Alfapump® for Ascites due to Liver Cirrhosis

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Summary

- The Alfapump® is a surgically inserted subcutaneous pump that works by automatically pumping ascitic fluid from the abdomen to the bladder, where it is excreted naturally from the body through urination.

- The Alfapump® system consists of the pump device, a peritoneal catheter, a bladder catheter, a smart charger, and a programmer.

- It is indicated for the management of refractory and recurrent ascites due to liver cirrhosis as well as the management of malignant ascites for palliative use.

- NICE IPG479 states that the current evidence on the safety and efficacy of subcutaneous implantation of a battery-powered catheter drainage system for managing refractory and recurrent ascites is inadequate in quantity and quality and that this procedure should only be used in the context of research.

- As yet there is no good quality published evidence which directly compares the Alfapump® system with large volume paracentesis (LVP) in a randomised clinical trial. The majority of the trial data is only available in conference abstracts.

- The cost of the entire system including pump device, catheters and programmer is £20,000 plus VAT. The battery in the pump device has a life-span of 2 years.

- A cost-utility analysis model carried out by the manufacturer suggests that the Alfapump® system in comparison with LVP over a time horizon of 9 months had lower cost (£26 798 and £39 702 respectively) and produced more benefits (0.87 QALYs and 0.67 QALYs respectively). Alfapump® dominates LVP from a UK NHS perspective with an incremental cost-effectiveness ratio (ICER) of (minus) -£64 841. This number falls well below the NICE willingness-to-pay threshold of £20,000.

- The product received European CE mark certification in July 2011.

- The Alfapump® system may offer some advantages in terms of patient acceptability and quality of life but good quality clinical trial data to support long-term clinical effectiveness and cost-effectiveness is lacking.
**Introduction and background**

Ascites is a common complication of cirrhosis of the liver and metastatic cancer in the abdomen. It is a build-up of fluid which causes the abdomen to swell and may lead to discomfort, difficulty breathing, fatigue, nausea and poor appetite. The aim of treatment of ascites is to mobilise or remove the abnormal collection of intra-abdominal fluid. Medical treatment with sodium restriction and diuretics is used in many patients for the management of ascites.

Ascites may occur in 60% of patients within 10 years of being diagnosed with cirrhosis of the liver.\(^1\,^2\) Refractory ascites can occur in up to 10% of patients with liver cirrhosis and ascites, and 50% of patients with refractory ascites will die within 6 months to 1 year.\(^1\) Ascites is considered to be refractory or diuretic resistant if there is no response to treatment with once daily 400mg spironolactone plus 160mg furosemide.

For patients with treatment-resistant or recurrent ascites, treatment options include large-volume paracentesis, albumin infusion and insertion of transjugular intrahepatic portosystemic shunts (TIPSS). These procedures may be used to support a patient before liver transplantation.

In 2006 guidelines were published by the British Society for Gastroenterology for the management of cirrhotic ascites, and in 2010 by the European Association for the Study of the Liver (EASL). Initial management of ascites includes treating the underlying cause where possible. Patients are initially advised to restrict dietary salt intake. First line medical treatment is with diuretics (water tablets) which are effective in the majority of patients with cirrhosis and non-refractory ascites.\(^1\)

The guidelines recommend that patients with large or refractory ascites will require paracentesis. Following paracentesis, restarting diuretic therapy prevents recurrence of ascites in 80% of patients. The time interval between paracentesis procedures varies from patient to patient but is defined as frequent if the procedure is required more than three times per month. Expert opinion suggests that typically 1 to 2 paracentesis per patient per month are undertaken. Complications from paracentesis (bleeding) occur in up to 1% of patients but are rarely serious or life threatening.\(^1\)

TIPSS may be used in selected patients who require frequent therapeutic paracentesis with appropriate assessment of the risk/benefit ratio. Clinical trials have shown TIPSS to be more effective in controlling ascites compared with large volume paracentesis and approximately two thirds of patients who undergo the procedure show an improvement in their ascites. The side effect of hepatic encephalopathy can occur in approximately 25% of patients after TIPSS insertion, with a higher risk in people aged over 60 years. TIPSS insertion should be considered as a treatment option for patients who require frequent abdominal drainage more than three times a month. However, patients with advanced liver disease and/or encephalopathy are...
not usually suitable for a TIPSS procedure due to an increased risk of complications.\textsuperscript{1}

