / Control Day 1: 57.8 ± 32 / 55.2 ± 21.9 14 days: 209 ± 111 / 122 ± 70.1 NS Prothrombin time (seconds) (mean ± SD) MARS® / Control Day 1: 35.7 ± 7.1 / 38.2 ± 6.5 NS 14 days: 53.1 ± 29.3 / 60.8 ± 30.0 NS Antithrombin III (%)(mean ± SD) MARS® / Control Day 1: 70 ± 15.6 / 67 ±11.5 NS 14 days: 70 ±19.3 / 57 ± 17.5 NS INR (mean ± SD) MARS® / Control Day 1: 1.4 ± 0.47 / 1.5 ± 0.52 NS 14 days: 1.3 ± 0.21 / 1.2 ± 0.13 NS Interleukin 6 (pg/ml) (mean ± SD) MARS® / Control Day 1: 142 ± 154 / 86 ± 62 NS 14 days: 35 ± 19 / no data —

Heeman et al (2002) * RCT was included in meta-analysis by Khuroo et al (2004)	II	Randomised controlled trial	24 patients with liver cirrhosis and a super-imposed acute liver injury. 12 patients randomised to MARS® treatment. 12 patients randomised to standard medical therapy.	Prothrombin time did not change significantly for either MARS® or control group (no data given)
Mitzner et al (2000) * RCT was included in meta-analysis by Khuroo et al (2004)	II	Randomised controlled trial	13 patients with hepatorenal syndrome. 8 patients assigned to MARS® treatment in conjunction with standard medical therapy and HDF. 5 patients assigned to standard medical therapy and HDF.	Prothrombin activity (%)(mean ± SD) MARS® Control pre 32 ± 13 36 ± 19 post 44 ± 12 42 ± 22 *p*<0.01 NS
Sen et al (2004)	II	Randomised controlled trial	18 patients with AoCLF and alcoholic aetiology. 9 patients assigned to MARS® treatment + standard medical care. 9 patients assigned to standard medical care alone.	Prothrombin time (secs) (mean) MARS® Control pre 22.1 20.4 range (14-33.5) (16.5-31.3) post 18.3 20.1 range (14.5-33) (13.7-28.2) NS NS INR (mean) MARS® Control pre 2 1.8 range (1.2-3.0) (1.5-2.8) post 1.7 1.7 range (1.3-2.7) (1.2-2.5) NS NS

Schmidt et al (2003)	I III-2	Non-randomised	13 patients with hyper-acute liver failure. 8 consecutive patients assigned to MARS® treatment. 5 consecutive patients assigned as temperature ** matched controls treated with standard medical care.	Platelets (10^6/L) (mean ± SD) MARS® Control pre 103 ± 60 123 ± 61 post 76 ± 41 101 ± 37 *p*<0.05 NS MARS® vs Controls NS No significant changes before and after treatment in both control and MARS® groups, or between groups for: INR, haemoglobin levels, haematocrit or white blood cells.
Steiner & Mitzner * (2002)	IV	International Register (case series)	176 patients 99/176 (56.3%) AoCLF 38/176 (21.6%) ALF 27/176 (15.3%) primary graft dysfunction (PGD) after LTX 7/176 (4.0%) liver failure/ dysfunction after liver surgery and 5/176 (2.8%) miscellaneous	**AoCLF patients** INR (mean ± SD) n Pre Post 58/99 2.4 ± 1.0 1.9 ± 0.7 *p*=0.005 Range (1.1-6.1) (1.0-4.5)

* Study by Mitzner et al 2000 and Heeman et al 2002 supported in part by Teralkin AG, manufacturer of MARS® system
** Temperature matched controls were used as treatment with MARS® has a cooling effect on the body
INR = international normalised ratio, HDF = haemo-diofiltration, LTX liver transplantation, NS = non-significant, AoCLF = acute on chronic liver failure

Bilirubin is found in the blood as two fractions – conjugated and unconjugated, both of which are elevated in liver disease. A total serum bilirubin test measures both forms of bilirubin and a normal total serum bilirubin value is less than 1 mg/dL. Conjugated bilirubin represents approximately 30 per cent (or 0.3 mg/dL) of this value. Ammonia is usually produced in high concentrations in patients with liver disease due to muscle wasting. Ammonia levels may be used to monitor liver function or as a means for detecting encephalopathy. Similarly creatinine is a by-product of protein metabolism and elevated levels are associated with liver disease. Normal levels of creatinine are between 0.6 to 1.2 mg/dL. Enzymes such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are usually present in the serum in low concentrations. Liver cell injury will result in elevated concentrations of both AST and ALT, with levels of 300 U/L considered to be non-specific but levels >1000 U/L are considered abnormal and indicative of extensive hepatocellular injury. MARS® treatment would be expected to lower bilirubin levels (Pratt & Kaplan 2001).

Six of the seven studies included in this assessment reported on biochemical variables (Table 7). The good quality study by El Banayosy et al (2004) found no statistically significant difference in the levels of these biochemical factors when the MARS® treated patients were compared to the control group (level II intervention evidence). No within group analysis was presented. Similar results were presented by Heeman et al (2002). All of the remaining studies reported a significant decrease in bilirubin levels, regardless of patient aetiology (ALF, AoCLF or primary graft dysfunction) for patients treated with MARS®. Results for other factors were highly variable with some showing a significant decline in some studies but not in others. This may reflect small patient numbers in the trials. It should also be noted that there were large standard deviations and ranges associated with all of the measurements of biochemical factors.

Table 7 Biochemical variables

Study	Level of Intervention Evidence	Study Design	Population	Outcomes
El Banayosy et al (2004) RCT was included in meta-analysis by Khuroo et al (2004)	II	Randomised controlled trial	27 patients with hypoxic liver failure caused by cardiogenic shock bought on as a result of cardiac surgery. 14 patients randomised to MARS® treatment. 13 patients randomised to standard medical therapy.	Bilirubin (mg/dL) (mean ± SD) MARS® Control Pre 11.1 11.12 14 days 8.14 ± 5.99 15.44 ± 7.8 NS Aspartate aminotransferase (U/L) (mean ± SD) MARS® Control Day 1 50 ± 39 76 ± 45 NS 14 days 50 ± 29 99 ± 41 NS Alanine aminotransferase (U/L) (mean ± SD) MARS® Control Day 1 29.6 ± 43.2 43.5 ± 60.9 NS 14 days 45 ± 47 36 ± 17 NS Alkaline phosphatase (U/L) (mean ± SD) MARS® Control Day 1 142 ± 58 138 ± 32 NS 14 days 411 ± 181 224 ± 85 NS Lactate dehydrogenase (U/L) (mean ± SD) MARS® Control Day 1 805 ± 449 1177 ± 415 NS 14 days 957 ± 430 1734 ± 216 *p*=0.024 Cholinesterase (U/L) (mean ± SD) MARS® Control Day 1 2999 ± 851 3576 ± 1050 NS 14 days 1551 ± 442 1432 ± 487 NS Blood urea nitrogen (mg/dL) (mean ± SD) MARS® Control Day 1 80 ± 31 85 ± 29 NS 14 days 72 ± 31 87 ± 47 NS Creatinine (mg/dL) (mean ± SD) MARS® Control Day 1 1.74 ± 0.57 1.82 ± 0.55 NS 14 days 1.56 ± 0.34 1.36 ± 0.6 NS

Heeman et al (2002) * RCT was included in meta-analysis by Khuroo et al (2004)	II	Randomised controlled trial	24 patients with liver cirrhosis and a super-imposed acute liver injury. 12 patients randomised to MARS® treatment. 12 patients randomised to standard medical therapy.	Primary endpoint of bilirubin <15mg/dL for 3 consecutive days was reached by 5/12 (41.7%) of MARS® group and 2/12 (16.6%) of control group. Those in MARS® group took a shorter time to reach this endpoint (3,6,6,8,21 days) than the control group (17, 24 days) but the difference was NS. There was no significant difference between MARS® and Control groups at 30-days for bile acids or bilirubin. The only parameter to demonstrate a significant difference between groups was creatinine. Creatinine (mg/dL) MARS® group (mean) Pre: 1.4 (0.5-3.7) Post: 0.84 (0.5-2.3) *p*<0.05 There was no significant change in any of these parameters from baseline to 30-days in either the MARS® or Control groups.
Mitzner et al (2000) * RCT was included in meta-analysis by Khuroo et al (2004)	II	Randomised controlled trial	13 patients with hepatorenal syndrome. 8 patients assigned to MARS® treatment in conjunction with standard medical therapy and HDF. 5 patients assigned to standard medical therapy and HDF	Serum sodium (mmol/L) (mean ± SD) MARS®: pre 130 ± 8; post 139 ± 7 Control: pre 124 ± 8; post 131 ± 7 *p*<0.01 NS Creatinine (mg/dL) (mean ± SD) MARS®: pre 3.8 ± 1.6; post 2.3 ± 1.5 Control: pre 4.4 ± 1.3; post 3.8 ± 0.5 *p*<0.01 NS Total bilirubin (mg/dL) (mean ± SD) MARS®: pre 26.8 ± 11.6; post 17.3 ± 7.5 Control: pre 24.0 ± 18.6; post 22.2 ± 12.4 *p*<0.01 NS Albumin (g/L) (mean ± SD) MARS®: pre 25.1 ± 6.4; post 29.9 ± 6.6 Control: pre 28.3 ± 5.4; post 25.7 ± 4.0 NS NS
Sen et al (2004)	II	Randomised controlled trial	18 patients with AoCLF and alcoholic aetiology. 9 patients assigned to MARS® treatment + standard medical care. 9 patients assigned to	Bilirubin (µmol/L) (mean) MARS®: pre 396 (281-708); post 182 (140-348) Control: pre 232 (115-416); post 280 (102-544) *p*<0.001 NS Creatinine (µmol/L) (mean) MARS®: pre 88 (62-267); post 86.5 (33-270) Control: pre 113 (35-203); post 62.5 (28-97) NS NS