**About the Alfapump®**

The Alfapump\textsuperscript{®}, produced by Sequana Medical, is a small 7 x 4cm-long subcutaneous device. It is smaller than an iPod and works by automatically pumping ascitic fluid from the abdomen to the bladder, where it is excreted naturally from the body through urination. Patients use a special device to recharge the battery, which needs to be run for about 15 minutes daily and the pump is switched off at night.\textsuperscript{1,3,4}

The Alfapump\textsuperscript{®} system was launched in the European market in 2013 and trials are currently underway in the USA to license the device there. It is indicated for the management of refractory and recurrent ascites due to liver cirrhosis as well as the management of malignant ascites for palliative use.\textsuperscript{4}

The Alfapump\textsuperscript{®} system received CE in July 2011 for patients with refractory ascites caused by advanced liver disease.\textsuperscript{5} The device has also been granted a CE-mark for use in patients suffering from ascites due to cancer.

Subcutaneous implantation of the Alfapump\textsuperscript{®} is required and is done under general anaesthesia, usually through 3 small incisions in the abdominal wall. A battery-powered pump with internal pressure sensors is implanted on the right side above the belt line. One catheter connects the pump to the peritoneal cavity, and another connects it to the urinary bladder. The pump and both catheters are secured with sutures to prevent migration. The pump moves fluid from the peritoneal cavity (via the first catheter) into the bladder (via the second catheter). Fluid is eliminated through normal micturition. The pump is programmed to move pre-set volumes of ascites to the bladder. The pressure sensors prevent it from over-distending the bladder. The implantation procedure takes under one hour and is minimally invasive.\textsuperscript{4,6}

Following surgical insertion the doctor programs the pump wirelessly via the external handheld charging device, according to the needs of the patient (based on previous large-volume paracentesis requirements, observed accumulation of ascites and body weight). The hand-held device can also be used to collect data from the pump which can be downloaded to a computer for review by the doctor.

**Components of system:**\textsuperscript{3,4}

- Alfapump\textsuperscript{®} - The Alfapump\textsuperscript{®} is a subcutaneously implanted battery powered pump that is charged through the skin. It ensures controlled and continual removal of ascites according to a programmed schedule set by the physician.
Pressure sensors monitor pressure in the peritoneal cavity and bladder to ensure optimal fluid management. The Alfapump® can move up to four litres of ascites per charge.

- **Smart Charger** - The handheld smart charger is used by the patient to charge the Alfapump® through the skin. During charging the smart charger collects and records pump activity which can be downloaded during follow-up visits.
- **Catheters** - Standard implantable grade silicone catheters are utilised to collect ascites from the peritoneal cavity and transport it to the bladder. The bladder catheter features a pigtail design that rests inside the bladder. Dacron cuffs facilitate tissue in-growth and help secure the catheters after implantation.
- **Alfapump® Programmer** - Physicians use the notebook and integrated software to download pump data and to change settings. Software enables adaption of patient-specific pumping programs.

**Key features of the system are:**

- Automatic and continual removal of ascites.
- Fully implantable system, with no external or visible components.
- Pump volumes can be tailored to the individual patient requirements.
- Brief recharging using wireless smart charge for 10 minutes twice a day – i.e. morning and evening. This involves placing the smart charger over the pump pocket site. Not only does this charge the pump itself but it also downloads data from the pump. If the patient forgets to do this, they will need to charge the pump when they remember.7
- The pump battery will last up to 2 years so the device has a lifespan of 2 years once inserted.7
- Very occasionally the peritoneal catheter may need to be replaced due to blockage, which is a very simple procedure taking 15 minutes. It can be performed under local anaesthesia. As yet there has been no requirement to change the bladder catheter in a patient.7
- The Alfapump® removes around 10-15ml of fluid from the abdomen every 15 minutes and can remove up to 4 litres of fluid every day if needed.4
Clinical Evidence

The majority of the trial data assessing the use of the Alfapump® system is only available in conference abstracts. A Medline and Embase search only found one trial that had been fully published to date.

Pioneer Study

The only published study available to support the use of the Alfapump® system is the Pioneer Study by Bellot et al.

The Pioneer study was a non-randomized trial to assess the safety and efficacy of the Alfapump® in the management of refractory ascites. The study enrolled 40 patients at nine centres in four European countries and patients were followed-up for 6 months after the insertion of the pump. The primary study outcome was safety and secondary outcomes included recurrence of tense ascites and pump performance. Patients were eligible for the trial if they had recurrence of ascites within 4 weeks of paracentesis, despite treatment with a maximum of 160 mg/day of furosemide and 400 mg/day of spironolactone (or equivalent doses of loop-acting and distal-acting diuretics), or intolerance related to diuretic-induced complications; expected survival of greater than 6 months; serum creatinine levels ≤ 2.0 mg/dl for at least 7 days before study entry; total bilirubin levels ≤ 5 mg/dl and minimum 18 years of age. Patients were excluded from the study if they had active systemic or local infections, such as spontaneous bacterial peritonitis (SBP), urinary tract infection (UTI), or cellulitis; malignancy, including hepatocellular carcinoma; evidence of extensive ascites loculation; portal hypertension-related gastrointestinal bleeding or hepatic encephalopathy in the two weeks prior to the inclusion in the study; obstructive uropathy or any contraindications for general anesthesia.8

Patients were recruited into two cohorts. Cohort 1 included those patients who had the pump inserted prior to changes to be the protocol on the advice of the trial Data Safety Monitoring Board in response to adverse events and problems with the insertion/function of the pump plus catheters in the initial trial recruits. Cohort 2 included those patients recruited after changes to the trial protocol were made.

The average age of patients included in the study was 59 years (range 34-80) and 70% of the patients were male. The median number of paracentesis procedures in the month prior to implantation of the Alfapump® per patient was 3.38 (25th percentile = 2.21, 75th percentile = 4.81).8

The Alfapump® was successfully inserted into all forty patients. An early problem of bladder catheter dislodgement was completely resolved by increasing the length of the catheter placed in the bladder and anchoring the catheter to the suprapubic
aponeurosis. However, this extra catheter length resulted in prolapse of the catheter into the urethra in three patients, requiring cystoscopic shortening of the bladder catheter. A new “pigtail” type bladder catheter has subsequently been developed which has addressed this problem.\(^8\)

In total, the 40 implanted Alfapump® systems removed 4630 L of ascitic fluid over 4659 patient days, a mean of 0.99 L per patient per day. The median number of paracentesis performed in the month preceding Alfapump® implant was 3.4 (range 1–6) which dropped to 0.24 (range 0–5) per month after implant (p <0.01), 40% of the patients had no paracentesis after receiving their pump. Overall, there was a 90% reduction in the volume of ascitic fluid removed by paracentesis. The requirement for paracentesis was significantly lower in patients from Cohort II, due to the reduced number of technical problems detected in comparison with Cohort I (2 LVPs in 2 out of 19 patients vs. 30 LVPs in 9 out of 21 patients, p = 0.034).\(^8\)

No significant changes were observed in mean arterial pressure, Model for End-Stage Liver Disease (MELD) score, Child-Pugh score, bilirubin, sodium or creatinine. The INR and serum albumin levels were significantly lower at 6 months when compared to baseline measures, (p<0.05) and (p <0.01) respectively.\(^8\)

Thirteen Alfapump® systems were surgically removed during the course of the study after implantation due to difficult-to-manage infections (n = 7), withdrawn consent following bladder or peritoneal catheter dislodgment issues (n = 3), withdrawal of patient consent (n = 2) and one case of emergency removal due to wound dehiscence. Eight patients died during the study (mean implant duration 116 days) due to sepsis (n = 3), progressive liver insufficiency (n = 2), acute renal failure (n = 1), and hepatorenal syndrome (n = 1), and one patient unexpectedly died at home and no cause of death was determined.\(^8\)

Five patients underwent orthotopic liver transplantation following Alfapump® support lasting between 102 and 163 days (mean 137 days), and the presence of the pump did not represent any additional complications to the process of transplantation.\(^8\)

**Studies only available as conference posters or abstracts**

The manufacturer provided details of eight clinical studies/reviews which have not been fully published and are available as conference abstracts only on the use the Alfapump® systems in patients with ascites due to cirrhosis. Three of these studies remain ongoing and preliminary results on one of them are included below.