			standard medical care alone.	Nitrate (µmol/L) (mean) MARS® Control pre 88.3 92 range (25.9-249) (49-247.3) post 73 61.2 range (15.4-89.4) (22.4-326) *p*<0.05 NS Nitrite (µmol/L) (mean) MARS® Control pre 8 3.9 range (2.3-17.5) (0-33.5) post 2.8 4.3 range (0.2-17) (0-12.8) *p*<0.05 NS No significant changes before and after treatment in both control and MARS® groups for: albumin, TNF-α, TNF-R1, TNF-R2, IL-6, IL-8, IL-10, MDA or arterial ammonia.
Schmidt et al (2003)	III-2	Non-randomised	13 patients with hyper-acute liver failure. 8 consecutive patients assigned to MARS® treatment. 5 consecutive patients assigned as temperature ** matched controls treated with standard medical care.	Creatinine (µmol/L) (mean ± SD) MARS® Control pre 256 ± 235 337 ± 212 post 151 ± 111 357 ± 217 *p*<0.05 NS Urea (mmol/L) (mean ± SD) MARS® Control pre 9.8 ± 10.8 12.9 ± 9.6 post 5.3 ± 6.6 12.8 ± 9.8 *p*<0.05 NS Bilirubin (µmol/L) (mean ± SD) MARS® Control pre 225 ± 100 204 ± 178 post 195 ± 73 217 ± 177 *p*<0.05 NS Alanine aminotransferase (U/L) (mean ± SD) MARS® Control pre 1827 ± 1538 2779 ± 2460 post 1510 ± 1302 2137 ± 1536 *p*<0.05 *p*<0.05 Differences between MARS® and controls not stated. No significant changes before and after treatment in both control and MARS® groups, or between groups for: ammonia or albumin.

Steiner & Mitzner * (2002)	IV	International Register (case series)	176 patients 99/176 (56.3%) AoCLF 38/176 (21.6%) ALF 27/176 (15.3%) primary graft dysfunction (PGD) after LTX 7/176 (4.0%) liver failure/ dysfunction after liver surgery and 5/176 (2.8%) miscellaneous	**AoCLF patients** Bilirubin (µmol/L) (mean ± SD) n: 70/99 — Pre: 499 ±192 (139-1248) — Post: 301 ± 130 (82-824) — *p*<0.0001 Creatinine (µmol/L) (mean ± SD) n: 70/99 — Pre: 248 ± 204 (27-884) — Post: 153 ± 108 (27-452) — *p*=0.0001 Urea (mmol/L) (mean ± SD) n: 70/99 — Pre: 20 ± 12 (1-50) — Post: 14 ± 10 (1-46) — *p*=0.0003 Ammonia (µmol/L) n: 37/99 — Pre: 91 ± 40 (28-197) — Post: 69 ± 35 (32-188) — *p*=0.003 Albumin (g/L) n: 55/99 — Pre: 29 ± 7.3 (15-48) — Post: 34 ± 9 (14-53) — *p*<0.0001 Sodium (mmol/L) n: 69/99 — Pre: 136 ± 10 (116-170) — Post: 137 ± 6 (119-164) — NS Potassium (mmol/L) n: 69/99 — Pre: 4.2 ± 0.7 (1.9-6.2) — Post: 4.1 ± 0.6 (2.8-5.6) — NS Calcium (mmol/L) n: 57/99 — Pre: 2.1 ± 0.4 (0.95-3.0) — Post: 2.3 ± 0.3 (1.2-2.8) — *p*=0.02 **ALF patients** Bilirubin (µmol/L) n: 30/38 — Pre: 456 ± 315 (82-1325) — Post: 271 ± 137 (35-751) — *p*<0.0003 Creatinine (µmol/L) n: 37/38 — Pre: 191 ± 131 (53-584) — Post: 146 ± 148 (78-762) — NS Urea (mmol/L) n: 23/38 — Pre: 13.2 ± 6.8 (1.9-26) — Post: 10.7 ± 6.5 (1.8-25) — NS **PGD patients** Bilirubin (µmol/L) n: 25/27 — Pre: 437 ± 246 (58-1009) — Post: 251 ± 167 (34-731) — *p*<0.0003

				Creatinine (µmol/L)		
				n	Pre	Post
				19/27	201 ± 208	120 ± 87 *p*=0.036
				Range	(27-850)	(27-319)
				Urea (mmol/L)		
				n	Pre	Post
				18/27	21 ±17.2	13.1 ± 6.8 *p*=0.033
				Range	(2.7-69.1)	(0.8-26.6)
				Ammonia (µmol/L)		
				n	Pre	Post
				13/27	117 ± 68	48 ± 34 *p*=0.033
				Range		(7-206)(3-105)

* Study by Mitzner et al 2000 and Heeman et al 2002 supported in part by Teralkin AG, manufacturer of MARS® system
** Temperature matched controls were used as treatment with MARS® has a cooling effect on the body
NS = not significant, TNF = tumour necrosis factor, TNF-R = tumour necrosis factor receptor, MDA = malondialdehyde, LTX = liver transplantation, HDF = haemo-diofiltration, ALF = acute liver failure, AoCLF = acute on chronic liver failure

Only one good quality study (level II Intervention evidence) reported on the length of stay in intensive care for both patient groups (Table 8). There was no statistically significant difference in the mean number of days spent in intensive care between MARS® treated and control patients, despite apparent large differences in the number of in-hospital days, which may indicate a large standard deviation (these data were not provided). This study was unusual in that enrolled patients had liver failure as a result of cardiogenic shock, and as such had complicating co-morbidities.

Table 8 Length of stay in ICU

Study	Level of Interventional Evidence	Study Design	Population	Outcomes
El Banayosy et al (2004) RCT was included in meta-analysis by Khuroo et al (2004)	II	Randomised controlled trial	27 patients with hypoxic liver failure caused by cardiogenic shock bought on as a result of cardiac surgery. 14 patients randomised to MARS® treatment. 13 patients randomised to standard medical therapy.	Average length of stay MARS® group = 42 days Control group = 27 days NS One patient in MARS® group had a total artificial heart and was to remain in ICU. If this patient is removed from analysis the average stay in ICU for the MARS® group was 16 days, which was still NS when compared to the control group.

ICU = intensive care unit

Cost Analysis

A cost-effectiveness study by Hassanein et al (2003) analysed the costs associated with the randomised trial conducted by Heemann et al (2002), where 24 patients were randomised to receive standard medical care (n=12) or MARS® therapy in addition to standard medical care (n=12) (level II Intervention evidence) (Hassanein et al 2003; Heemann et al 2002). Heemann et al (2002) reported an improvement in encephalopathy and renal function in addition to a statistically significant improvement in 30-day survival in the MARS® therapy patients. The majority of patients enrolled in this study consisted of patients with acute decompensation associated with alcoholic liver cirrhosis. This study referred to a previous study that established the median charge per hospitalisation without liver transplant was $US 9600 (range ($US 5400-17,800). Median charges with liver transplant were higher at $US 132,700 (range $US 87,900-204,800).[2] Important factors influencing hospitalisation charges for patients with alcoholic liver disease are in-hospital death, worsening of hepatic encephalopathy, worsening of renal function (development of hepatorenal syndrome), formation of ascites and variceal bleeding. According to the study by Heemann et al (2002), MARS® therapy had a beneficial impact on in-hospital death, reduced hepatic encephalopathy and improved renal function. The total cost of *hospitalisation* for both groups was calculated (these totals don't include the actual costs of treating patients with MARS® therapy) (Table 9).

Table 9 Cost of hospitalisation for standard medical care group vs MARS® therapy plus standard medical care (excluding the costs of MARS® treatment)

		Standard medical care		MARS® + standard medical care	
	Cost per case ($US)	N	Cost in whole group ($US)	N	Cost in whole group ($US)
Average hospitalisation charges	9600	11	105,600	12	115,200
In-hospital deaths	6336	6	38,016	1	6336
Worsening renal function	3360	7	23,520	1	3360
Worsening hepatic encephalopathy	1632	3	4896	0	0
Formation of ascites	2112	1	2112	0	0
Variceal bleed	5376	1	5376	0	0
Total cost			**179,520**		**124,896**

To save five lives in the standard medical care group the estimated expenditure was $US 179,500, translating to a cost of $US 35,904 per survivor. Using these

[2] Current Australian values (14th December 2005): median charge per hospitalisation without liver transplant was $AUD 12,756 (range ($AUD 7,175-23,645). Median charges with liver transplant were higher at $AUD 176,277 (range $AUD 116,801-272,138).

figures, up to $US 394,144 could have been spent to save the 11 lives in the trial. The total estimated cost in the MARS® group was $US 124,896, a saving of $US 270,048 which would be made available to pay for the MARS® treatment, an average of $US 22,504 per patient. Patients in the MARS® treated group (n=12) received a total of 91 MARS® treatment sessions at an average cost of $US2,500 per session and a total cost of $US 227,500. Therefore the total cost incurred by the MARS® treatment group is $US 352,396 (cost of hospitalisation plus the cost of MARS® therapy). This translates to an expenditure of $US 32,036 per survivor in the MARS® therapy group compared to $US 35,904 per survivor in the standard medical care group, a saving of $US 4000 per survivor. Hassanein et al concluded that the benefits of MARS® therapy appear to justify the cost of treatment, however this was a small patient group and further research should be conducted (Hassanein et al 2003).