A study by De Gottardi et al further assessed the performance and safety of the Alfapump® following the initial Pioneer study in an additional 33 patients with cirrhosis and refractory ascites. The mean age of patients included was 61 years (range 49-75, men 74%), cirrhosis was due to alcohol in 84% of patients, Hepatitis C (12%) or non-alcoholic steatohepatitis (4%). At the end of the study, use of the Alfapump® was ongoing in 10 (30%) patients with a mean implant duration of 9.5
months, 13 patients (39%) died after a mean of 5 months, 4 patients (12%) underwent liver transplantation after 2.7 months and in 6 patients (18%) the pump was removed after 3.9 months. The number of paracentesis decreased from 2.2 (1.4-3.8) to 0 (0.0-0.5) per month (p<0.0001) and the median ascites volume/LVP decreased from 8.0 (5.8-9.0) to 4.7 (3.0-6.0) litres/LVP (p=0.0001). The mean ascites volume increased from 0.62 to 0.98 litres/day (p=0.015) likely due to a relaxation of dietary sodium restriction. The average daily ascites volume pumped was 870 mL. Complications leading to removal of the pump included pump pocket infections (n=2), bacterial peritonitis (n=3) and skin infection with wound dehiscence (n=1).9

A second study by Stirnimann et al between April 2012 and June 2015 enrolled a total of 81 patients at 12 sites in Switzerland (2 sites, n=41), Germany (7 sites, n=34), Spain (1 site, n=2), and the United Kingdom (2 sites, n=4). Patients with refractory or recurrent ascites due to cirrhosis were eligible to receive the Alfapump® as part of the study and planned follow-up was for 24 months. The mean age of the patients was 64 years old (range = 44 -82) and 79% of the patients were male. 69% of patients received the pump due to alcohol related cirrhosis. All pumps were implanted under general anaesthesia except ten (one under local anaesthesia and nine unknown), with the median duration of implantation procedure being 59 minutes, and the median length of hospital stay after implantation was 7 days. Use of the Alfapump® resulted in a reduction in the number and volume of paracentesis from a median of 2.17 procedures/month pre-implant to 0 procedures/month post-implant, and from 7.0 litres pre-implant to 3.85 litres post-implant. Median survival after implantation was 10.1 months; actuarial survival was 88.0% at 3 months and 68.8% at 6 months.10

A previous study by Adebayo et al recruited 51 patients with decompensated cirrhosis of the liver with refractory ascites RA undergoing regular large volume paracentesis (LVP), who met specified inclusion/exclusion criteria, in a multi-centre, open-label, controlled trial. Patients were randomised to either the Alfapump® or LVP. The primary end-point of the study was the time to first LVP with secondary end-points including cirrhosis-related complications and survival. Forty-nine patients (mean age 62 (43-80), 78% male) were analysed (Alfampump-24, LVP-25). At 1 month, the probability of LVP was 0.13 in the Alfapump® group compared with 0.75 in the LVP group (p <0.0001). The median number of paracentesis per month (25%:75%) were 0.2 (0:0.6) vs. 1.4 (0.6:2.6), respectively (p <0.0001). There was no difference in survival between groups at 6 months (Alfapump®-0.84 vs. LVP-0.83).13

A retrospective case note review by Nair et al of patients who had an Alfapump® implanted for refractory ascites outside of clinical trials at 4 NHS hospitals since Sept 2013 included 9 patients (6 male, 3 female; median age 74, range 41–81) at four centres (4 Newcastle-upon-Tyne, 2 UCL (London), 2 Cambridge, 1 QEH(Birmingham)). Seven of the patients had ascites related to cirrhosis (4 Child-Pugh B, 3 Child-Pugh C); one due to congestive cardiac failure and one had portal
hypertension due to arterio-venous malformation. Prior to insertion of the Alfapump®
the median frequency of paracentesis was every 10 days (range 7 – 20) and the
median volume of ascites drained was 9 litres (range 8 to 12). The requirement for
paracentesis was substantially reduced post Alfapump® implantation with seven
patients no longer requiring any paracentesis. In one patient the pump blocked after
3 weeks and required re-implantation with a second pump that also blocked and the
patient returned to LVP. In another patient the pump blocked after 8 months and a
second Alfapump® was successfully implanted. All 9 patients had Alfapump® related
complications including 4 post-operative seromas, 3 bladder catheter
migrations/occlusions, 5 site related infections, 6 acute kidney injury/electrolyte
disturbance and 1 urinary incontinence. Five of the nine patients remained alive with
a functioning pump 6 months after implantation.¹⁴