A lower quality case-control study (Intervention level III-2 evidence) examined 1-year survival, costs and cost-effectiveness of AoCLF patients treated with MARS® plus standard medical care (n=13) compared to AoCLF patients treated with standard medical care alone (n=23) (Hessel et al 2003). The mean 1-year survival time was 261 days and 148 days in the MARS® treatment and control groups, respectively. Kaplan-Meier survival analysis suggested an advantage for MARS® treatment, however this was not statistically significant (p=0.057). Initial inpatient hospital costs per patient (provider's perspective approximating a societal perspective) were an average of €28,178 in the MARS® therapy group and €6,395 in the control group. From a societal perspective the 1-year follow-up costs were €3,988 per patient in the MARS® therapy group and €1,419 per patient in the control group. Total costs from a societal perspective were therefore €32,167 and €7,813 for the MARS® and control groups respectively.[3] It should be noted that the costs of the MARS® treatment group were higher when compared to the control group due to the better survival rates in the MARS® group, leading to longer treatment times and therefore higher costs. To account for this discrepancy the total cost per patient were adjusted by survival, calculating the costs per treatment time period. Average costs per month of treatment from a societal perspective were €351 and €135 in the MARS® therapy and control groups, respectively. From a societal perspective the cost per life year gained was €79,075 and the cost per quality adjusted life year (QALY)[4] gained were €119,162 for patients treated with MARS® therapy. Cost-effectiveness could improve if the time horizon was increased, however the authors concluded that the

[3] Current Australian values (14th December 2005): total costs from a societal perspective were therefore $AUD 51,216 and $AUD 12,442 for the MARS® and control groups respectively.
[4] The Quality Adjusted Life Year (QALY) has been created to combine the quantity and quality of life. The QALY takes one year of perfect health-life expectancy to be worth a utility of 1, but regards one year of less than perfect health life expectancy as less than 1. QALYs can provide an indication of the benefits gained from a variety of medical procedures in terms of quality and life and survival for the patient. Phillips, C. (2005). *So what is a QALY?* [Internet] Bandolier. Available from: http://www.jr2.ox.ac.uk/bandolier/booth/glossary/QALY.html [Accessed 14th December 2005].

trade-off between clinical benefit and higher costs was acceptable at 1-year (Hessel et al 2003).

An earlier case-control study (Intervention level III-2 evidence) by Hessel et al (2002) reported a cost utility analysis of patients treated with MARS® therapy (n=69) and a control group treated with standard medical care alone (n=72). The average 1-year survival was 44 per cent and 33 per cent in the MARS® treatment and control groups, respectively. Kaplan-Meier survival analysis revealed a significant advantage for MARS® treatment after 100 days (p=0.036). A subgroup of patients were analysed for health related quality of life and there was no significant difference between the control (n=10) and the MARS® (n=15) groups. Calculations of QALYs result in 0.116 QALYs gained by treatment of one patient with MARS® in one year (Hessel et al 2002).

The cost of the MARS® device and a single treatment cost is approximately $AUD 30,000 and $AUD 5000, respectively. Due to the high cost of MARS® treatment in Australia, patients are averaging only three to five treatments and are being treated at a later stage of disease than ideal (personal communication, Teraklin AG company representative). A conservative estimate of the number of patients who may benefit from MARS® therapy in Australia and New Zealand is approximately ten per cent of patients on the liver transplant waiting, or 20 patients annually (personal communication, New Zealand liver transplant surgeon). If all of these patients received 3-5 treatments with MARS® therapy, the estimated cost to the health care system would range from $300-500,000 per year, not including the cost of the MARS® apparatus. It is unclear from studies included in this assessment whether repeat MARS® treatments would be needed.

If treatment with the MARS® device was effective at improving morbidity and mortality, it is likely that the high costs of treatment would be offset by a reduction in patients requiring liver transplants and hospital costs of intensive care compared to current supportive therapy and transplantation. At the time of reporting there were no Australian data examining the cost impact of treatment with the MARS®.

A study by Kraus et al (2005) reported on the actual costs of performing liver transplantation in Germany in 38 consecutive patients (Intervention level IV evidence). Costs included disposable products, medication, operating time and resources, procedural time and resources. The mean cost of liver transplantation was €49,000 ($AUD 77,973), with a large variation ranging from €18,000 ($AUD 28,647) to €189,000 ($AUD 300,987) per case. These figures do not take into account future costs such as ongoing immunosuppressant medication (Kraus et al 2005). If all patients on the liver transplant list in Australia were able to receive a liver transplant the estimated cost to the health care system would be a minimum of $7.8 million. This is an annual cost as the number of patients on the transplant waiting list has remained steady and may increase due to the increase in hepatitis C infections. No data were available on the cost of supporting patients on standard medical therapy while waiting for a suitable transplantation organ.

Ethical and social issues

Uncertainty of outcome

A key ethical issue for treatment with MARS® is the uncertainty concerning outcomes of treatment. Studies included in this assessment reported increased survival as the primary outcome, however whether treatment with MARS® confers any long-term benefit is unclear. Although some studies presented prognostic score data, there was no overall quality of life data. This is a significant omission, because judgements about life quality can be very important for severely ill patients with limited life expectancy. There are key ethical questions about the trade off between quality and quantity of life that can only be answered by individual patients and their families in consultation with health care providers.

It is also possible that the evidence base for treatment with MARS® will remain limited, because the primary outcome is *survival.* Two studies included in this assessment were halted by the Ethics Committee as it had become apparent that survival was increased in those patients offered MARS® treatment. It was felt that patients on standard medical therapy alone should be offered MARS® treatment as an alternative. Future trials may include a crossover arm, where patients randomised to standard medical treatment who shows signs of clinical deterioration (by measurement of surrogate outcomes), would be allowed to cross over to MARS® treatment.

The ethical problem here is that, despite the desire for more conclusive evidence, policy makers and clinicians will be forced to continue to make decisions about treatment with MARS® in the absence of adequate evidence.

Informed Consent

As with all other patients, patients offered treatment with MARS® must be fully informed of the potential benefits and harms associated with the treatment, especially in view of the experimental nature of the technology, compared to the usual practice of medical therapy alone. The United Kingdom's National Institute for Clinical Evidence advises that:

- special arrangements need to be in place to ensure that patients fully understand that treatment outcomes with MARS® are uncertain; and
- careful audit and review arrangements are needed to help reduce the uncertainty surrounding this treatment.

The serious nature of patients' illnesses can further complicate consent to treatment with MARS®. First, patients being treated for acute or acute-on-chronic liver failure may have impaired capacity to provide written or verbal consent. In

this situation, arrangements need to be made for patients to "receive information and to express their wishes in other ways" (NHMRC Second Draft of the National Statement on Ethical Conduct on Research in Humans, 2006). In addition, steps must be taken to ensure that the autonomy of decision making by patients is not compromised by their dependence on medical personnel and other health professionals. For example, if the treating clinician is also the researcher, it may be more appropriate for consent to be sought by an independent person.

MARS® as a bridge to transplantation

Further ethical problems arise for patients offered treatment with MARS® as a bridge to transplantation. With organs already in short supply, treatment with MARS® may further increase the number of patients on waiting lists for transplantation. Prioritising patients for access to transplants is an extraordinary complex and difficult ethical area, and it beyond the scope of this report to do more than flag this as an area of concern.

Access Issues

From a societal perspective, MARS® therapy is of questionable value. The price of this technology, and the small group of individuals who would have access to it for relatively short periods of time, raise concerns about the appropriateness of allocating resources to this therapy that might be better used in other areas. However, it is ethically unacceptable to refuse access to a technology based on these grounds alone.

MARS® is likely to be accessible in only large, tertiary hospitals or centres of excellence where intensive care facilities and liver specialists would be available, and as such it would be highly unlikely to benefit individuals living in rural or remote areas.

Training and Accreditation

Training

Clinicians and nursing staff would be required to undergo training in the use and principles of operation of the MARS® system, although this may be minimal as patients would already be situated in high-dependency intensive care units. Appropriate medical staff would be required to monitor patients during treatment. ASC Biotech distributes MARS® in Australia and the company organises training courses at the time of initial purchase. The procedure is considered straightforward for an experienced dialysis nurse in an intensive care unit (personal communication ASC Biotech, January 2006).

Clinical Guidelines

There are no current Australian guidelines for the treatment of liver failure. Liver failure may result from a number of causes, however the most common reason is as a result of cirrhosis caused by excessive alcohol intake or hepatitis. The American College of Gastroenterology have developed guidelines for the recommended treatment of alcoholic liver disease, which has some therapeutic options for those patients who progress to acute liver failure (McCullough & O'Connor 1998). In addition the World Congress of Pediatric, Hepatology and Nutrition are developing guidelines for the treatment of hepatic failure in children (Baker et al 2004).

The American Association for the study of Liver Diseases (AASLD) published guidelines for the management of acute liver failure in 2005, including management by aetiology (Table 10) (National Guidelines Clearinghouse 2005). Routine treatment of patients suffering from ALF or AoCLF in an acute care facility would include:

- routine monitoring of complete blood count, prothrombin time with INR[5], serum creatinine, total bilirubin, alanine aminotransferase, aspartate aminotransferase, pH and factor V levels;
- protein restriction;
- bowel decontamination;
- administration of lactulose, intravenous H_2-blocker or proton pump inhibitors;
- administration of broad spectrum antimicrobial agents;
- an intracranial pressure monitor may be placed in some patients and cerebral perfusion pressure maintained above the 60-70 mmHg range;
- hyperventilation to keep PCO_2 below 30 mmHg;
- intravenous administration of mannitol 20%;
- sedation with phenobarbitone;
- administration of vasoconstrictive agents for the maintenance of mean arterial pressure; and
- total plasma exchange may be performed to correct severe coagulopathy and to avoid toxic effects of hyperbilirubinaemia (Aladag et al 2004).

[5] INR = international normalised ratio - is the ratio of the patient's clotting time to the laboratory's mean reference value

Table 10 Management of acute liver patients by aetiology

Aetiology	Management options
Acetaminophen hepatoxicity	1. Activated charcoal 2. N-acetylcysteine
Mushroom poisoning	1. Penicillin G 2. Silymarin 3. Placement on transplant list
Drug-induced hepatoxicity	1. Discontinuation of all but essential medications
Viral hepatitis	1. Supportive care 2. Nucleoside analogs 3. Acyclovir
Wilson Disease	1. Immediate placement on transplant list
Autoimmune hepatitis	1. Corticosteroids (prednisone) 2. Placement on transplant list
Acute fatty liver of pregnancy/ haemolysis, elevated liver enzymes, low platelets syndrome (HELLP)	1. Consultation with obstetrician and expeditious delivery
Acute Ischaemic injury	1. Cardiovascular support
Budd-Chiari syndrome	1. Liver transplantation

Transplantation is widely accepted as the only effective therapy for liver failure once supportive measures have failed. Approximately 40 per cent of patients with ALF may survive the acute episode with medical therapy alone, however there is currently no means of identifying those patients who will survive. Few effective treatment options apart from transplantation are available for patients with AoCLF. Therapeutic options such as treatment with MARS® or haemodialysis may be administered to patients awaiting transplantation and may give sufficient benefit to allow this patient group to regenerate the native liver, making the need of a liver transplantation redundant. For AoCLF patients, treatment with MARS® or haemodialysis may allow them to remain well enough until a suitable organ became available for transplantation (Barshes et al 2005).

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

An Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, an Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of the molecular adsorbents recirculating system (MARS®), its present and potential use in the Australian public health system, and future implications for the use of this technology.

Search Strategy used for the Report

The medical literature (Table 12) was searched utilising the search terms outlined in Table 11 to identify relevant studies and reviews, until November 2005. In addition, major international health assessment databases were searched.

Table 11 Search terms utilised

Search terms
MeSH
Hepatic insufficiency; liver cirrhosis; hemoperfusion; sorption detoxification; liver, artificial
Text words
H?emoperfusion, molecular adsorbent recirculating system, MARS, albumin dialysis, artificial liver support device*
Limits
English, human

Table 12 Literature sources utilised in assessment

Source	Location
Electronic databases	
AustHealth	University library
Australian Medical Index	University library
Australian Public Affairs Information Service (APAIS) – Health	University library
Cinahl	University library
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	University library
Current Contents	University library
Embase	Personal subscription
Pre-Medline and Medline	University library
ProceedingsFirst	University library
PsycInfo	University library
Web of Science – Science Citation Index Expanded	University library
Internet	
Current Controlled Trials metaRegister	http://controlled-trials.com/
Health Technology Assessment international	http://www.htai.org
International Network for Agencies for Health Technology Assessment	http://www.inahta.org/
Medicines and Healthcare products Regulatory Agency (UK).	http://www.medical-devices.gov.uk/
National Library of Medicine Health Services/Technology Assessment Text	http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat
National Library of Medicine Locator Plus database	http://locatorplus.gov
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/grey.shtml
Trip database	http://www.tripdatabase.com
U.K. National Research Register	http://www.update-software.com/National/
US Food and Drug Administration, Center for Devices and Radiological Health.	http://www.fda.gov/cdrh/databases.html

Availability and Level of Evidence

There is considerable literature describing the use of MARS® treatment for patients with liver failure. The majority of this literature is case series evidence (level IV Intervention evidence) and is therefore poor quality. Only higher quality evidence is presented and analysed in the body of this report, however a list of studies and their abbreviated results are presented in Appendix C. This list is by no means exhaustive. This report included one meta-analysis (level I Intervention evidence), four randomised controlled trials (level II Intervention evidence), one non-randomised study (level III-2 Intervention evidence) and one study from an International Register of case series (Level IV Intervention evidence). See Appendix B for profiles of these studies.

Sources of Further Information

A randomised controlled trial is currently being conducted by the Gastroenterology and Liver Unit in the Southern Derbyshire Acute Hospitals NHS Trust. Patients with stable alcoholic liver disease, currently abstinent from alcohol, will be recruited into the study and randomised to either the control, non-treatment group or to MARS® therapy. Those in the MARS® group will be further randomised into groups A or B. Those in group B will receive MARS® therapy every two weeks and studied for eight weeks. It was not stated what treatment regime the patients in Group A would receive. Outcomes measures include quality of life and symptom load, level of hepatic encephalopathy and biochemical parameters, and level of portal hypertension and systemic haemodynamics. Recruitment of patients was scheduled to end as of October 2005 (Current Controlled Trials 2005). A phase III study is currently being conducted in Paris, France. Approximately 110 patients with fulminant and sub-fulminant hepatic failure will be enrolled and the primary outcome will be patient survival at six months. Expected completion date is March 2008. In addition, a phase III study is being conducted in Madrid, Spain on 172 patients with exacerbated liver insufficiency with hyper-bilirubinaemia, encephalopathy and/or renal failure. The primary outcome is patient survival (transplant free) at 28 days and this study is due for completion in August 2007.

Conclusions

Molecular adsorbents recirculating system (MARS®) is intended to treat acute liver failure (ALF) or acute-on-chronic liver failure (AoCLF). Both conditions are characterised by hepatic encephalopathy, renal dysfunction and circulatory changes. Metabolites such as bilirubin, aromatic amino acids and bile acids accumulate during ALF and AoCLF and these are toxic if not cleared effectively by the liver. These metabolites bind tightly to human serum albumin. MARS® is intended to selectively remove these albumin bound metabolites and in so doing, stabilise liver function by decreasing circulating levels of toxins.

Cirrhosis is one of the most common causes of liver failure, and this may be caused by hepatitis infection or excessive alcohol intake. The prevalence of hepatitis infection is rising in both Australia and New Zealand, with modelling suggesting a tripling in the prevalence of hepatitis C related liver failure by the year 2020.

There are few treatment options available for patients with ALF or AoCLF and transplant is widely accepted as the only effective therapy once supportive measures have failed. Liver transplantation is capable of curing 90 per cent of patients with liver failure, however due to the scarcity of organ availability mortality rates are still approximately 80 per cent. A large proportion of ALF patients will spontaneously recover (40%), however it is impossible to determine which patients will be survivors. MARS® may be considered as a bridge-to-transplantation, keeping patients alive until a suitable organ becomes available. However, many AoCLF patients are not suitable for transplantation due to the chronic nature of the disease and many ALF patients do not receive transplantation in time. The Australia and New Zealand Organ Donation registry reported that there were 213 liver transplants performed in the two countries in 2004. Approximately ten percent of patients on the liver transplant waiting list would benefit from MARS® therapy. In January 2005 there were 116 patients on the transplant waiting list.

There is considerable literature describing the use of MARS® for the treatment of liver failure in small, uncontrolled case series. This poorer quality evidence (level IV intervention evidence) was not assessed in this report.

Of the high quality evidence assessed, mortality or increased survival was the main effectiveness outcome reported. The highest level of evidence (level I intervention evidence) reported no statistically significant difference in the risk of death between MARS® treated and control patients. However, this meta-analysis did report a large reduction in the risk of death (44%) for all MARS® treated patients (RR= 0.56, 95% CI 0.28, 1.14) relative to patients receiving usual care. This analysis was under powered due to the small numbers of patients enrolled in the trials included in this meta-analysis.

The absolute risk difference between the control and MARS® treated group was -5.3 per cent. The inverse of this provides an estimate of the number of patients with liver failure that would be needed to be treated with MARS® therapy as opposed to standard medical management, *to prevent one death.* Therefore the number needed to treat to *benefit (prevent one death)* is 19 patients. The meta-analysis also reported a stratified analysis which demonstrated no effect modification by type of liver failure as there was no statistically significant difference in mortality of AoCLF (RR= 0.50) and ALF patients (RR= 0.50) (treated with MARS® compared to controls).

Two studies were halted prematurely by the ethics committee after interim analysis revealed a greater mortality in the control group when compared to MARS® treated patients, limiting the power of these studies in the final analysis.

Most studies reported on surrogate outcomes, however these data were variable with few studies conducting statistical tests to assess differences between MARS® treated patients and the control group. Most studies were able to demonstrate statistically significant differences between baseline values and post-MARS® treatment values, although this was not always the case.

Only one study reported on adverse events associated with the treatment of patients with MARS®. In this extremely ill population it may be difficult to differentiate between normal adverse events associated with liver failure and those associated with MARS® treatment. However, patients treated with MARS® therapy experienced fewer adverse events for most morbidity, excluding coagulopathy, when compared to patients treated with standard medical care.

Follow-up was short in the majority of studies ranging from six hours to 30 days. In addition, there was *considerable* variation in the characteristics of patients enrolled in these studies (patients with cardiogenic shock, AoCLF, ALF, hepatorenal syndrome) and in the *stage of illness* when patients commence treatment with MARS®. This has implications for the generalisability of these results and for patient selection. In addition, timing of treatment may be a critical issue as patients may already be too critically ill to benefit from MARS® therapy.

A cost-effectiveness study by Hassanein et al (2003) analysed the cost of liver failure patients randomised to either treatment with MARS® or standard medical care. To save five lives in the standard medical care group the estimated expenditure was $US 179,500, translating to a cost of $US 35,904 per survivor. Using these figures, up to $US 394,144 could have been spent to save the 11 lives in the trial. The total estimated cost in the MARS® group was $US 124,896, a saving of $US 270,048 which would be made available to pay for the MARS® treatment, an average of $22,504 per patient. The total cost incurred by the MARS® treatment group was $US 352,396 (cost of hospitalisation plus the cost of MARS® therapy). This translated to an expenditure of $US 32,036 per survivor in

the MARS® therapy group compared to $US 35,904 per survivor in the standard medical care group, a saving of $US 4,000 per survivor (length of survival not stated).