A further case report was provided by the manufacturer on the use the Alfapump®
system in two patients with ascites due to platinum resistant ovarian cancers. A
EUTROC multicentre European randomized trial (AMAZE) is planned for evaluation
of clinical and translational implications of the Alfapump® in platinum resistant
ovarian cancers.⁷

The Agua Trial is an ongoing multicentre randomised controlled study of the
Alfapump® system versus transjugular intrahepatic portosystemic shunt and
paracentesis in the treatment of ascites. A total of two hundred sixty male and
female patients’ ≥18 years with recurrent/refractory ascites with underlying cirrhosis
will be recruited at up to 20 European centres in Germany and the UK. It is the first
large-sale clinical trial to evaluate the efficacy as well as the complications of
Alfapump® in comparison with TIPSS in patients with recurrent or refractory ascites
qualifying for both treatments. Results of the trial are not yet available.¹¹

A study by Adebayo et al called the APTRIAL aims to compare the Alfapump® to
large volume paracentesis in the management of patients with refractory ascites not
suitable for TIPSS. Sixty patients ≥18 years with refractory or recurrent ascites and
underlying cirrhosis will be recruited at 7 European Centres with follow-up of 12
months.¹²
Safety

There is limited fully published safety data available on the use of the Alfapump® device.

In general, safety issues associated with the Alfapump® include catheter occlusions, infections of the pump pocket, and pump malfunctions.

The only fully published study carried out by Bellot et al reported that 9 patients (22.5%) had 10 SAEs related to the bladder catheter. There were 5 bladder catheter dislodgements in 5 patients (12.5%), 4 cases of prolapse of the bladder catheter into the urethra in 3 patients (7.5%), and one bladder catheter that became kinked, and requiring repair (2.5%) during the study.8

Other procedure related complications included 3 cases of ascitic fluid leakage through the implant wounds (7.5%). In one patient there was an intra-bladder haemorrhage during catheter implantation and the surgeon decided to remove the Alfapump® system within 24 hours of the implant. There were two Alfapump® failures (5%) during the Pioneer Study; one caused by a motor malfunction and one caused by a microprocessor communication error.8

A significant number of infectious events were detected in Cohort I. After implementing changes to the protocol regarding antibiotic prophylactic measures, a decrease in the incidence of infectious episodes in Cohort 2I was observed. Cohort 1 included those patients who had the pump inserted prior to changes to the protocol on the advice of the trial Data Safety Monitoring Board in response to adverse events and problems with the insertion/function of the pump plus catheters in the initial trial recruits. Cohort 2 included those patients recruited after changes to the trial protocol were made. UTIs did not represent a relevant problem during this investigation and all detected episodes related to three patients.8

Table: Number of patients with cirrhosis and device-related adverse events appearing within 6 months following pump implantation in the Pioneer study8

<table>
<thead>
<tr>
<th>Serious adverse events</th>
<th>Number of patients</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort 1 (n=21)</td>
<td>Cohort 2 (n=19)</td>
</tr>
<tr>
<td>Cirrhosis related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Infections - Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of occurrences = 0</td>
<td>5 (24%)</td>
<td>11 (58%)</td>
</tr>
<tr>
<td>No of occurrences = 1</td>
<td>12 (57%)</td>
<td>7 (37%)</td>
</tr>
<tr>
<td>No of occurrences &gt;1</td>
<td>4 (19%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Infections –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of occurrences = 0</td>
<td>13 (62%)</td>
<td>15 (79%)</td>
</tr>
</tbody>
</table>
In the unpublished study of 51 patients by Adebayo et al the most common serious adverse events (SAEs; events/patients) were infection (Alfapump® 9/9, LVP 12/9), acute kidney injury (Alfapump® 8/5, LVP 2/2), GI haemorrhage (Alfapump® 4/4, LVP 0/0), electrolyte disturbance (Alfapump® 5/5, LVP 1/1) and hepatic encephalopathy (Alfapump® 3/3, LVP 2/2). All episodes of acute kidney injury were grade 1 except one (grade 2, Alfapump® group) and all resolved with fluid therapy. There were 6 serious adverse device effects (SADEs); blockage of peritoneal catheter (3) and bladder catheter (3), in 5 patients, requiring re-intervention to replace or reposition.\textsuperscript{13}