The cost of the MARS® device and a single treatment cost is approximately $AUD 30,000 and $AUD 5,000, respectively. In Australia, patients average only three to five treatments and are being treated at a later stage of disease than ideal (personal communication Teraklin AG representative, May 2005). A conservative estimate of the number of patients who may benefit from MARS® therapy in Australia and New Zealand is approximately ten per cent of patients on the liver transplant waiting, or 20 patients annually (personal communication, New Zealand liver transplant surgeon). If all of these patients received 3-5 treatments with MARS® therapy, the estimated cost to the health care system would range from $300-500,000 per year, not including the cost of the MARS® apparatus. However, if treatment with the MARS® device was effective in improving morbidity and mortality, it is likely that the high costs of treatment would be offset by a reduction in patients requiring liver transplants and hospital costs of intensive care compared to current supportive therapy and transplantation.

In conclusion, the highest level of evidence indicates that treatment of liver failure patients with MARS® therapy may increase their survival compared to patients who receive standard medical care. Further data from a randomised controlled trial, with a large number of enrolled patients should be conducted with sufficient power (80%) to detect a statistically significant difference between the MARS® intervention and control groups. In addition, treatment with MARS® therapy appears to have a beneficial effect on surrogate physiological outcomes.

It has to be noted that critically ill patients with liver failure have very few treatment options available to them.

Appendix A: Levels of Evidence

Designation of levels of evidence according to type of research question

Level	Intervention [§]	Diagnosis [**]	Prognosis	Aetiology [†††]	Screening
I [*]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, [§§] among consecutive patients with a defined clinical presentation [††]	A prospective cohort study [***]	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, [§§] among non-consecutive patients with a defined clinical presentation[††]	All or none [§§§]	All or none [§§§]	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial [†] Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study [‡] Interrupted time series without a parallel control group	Diagnostic case-control study [††]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) [‡‡]	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Tablenotes

A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

§ Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b*)*.

† This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C).

‡ Comparing single arm studies ie. case series from two studies.

** The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See *MSAC (2004) Guidelines for the assessment of diagnostic technologies*. Available at: www.msac.gov.au .

§§ The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology*, 2003, 3: 25.

†† Well-designed population based case-control studies (eg population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. These types of studies should be considered as Level II evidence. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice.

‡‡ Studies of diagnostic yield provide the yield of diseased patients, as determined by an index test, without confirmation of accuracy by a reference standard. These may be the only alternative when there is no reliable reference standard.

*** At study inception the cohort is either non-diseased or all at the same stage of the disease.

§§§ All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

††† If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence etc.

Hierarchies adapted and modified from: NHMRC 1999; (Lijmer et al 1999; Phillips et al 2001; Bandolier editorial 1999)

Appendix B: Profiles of Included Studies

Study	Location	Study design	Study population	Study details	Outcome assessed	Length of follow-up
El Banayosy, A. Kizner, L. Schueler, V. Bergmeier, S. Cobaugh, D. Koerfer, R. (2004)	Bad Oeynhausen, Germany	RCT Intervention evidence level II. Random-isation carried out 1:1.	27 patients with hypoxic liver failure caused by cardiogenic shock brought on as a result of cardiac surgery. 14 patients randomised to MARS® treatment 13 patients randomised to standard medical therapy and CVVH	Patients underwent MARS® treatment for 3 consecutive days for 8 hours. If bilirubin was not < 6mg/dL after initial 3 treatments, then MARS® therapy was continued. Control group received haemo-filtration. If bilirubin levels persisted >15-20 mg/dL patients were allowed to cross over and receive MARS® treatment. Exclusion criteria: Chronic renal failure, chronic hepatic failure, sepsis, WBC >12,500 g/L or hyperdynamic circulation. Inclusion criteria: Bilirubin >8 mg/ml, cardiogenic shock after cardiac surgery.	Survival, haemo-dynamic variables, biochemical variables	14 days

Heeman, U. * Treichel, U. Loock, J. Philipp, T. Gerken, G. Malago, M. Klammt, S. Loehr, M. Liebe, S. Mitzner, S. Schmidt, R. Stange, J. (2002) (Heemann et al 2002)	Rostock, Germany and San Diego, United States	RCT Intervention evidence level II. Random-isation carried out on a 1:1 treatment: control in blocks of 6 patients, with concealment of allocation.	24 patients with liver cirrhosis and a super-imposed acute liver injury.	24 patients randomised. MARS® treatment group (n=12) received a maximum of 10 treatments over 2 weeks. MARS® treatment continued only if bilirubin levels >15mg/dL and was discontinued if bilirubin was <15mg/dL for 3 consecutive days. Mean treatment duration 6 hours. Control group received standard medical care. Inclusion criteria: severe hyper-bilirubinaemia (>20mg/dL), cirrhosis with Child-Turcotte-Pugh index >7	Primary endpoint: bilirubin <15mg/dL. Secondary endpoints: in-hospital survival, prothrombin time, mean arterial pressure, hepatic encephalo-pathy, serum creatinine and bile acids.	30 days or until death
Khuroo, M.S. Khuroo, M. S. Farahat, K.L.C. (2004) (Khuroo et al 2004)	Chennai, India	Meta-analysis Intervention level evidence I	Study included data from 4 RCTs (n=67 patients) and 2 non-randomised trials (n=61 patients)	Studies included in meta-anlysis included Heeman et al (2002), El Banayosy et al (2004), Mitzner et al (2000), Schmidt et al (2003) and 2 non-randomised studies by Hessel et al (2003) and Chen et al (2002)	Mortality	No follow-up time period stated.

Mitzner, S.R. * Stange, J. Klammt, S. Risler, T. Erley, C.M. Bader, B.D. Berger, E.D. Lauchart, W. Peszynski, P. Freytag, J. Hickstein, H. Loock, J. Löhr, J-M. Liebe, S. Emmrich, J. Korten, G. Schmidt, R. (2000) (Mitzner et al 2000)	Rostock & Tübingen, Germany	RCT Intervention evidence level II. Random-isation performed by individual not involved with diagnostic or therapeutic process. Sealed envelopes containing treatment allocation as given by computerised random number generating programme	13 patients with hepatorenal syndrome. 8 patients assigned to MARS® treatment in conjunction with standard medical therapy and HDF. 5 patients assigned to standard medical therapy and HDF	Patients underwent MARS® treatment for 6-8 hours per day, with a maximum number of 10 treatments. A maximum of 2 treatment pauses of 1 day/week was allowed to perform HDF. Exclusion criteria: Fulminant hepatic failure, sepsis, severe acute haemorrhages, malignancy, obstructive/ chronic renal failure, pregnancy, severe cardiopulmonary disease. Inclusion criteria: >18 years of age, hepatorenal syndrome, chronic liver failure (at least 3 of 4 criteria) **	30-day survival, haemo-dynamic variables, biochemical variables	30 days
Schmidt, L.E. Wang, L.P. Hansen, B.A. Larsen, F.S. (2003) (Schmidt et al 2003)	Copenhagen, Denmark	Non-randomised Intervention evidence level III-2	13 patients with hyper-acute liver failure. 8 consecutive patients assigned to MARS® treatment, median age 47 years (range 23-60) 5 consecutive patients assigned as temperature matched controls, median age 40 years (range 18-63)	Patients studied on the day after onset of hepatic encephalopathy of grade III or IV. Patients in treatment group received a single 6-hour MARS® treatment Control patients received standard medical care.	Mortality, haemo-dynamic variables, biochemical variables	Not stated

Sen, S. Davies, N.A. Mookerjee, R.P. Cheshire, L.M. Hodges, S.J. Williams, R. Jalan, R. (2004) (Sen et al 2004)	London, United Kingdom	RCT Intervention evidence level II. Random-isation performed by sealed envelopes containing treatment allocation as given by computerised random number generating programme	18 patients with AoCLF and alcoholic aetiology. 9 patients assigned to MARS® treatment + standard medical care. 9 patients assigned to standard medical care alone.	MARS® treatment: patients treated for 4 sessions of 8 hours over the 7-day study period. Exclusion criteria: Uncontrolled infection, gastrointestinal bleeding, malignancies, pregnancy, severe cardiorespiratory disease, HIV infection or prior treatment with terlipressin for HRS. Inclusion criteria: >18 years of age, alcoholic liver disease with AoCLF, deterioration in liver function, increasing jaundice (serum bilirubin >100µmol/L) and either encephalopathy (≥ grade II) or HRS in a patient with evidence of cirrhosis.	Encephalo-pathy grade, haemo-dynamic variables, biochemical variables, prognostic markers and cytokines.	7 days
Steiner, C. Mitzner, S. (2002) (Steiner & Mitzner 2002)	London, UK and Rostock, Germany	International Register (case series) Intervention evidence IV	176 patients 99/176 (56.3%) AoCLF patients, treated with an average of 4.3±2.6 (range (1-15) treatments of 8.2±5.4 hours durations (range 1-27) 38/176 (21.6%) ALF patients, treated with an average of 3.97±2.68 (range 1-12) treatments of 10.8±7.3 (range	Treated with MARS®	Survival, prognostic scores, clinical parameters, biochemical parameters.	

			3-48) duration 27/176 (15.3%) primary graft dysfunction after LTX patients treated with an average of 4.7±4.5 (range 1-24) treatments 7/176 (4.0%) liver failure/ dysfunction after liver surgery patients and 5/176 (2.8%) miscellaneous			

RCT = randomised controlled trial, CVVH = continuous veno-venous haemofiltration, WBC = white blood cell count, LTX = liver transplantation, HRS = hepatorenal syndrome

* Study by Mitzner et al 2000 and Heeman et al 2002 supported in part by Teralkin AG, manufacturer of MARS® system, HDF = haemo-diofiltration,

** Criteria for chronic liver failure: Ultrasonic signs of chronic damage (cirrhosis), impaired synthesis function (hypo-albuminaemia <30g/L, prothrombin time <70%, antithrombin III <70%, serum cholinesterase <40 µmol/s/L or <2.3 kU/L), hyperbilirubinaemia (>15mg/dL), hepatic encephalopathy (grade I-IV).

Appendix C: Lower Level Evidence

Study	Location	Study design	Study population	Study details	Outcome
(Krisper et al 2005)	Graz, Austria	Intervention level III-3 evidence	8 patients with AoCLF treated alternatively with MARS® and fractionated plasma separation (FPS)	Patients assigned to begin either MARS® or FPS treatment. Each treatment was of 6 hour duration. A total of 32 treatments (16 treatment pairs) were performed.	There was a significantly reduction in the ratio of total, unconjugated or conjugated bilirubin and urea after treatment with FPS compared to MARS®. Plasma concentrations of total, unconjugated or conjugated bilirubin, ammonia and urea fell with both MARS® and FPS treatment but there was no significant difference between the 2 groups.
(Sen et al 2005)	London, United Kingdom	Intervention level III-3 evidence	11 patients with alcoholic hepatitis and portal hypertension.	8 patients treated with MARS® and 3 patients treated with haemofiltration	6/8 (75%) MARS® died in-hospital 2/3 (66.6%) haemofiltration died in-hospital Remaining 3/11 (27.3%) patients still alive at 3 months Hepatic venous pressure gradient reduced significantly in MARS® group (p=0.003) at end of MARS® treatment session and remained unaltered in haemofiltration patients. Mean arterial pressure increased in MARS® patients (*p*=0.02) and remained unaltered in haemofiltration patients.
(Auth et al 2005)	Essen, Germany	Case series Intervention level IV evidence	2 children with Wilson's disease	Each patient underwent 4 treatments with MARS® as bridging to LTX	Removal of toxic metabolites and inflammatory mediators into the albumin circuit of MARS® was detected with every treatment, but *also hepatic growth factors* which may affect liver regeneration. Successful in both patients as a bridge to LTX.

(Doria et al 2003b)	Pittsburgh, USA	Case series Intervention level IV evidence	3 patients with intractable pruritus secondary to hepatitis C cirrhosis	Each patient underwent 7 MARS® sessions 9 month follow-up	Subjective improvement in pruritus and quality of life, decrease in serum bile acid concentration, no patient required re-treatment and/or LTX. One patient died 201 days post-MARS® treatment.
(Pares et al 2004)	Barcelona, Spain	Case series Intervention level IV evidence	4 patients with primary biliary cirrhosis and resistant pruritus.	Each patient treated with two 7-hour MARS® sessions, one day apart.	Complete relief of pruritus symptoms in 2/4 (50%) patients. Remaining 2/4 patients experienced mild relief. Relief lasting 18 months in 1 patient, 4 months in another (returning symptoms mild). Circulating bile acids reduced in 4/4 (100%) patients post-MARS® treatment.
(Novelli et al 2005a)	Roma, Italy	Case series Intervention level IV evidence	5 patients with hepatitis B positive lymphoma with acute hepatic failure due to chemotherapy	An average number of 2 MARS® treatments per patient (range 1-6), mean length of application 6 hours (range 4-12) Follow-up for 12 months	3/5 (60%) patients demonstrated a decrease in aminotransferase levels, total and direct bilirubin levels and improved haematological results. 2/5 (40%) patients failed to improve and died later. The condition of these 2 patients had seriously deteriorated prior to MARS® treatment and treatment may have started too late to be of benefit.
(Peek et al 2002)	Leicester, UK	Retrospective case series Intervention level IV evidence	5 patients receiving respiratory extracorporeal membrane oxygenation (ECMO) with bilirubin >300µmol/l, who developed liver failure secondary to respiratory illness.	Patients received between 1-8 MARS® treatments	Patients with respiratory ECMO and no MARS® treatment had 66% survival rate, once hepatic failure bilirubin >300µmol/l predicts death with 87.8% sensitivity and 90.3% specificity. Patients treated with MARS® Mean reduction in serum bilirubin ranged between 30-162 µmol/l. 2/5 (40%) survived

(Rittler et al 2004)	Munich, Germany	Case series Intervention level IV evidence	5 liver failure patients with post-surgical septic multiple organ failure	Patients received 13.4 ± 1.9 MARS® treatments over a time period of 17.2 ± 5.2 days	5/5 (100%) patients died of progressive septic organ malfunction. MARS® treatment not recommended for this patient group. Bilirubin levels fell significantly Pre: 23.0 ± 1.4 mg/dl Post: 16.6 ± 0.6 mg/dl (p<0.01) Partial thromboplastin time increased significantly Pre: 57.2 ± 3.6 seconds Post: 79.8 ± 7.7 seconds, (p<0.05), indicating a deterioration of clotting system. Ammonia concentration: NS Thrombocyte count: NS
(Zocco et al 2005)	Rome, Italy	Case series Intervention level IV evidence	5 patients with chronic hepatitis C infection with acute liver decompensation	Patients received an average of 3.2 MARS® treatments each.	90 day follow-up: 4/5 (80%) died despite MARS® treatment: 2/5 (40%) due to cardiac failure, 1/5 (20%) due to organ failure, 1/5 (20%) due to sepsis. Parameters Total bilirubin (mg/dl): pre 40.8 ± 8.4 post: 33.4 ± 8.5, p<0.01 Conjugated bilirubin (mg/dl) pre: 27.3 ± 6.0 post: 16 ± 7, p=0.01 Unconjugated bilirubin (mg/dl) pre: 15.3 ± 6.3 post: 13.3 ± 3.6, NS Bile acids (µmol/L) pre: 189.3 ± 74.6 post: 129.3 ± 88.1, p=0.01 BUN (mg/dl) pre: 60.1 ± 25.3 post: 46.2 ± 30.5, p=0.01 Creatinine (mg/dl) pre: 3.02 ± 2.04 post: 2.31 ± 1.65, p=0.05 Significant improvements in mitochondrial function

(Kellersmann et al 2002)	Würzburg, Germany	Case series Intervention level IV evidence	5 patients with liver failure after hepatic resection or LTX	Each patient received 2-5 MARS® treatments	4/5 (80%) patients died: 1/5 (20%) sepsis 1/5 (20%) cardiac failure 1/5 (20%) bacterial pericarditis 1/5 (20%) multi-organ failure 1/5(20%) successfully treated with normalised bilirubin levels and liver function
(Lee et al 2002)	Singapore	Case series Intervention level IV evidence	5 patients with liver failure	A total of 29 MARS® treatments lasting a minimum of 6 hours	Significant correlation between the pre-dialysis molar ratio of bilirubin (total and conjugated) to albumin to the reduction in bilirubin (total and conjugated) R^2 = 0.27 and 0.62 respectively, p<0.005 Ratio of change in total bilirubin µmol/l to the pre-dialysis molar ratio of total bilirubin to albumin were 6.2±4.2 And Ratio of change in conjugated bilirubin µmol/l to the pre-dialysis molar ratio of total bilirubin to albumin were 10.8 ±4.3
(Mullhaupt et al 2002)	Zurich, Switzerland	Case series Intervention level IV evidence	6 patients with severe liver insufficiency	Patients received 1-16 MARS® treatments	6/6 (100%) significantly reduced bilirubin levels 3/6 (50%) improved encephalopathy 3/6 (50%) suffered kidney failure and required kidney replacement therapy 2/6 (33.3%) MARS® treatment precipitated a disseminated intravascular coagulation 5/6 (83.3) patients died 30 days (range 2-74) after starting MARS® 1/6 (16.7%) successfully bridged to LTX

(Di Campli et al 2003)	Rome, Italy	Case series Intervention level IV evidence	7 patients with chronic liver failure with severe cholestasis, bilirubin >25mg/dl, hepatorenal syndrome and/or hepatic encephalopathy grade >II	Patients received a total of 21 MARS® treatments (average 3) lasting 6 hours each	Significant reductions in total bilirubin, conjugated bilirubin, bile acids, BUN and creatinine from pre to post MARS® treatment. Significant improvement in prothrombin time. All patients experienced a reduction in hepatic encephalopathy grade Overall survival at 3 months 3/7 (43%) who were successfully bridged to LTX. 2/7 (28.6%) died due to multiple organ failure 1/7 (14.3%) died due to bacterial pneumonia 1/7 (14.3%) died due to sepsis
(Bellman et al 2004)	Groningen, Netherlands	Case series Intervention level IV evidence	7 liver transplant recipients receiving MARS® treatment for intractable pruritus	All patients received 3 MARS® treatments, mean treatment time 16.4 ± 4.5 hours for first cycle, 15.3 ± 4 hours for second cycle and 15.2 ± 6.1 hours for third cycle.	6/7 (85.7%) patients experienced relief from pruritus symptoms. These patients experienced a significant decrease in serum concentrations of bile acids, total and direct bilirubin (p=0.028) 2/7 (28.6%) patients relapsed at 3 months (bile levels returned to those before MARS® treatment) and re-listed for LTX, and 1 of these patients died of biliary sepsis.
(Inderbitzin et al 2005)	Bern, Switzerland	Case series Intervention level IV evidence	7 patients with acute liver failure	MARS® responders (n=3) received 3 MARS® treatments each MARS® non-responders (n=4) received a total of 14 MARS® treatments. 10/23 (43.5%)	3/7 (42.9%) successfully treated and discharged after 17, 31 and 47 days. 2/7 (28.6%) died 1 and 2 days post-MARS® treatment 2/7 (28.6%) bridge to LTX then discharged 17 and 45 days post-LTX Bilirubin levels only decreased significantly (p<0.05) in the MARS® non-responders group

				treatments lasted 8 hours, 13/23 (56.5%) treatments discontinued early (6.3 ± 1.5 hours) due to filter obstruction.	Creatinine levels were significantly decreased in both MARS® responders and non-responders (p<0.05)
(Mitzner et al 2001a)	Rostock, Germany	Case series Intervention level IV evidence	8 patients with hepatorenal syndrome	Patients received a mean of 5.9 ± 3.4 MARS® treatments. Treatment duration ranged between 4-8 hours.	In-hospital survival rate 5/8 (62.5%) 12 month survival 5/8 (62.5%) 1/8 (12.5%) patient underwent LTX 18 months post-MARS® Bilirubin (γmol/L) pre: 466 ± 146 post: 284 ± 134, p<0.01 Creatinine (µmol/L) pre: 380 ± 182 post: 163 ± 119, p<0.01 Urea (mmol/L) pre: 26.4 ± 10.3 post: 12.9 ± 4.9, p<0.01 Plasma sodium (mmol/L) pre: 127.5 ± 7.7 post: 137.5 ± 4.8, p<0.01 Mean arterial pressure (Torr) pre: 71.9 ± 12.8 post: 95.6 ± 7.8, p<0.001 Ascites present in all patients pre-MARS® and absent post-MARS® treatment. Hepatic encephalopathy grade decreased pre: 2.8 ± 0.8 post: 0.8 ± 0.7, p<0.0001
(Jalan et al 2003)	London, UK	Case series Intervention level IV evidence	8 patients with hepatorenal syndrome (Type 1 n=5, Type 2 n=3), all encephalopathic	Patients received a mean of 4.5 (range 3-12) MARS® treatments each with duration of 8 hours (range 1-24).	Overall survival at 3 months 4/8 (50%) and of these 1/4 (25%) received successful LTX Significant improvement in bilirubin (p=0.008), creatinine (p=0.02), prothrombin (p=0.04) and grade of encephalopathy (p=0.05). Sustained improvements in arterial pressure and cardiac output.

					Thrombocytopenia was reported as an adverse event of MARS®
(Schmidt et al 2001a) And (Schmidt et al 2001b)	Copenhagen, Denmark	Case series Intervention level IV evidence	8 patients with AoCLF	Treated with a single 10 hour MARS® treatment	4/8 (50%) died within 10-42 days of MARS® treatment 3/8 (37.5%) improved hepatic encephalopathy, unchanged in 5/8 (62.5%), p=0.11 Middle cerebral artery mean flow velocity increased from 42 cm/sec (range 26-59) to 72 cm/sec (range 52-106), p<0.05 Arterial ammonia and bilirubin decreased significantly p<0.05 Mean arterial pressure increased significantly from 67 ± 9 to 76 ± 6 mm Hg, p<0.05 Systemic vascular resistance index increased significantly, p<0.05 Cardiac index remained unchanged
(Doria et al 2004)	Pittsburgh, USA	Case series Intervention level IV evidence	9 patients with cirrhosis. 6/9 with AoCLF and 3/9 with pruritus	Patients underwent 7 MARS® treatments on consecutive days. Treatment duration was 6 hours.	4/9 (44%) survival. Of these 1/4 (25%) had LTX at day 351 5/9 (56%) died from bleeding and multiple organ failure at Day 6- Day 201. Statistically significant difference (p<0.05) in platelet count, prothrombin time, all thromboelastograph variables, Factor VIII, von Willebrand and D-dimer between pre- and post-MARS® treatment. MARS® may induce coagulopathy through a platelet-mediated mechanism.
(Lai et al)	Birmingham, UK	Case series Intervention level IV evidence	10 consecutive patients with acute liver failure with grade III or IV hepatic encephalopathy.	Patients received MARS® for 8 hours on 2 consecutive days.	Overall survival 3/10 (30%) Significant increase in systemic vascular resistance index (p=0.02). Significant decrease in cardiac index (p=0.01) Significant decrease in urea (p=0.023), creatinine (p=0.002), haemoglobin (p=0.028), platelets

					(*p*=0.002), INR (*p*=0.004). No significant difference in bilirubin or albumin.
(Tsai et al 2005)	Taiwan	Case series Intervention level IV evidence	10 consecutive patients with fulminant hepatic failure	Patients received at least one MARS® treatment (range 1-12) with treatment duration of 8 hours. Follow-up 90 days	Overall survival 3/10 (30%) Of these, 1/3 (33.3%) a transplant recipient. Patients died from septic shock, multiple organ failure or gastrointestinal bleeding. Significant decreases in between pre-and post-MARS® treatment in MELD (*p*=0.03), APACHE II and III (*p*<0.001), SOFA (*p*=0.006), OSF (*p*=0.009) scores. Significant decreases between pre-and post-MARS® treatment in mean arterial pressure (p<0.001), plasma renin activity (0.027), hepatic encephalopathy grade (*p*=0.001), bilirubin (*p*<0.001), ammonia (*p*=0.001), blood urea nitrogen (*p*<0.001), creatinine (*p*<0.001) and platelet count (*p*<0.001).
(Felldin et al 2003)	Göteburg, Sweden	Case series Intervention level IV evidence	10 patients with ALF and renal failure	Patients received at least 1 treatment with MARS® (range 1-15) with treatment duration ranging from 6-12 hours.	Overall survival 7/10 (70%) Of these, 5/7 (74.1%) patients successfully bridged to LTX. No adverse events reported apart from a slight decrease in platelet count.
(Schmidt et al 2004)	Copenhagen, Denmark	Case series Intervention level IV evidence	12 consecutive patients: 7 patients with hepatic encephalopathy from fulminant hepatitis and 5 patients with hepatic encephalopathy from AoCLF.	Duration of MARS® treatment 6 hours.	5/5 (100%) AoCLF patients died within 14 days of MARS® treatment. 4/7 (57%) survival. Of these, 2/4 (50%) successful LTX Significant decrease between pre-and post-MARS® treatment in total arterial amino acid concentration (*p*<0.05). The concentration decreased in all amino acids with the exception of the branched chain amino acids. Fischer's ration of branch chain to aromatic amino acids increased significantly (*p*<0.05). A reduction in amino acids may be beneficial to patients

					with hepatic encephalopathy.
(Lee et al 2005)	Singapore	Case series Intervention level IV evidence	13 consecutive patients with drug-induced liver failure	The 13 patients received a total of 40 MARS®, with treatment being administered daily for 3 consecutive days. Treatment duration lasted at least 6 hours.	Overall mortality 11/13 (85%). Median time to death from commencement of MARS® treatment was 8 days. 1/13 (7.7%) recovered spontaneously and 1/13 (7.7%) successful LTX.
(Wilmer et al 2002)	Leuven, Belgium	Case series Intervention level IV evidence	13 patients with severe LF	Patients received at least 1 MARS® treatment (range 1-5). Treatment duration lasted 6-12 hours.	Intensive care survival rate 9/13 (69%) Of these 5/9 (55.6%) survived to hospital discharge Of these 3/5 (60%) were still alive at 12 month follow-up, with 2/5 (40%) lost to follow-up Overall survival at 12 months 3/13 (23%) Median overall reduction in bilirubin 28.2%, however the median reduction in survivor group was 37.7% and in the patients who died was 15.9%.
(Zhou et al 2004)	Xi'an, China	Case series Intervention level IV evidence	14 patients with drug-induced liver failure	Patients received at least 1 MARS® treatment (median 1.7, range 1-7). Median duration of treatment was 8 hours (range 6-12).	Overall survival at 12 months 11/14 (78.6%) 1/14 (7.1%) died in-hospital 2/14 (14.2%) died at 6-12 months follow-up from gastrointestinal bleed following postnecrotic cirrhosis. Total bilirubin and ammonia decreased significantly between pre-and post-MARS® treatment (p<0.01) and prothrombin activity increased significantly (p<0.05). Improvement in kidney function indicated by reduced urea nitrogen but this was NS.

(Klammt et al 2002)	Rostock, Germany	Case series Intervention level IV evidence	15 patients with ALF (n=1) or AoCLF (n=14)	Patients received an average of 6.3 ± 3.8 MARS® treatments with an average duration of 6.0 ± 1.3 hours.	8/15 (53%) patients discharged with improved liver function Overall survival 9/15 (60%) and of these 4/9 (44.4%) had an expected survival of 7 days without LTX. Significant decreases in bilirubin, bile acids, creatinine, urea, platelet count and aspartate amino transferase between pre-and post-MARS® treatment. Significant increases in coagulation parameters antithrombin III and activated prothrombin time between pre-and post-MARS® treatment.
(Lamesch et al 2001)	Leipzig, Germany	Case series Intervention level IV evidence	17 consecutive patients with liver failure with varying aetiologies.	Each patient received 2-9 MARS® treatments (median 4.3), with median duration of treatment was 18 ± 10.7 hours.	Overall survival 9/17 (52.9%) 5/17 (29.4%) underwent transplantation with 4/5 (80%) successful and still alive 1-14 months post-LTX.
(Di Campli et al 2005)	Rome, Italy	Case series Intervention level IV evidence	20 patients with ALF (n=3), transplantation failure (n=4), or AoCLF (n=13)	A total of 72 MARS® treatments were performed on 20 patients.	**Survival at 90 days** AoCLF patients: 4/13 (30.8%) of these 2/4 (50%) recovered and 2/4 (50%) received a liver transplant. Survival time after MARS® treatment ranged from 2-31 days. LTX failure patients 2/4 (50%). Survival time after MARS® treatment ranged from 21-30 days. ALF patients 2/3 (66.6%) Survival time after MARS® treatment 6 days. **Expected survival** 5 patients with MELD score 20-29 had a 60% survival rate vs expected survival rate of 24% 7 patients with MELD score 30-39 had a survival rate of 29% vs an expected survival rate of 17% Patients with MELD score >40 mortality was 100% as

					expected.
(Doria et al 2003a)	Palermo, Italy	Retrospective case series Intervention level IV evidence	23 consecutive patients (1 child) with AoCLF (n=12), fulminant hepatic failure (n=4), intractable pruritus (n=3), primary non function (n=2) and liver resection (n=2)	Patients received 1-7 MARS® treatments each of 6 hours duration	Overall survival 9/23 (39.1%) of these 6/9 (66.6%) received a transplant. Statistically significant increase in serum concentrations of sodium and calcium between pre- and post-MARS® treatment (p<0.05). Statistically significant decrease in serum concentrations of magnesium between pre-and post-MARS® treatment (p<0.05). These differences were very small and not considered clinically relevant.
(Stange et al 2000)	Rostock, Germany	Retrospective case series Intervention level IV evidence	26 patients with ALF or AoCLF with intrahepatic cholestasis	Patients received at least 1 treatment, unclear if more treatments were given.	Overall survival 17/26 (65.4%) Statistically significant decrease in bilirubin (p<0.001) and ascites (p<0.05) between pre-and post-MARS® treatment. Statistically significant increase in antithrombin III (p<0.001) and albumin (p<0.05) between pre-and post-MARS® treatment. Improvement was sustained in all long term survivors.
(Doria & Marino 2005)	Palermo, Italy	Retrospective case series Intervention level IV evidence	30 patients with AoCLF	Patients received at least 1 treatment (range 2-11)	Overall survival 21/30 (70%) 9/30 (30%) died from sepsis Bacteraemia was a negative prognostic factor for MARS® treatment. Infection should be ruled out prior to commencement of treatment and broad spectrum antibiotic prophylaxis should be considered for all patients.
(Novelli et al 2002)	Rome, Italy	Case series Intervention level IV evidence	34 patients: primary non-function (n=9), fulminant hepatitis (n=9), delayed non-function (n=6) and AoCLF (n=10).	Patients received a median of 6.4 MARS® treatments with a median duration of 8 hours.	PNF patients: 8/9 (88.9%) survived 4/8 (50%) discharged at 48 days 4/8 (50%) required and received LTX DF patients 5/6 (83.3%) survived and discharged at average 55.5

					days FH patients 3/9 (33.3%) survived with no LTX 6/9 (66.6%) required LTX and of these 2/6 (33.3%) died due to sepsis AoCLF patients 1/10 (10%) survived with no LTX 7/10 (70%) survived and of these 4/10 (40%) required and received LTX and 3/10 (30%) are on waiting list. Statistically significant decrease in bilirubin (p<0.01) and ammonia (p<0.01) between pre-and post-MARS® treatment. NS change in INR
(Isoniemi et al 2005)	Helsinki, Finland	Case series Intervention level IV evidence	49 patients with ALF	Median number of MARS® treatments 3.1 (range 1-9), median follow-up time 15.5 months (range 6-36)	Overall survival 40/49 (82%) at 6 months Of these 26/40 (65%) native liver recovered 14/40 (35%) successful LTX. Serum ammonium, bilirubin, alanine aminotransferase, urea and creatinine levels improved significantly (p<0.05). Mean grade encephalopathy improved from 1.6 $\pm$ 1.6 to 1.0 $\pm$ 1.5 Anti-inflammatory cytokine IL-10 reduced significantly Pro-inflammatory cytokines IL-8 and IL-6 transient effects TNFα levels unchanged
(Novelli et al 2003)	Rome, Italy	Case series Intervention level IV evidence	63 patients with liver failure 10 patients with primary non-function (PNF) 16 with fulminant hepatitis (FH) 10 with delayed non-function (DNF) 23 with AoCLF 4 hepatic resection	Mean number of MARS® treatments = 6 (range 1-24). Mean length of treatment 9 hours (range 8-20)	INR Pre Post AoCLF 4.2 3.5 p=0.001 FH 2.8 1.8 p=0.04 PNF 3.5 2.8 p=0.56 DNF 2.0 1.6 p=0.002 Glasgow Coma Score Pre Post AoCLF 8.9 12, p=0.001 FH 7.5 12.2 p=0.002 PNF 8.6 9.2 *NS* DNF 9.6 14.3 p=0.004

					Bilirubin (mg/dL) Pre Post AoCLF 26 14.5, *p*=0.002 FH 25 14.4 *p*=0.02 PNF 21.8 14.4, *p*=0.001 DNF 19.4 8.7 *p*=0.001 Ammonium (mg/dL) Pre Post AoCLF 206 100 *p*=0.002 FH 260 109 *p*=0.004 PNF 252 150 *p*=0.007 DNF 155 62 *p*=0.005
(Lahdenpera et al 2005)	Helsinki, Finland	Case series Intervention level IV evidence	88 patients 45 with ALF 31 with AoCLF 8 with graft failure 4 with miscellaneous conditions		ALF patients 36/45 (80%) survived Of these 23/36 (64%) native liver recovered and 13/36 (36%) underwent successful LTX. Best results in ALF patients were achieved for those patients who had been intoxicated with lethal dose of toxin. AoCLF patients 7/31 (23%) survived and were not eligible for LTX.
(Novelli et al 2005b)	Rome, Italy	Case series Intervention level IV evidence	110 patients with liver failure 13 patients with primary non-function 24 with fulminant hepatitis 17 with delayed non-function 56 with AoCLF	Mean number of MARS® treatments = 6 (range 1-24). Mean length of treatment 9 hours (range 8-20)	Bilirubin (mg/dL) pre: 22.37 ± 11.6 post: 11.36 ± 7.5, *p*<0.01 Ammonium (µg/dL) pre: 238.2 ± 19 post: 115.4 ± 12, *p*<0.01 Lactates (mmol/L) pre: 3.48 ± 1.3 post: 1.76 ± 1.1, *p*<0.02 Creatinine (mg/dL) pre: 2.36 ± 0.18 post: 1.26 ± 0.67, *p*<0.04 Glasgow Coma Score pre: 8.6 ± 1.4 post: 11.9 ± 3.9, *p* <0.05 Decreased cerebral oedema, NS

NS = not significant, BUN = blood urea nitrogen, INR = international normalised ratio - is the ratio of the patient's clotting time to the laboratory's mean reference value, MELD = Mayo end-stage liver disease, APACHE = acute physiology and chronic health evaluation, SOFA = sequential organ failure assessment, OSF organ system failure, PNF = primary non-function, DF= delayed non function, FH = fulminant hepatitis

Appendix D: HTA Internet Sites

AUSTRALIA

- Centre for Clinical Effectiveness, Monash University
  http://www.med.monash.edu.au/healthservices/cce/evidence/

- Health Economics Unit, Monash University
  http://chpe.buseco.monash.edu.au

AUSTRIA

- Institute of Technology Assessment / HTA unit
  http://www.oeaw.ac.at/ita/welcome.htm

CANADA

- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/en/

- Alberta Heritage Foundation for Medical Research (AHFMR)
  http://www.ahfmr.ab.ca/publications.html

- Canadian Coordinating Office for Health Technology Assessment (CCHOTA) http://www.ccohta.ca/entry_e.html

- Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database http://www.mycabot.ca

- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org

- Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca

- Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm

- Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca

DENMARK

- Danish Institute for Health Technology Assessment (DIHTA)
  http://www.dihta.dk/publikationer/index_uk.asp

- Danish Institute for Health Services Research (DSI)
  http://www.dsi.dk/engelsk.html

FINLAND

- FINOHTA http://www.stakes.fi/finohta/e/

FRANCE

- L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) http://www.anaes.fr/

GERMANY

- German Institute for Medical Documentation and Information (DIMDI) / HTA http://www.dimdi.de/dynamic/en/

THE NETHERLANDS

- Health Council of the Netherlands Gezondheidsraad http://www.gr.nl/adviezen.php

NEW ZEALAND

- New Zealand Health Technology Assessment (NZHTA) http://nzhta.chmeds.ac.nz/

NORWAY

- Norwegian Centre for Health Technology Assessment (SMM) http://www.oslo.sintef.no/smm/Publications/Engsmdrag/FramesetPublications.htm

SPAIN

- Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I/Health Technology Assessment Agency (AETS) http://www.isciii.es/aets/

- Catalan Agency for Health Technology Assessment (CAHTA) http://www.aatrm.net/html/en/Du8/doc7856.html

SWEDEN

- Swedish Council on Technology Assessment in Health Care (SBU) http://www.sbu.se/www/index.asp

- Center for Medical Health Technology Assessment http://www.cmt.liu.se/

SWITZERLAND

- Swiss Network on Health Technology Assessment (SNHTA)
  http://www.snhta.ch/

UNITED KINGDOM

- Health Technology Board for Scotland
  http://www.nhshealthquality.org/nhsqis/qis_display_home.jsp?p_applic=CCC&p_service=Content.show&pContentID=43&

- National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA)
  http://www.hta.nhsweb.nhs.uk/

- University of York NHS Centre for Reviews and Dissemination (NHS CRD)
  http://www.york.ac.uk/inst/crd/

- National Institute for Clinical Excellence (NICE)
  http://www.nice.org.uk/

UNITED STATES

- Agency for Healthcare Research and Quality (AHRQ)
  http://www.ahrq.gov/clinic/techix.htm

- Harvard School of Public Health – Cost-Utility Analysis Registry
  http://www.hsph.harvard.edu/cearegistry/

- U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (TEC) http://www.bcbs.com/tec/index.html

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