The table below lists the reported safety issues arising in the analysis of the registry of 81 patients receiving the Alfapump® between April 2012 and June 2015 by Stirnimann et al.\textsuperscript{10}

<table>
<thead>
<tr>
<th>Device deficiency (reported related or possibly related to study device)</th>
<th>Number of events</th>
<th>Number of patients with this complication</th>
<th>Percentage of patients with this complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>13</td>
<td>12</td>
<td>14.8%</td>
</tr>
<tr>
<td>Infection - peritonitis</td>
<td>4</td>
<td>?</td>
<td>4.9%</td>
</tr>
<tr>
<td>Infection – pocket/wound</td>
<td>5</td>
<td>?</td>
<td>6.2%</td>
</tr>
<tr>
<td>Infection – Sepsis/SIRS</td>
<td>2</td>
<td>?</td>
<td>2.5%</td>
</tr>
<tr>
<td>Infection - UTI</td>
<td>2</td>
<td>?</td>
<td>2.5%</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>3</td>
<td>3</td>
<td>3.7%</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>3</td>
<td>3</td>
<td>3.7%</td>
</tr>
<tr>
<td>Dehydration/hypovolemia</td>
<td>3</td>
<td>?</td>
<td>3.7%</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>1</td>
<td>?</td>
<td>1.2%</td>
</tr>
<tr>
<td>Device related issue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<table>
<thead>
<tr>
<th>Spontaneous bacterial peritonitis</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No of occurrences = 1</td>
<td>6 (29%)</td>
<td>4 (21%)</td>
<td></td>
</tr>
<tr>
<td>No of occurrences &gt;1</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infection – Systemic Inflammatory Response Syndrome (SIRS)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No of occurrences = 0</td>
<td>15 (71%)</td>
<td>18 (95%)</td>
<td></td>
</tr>
<tr>
<td>No of occurrences = 1</td>
<td>6 (29%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>No of occurrences &gt;1</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infection - UTI</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No of occurrences = 0</td>
<td>18 (86%)</td>
<td>19 (100%)</td>
<td></td>
</tr>
<tr>
<td>No of occurrences = 1</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>No of occurrences &gt;1</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infection - Other</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No of occurrences = 0</td>
<td>20 (95%)</td>
<td>15 (79%)</td>
<td></td>
</tr>
<tr>
<td>No of occurrences = 1</td>
<td>1 (5%)</td>
<td>3 (16%)</td>
<td></td>
</tr>
<tr>
<td>No of occurrences &gt;1</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

<p>| Bladder catheter dislocations | Total | 5 (24%) | 0 (0%) | 0.04 |
| Peritoneal catheter issues | Total | 3 (9.5%) | 2 (10.5%) | Not significant |
| Other | Wound dehiscence | 1 (5%) | 1 (5%) | Not significant |
| | Bladder perforation | 1 (5%) | 0 | Not significant |
| | Pump malfunction | 2 (10%) | 0 | Not significant |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Count 1</th>
<th>Count 2</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outflow tract problems (Obstruction, hematuria)</td>
<td>2</td>
<td>2</td>
<td>2.5%</td>
</tr>
<tr>
<td>Blocking of tubes</td>
<td>20</td>
<td>13</td>
<td>16.0%</td>
</tr>
<tr>
<td>Displacement of tube (peritoneal catheter disconnected)</td>
<td>1</td>
<td>1</td>
<td>1.2%</td>
</tr>
<tr>
<td>Displacement of tube (migration)</td>
<td>3</td>
<td>3</td>
<td>3.7%</td>
</tr>
<tr>
<td>Pump failure due to technical problems</td>
<td>8</td>
<td>8</td>
<td>9.9%</td>
</tr>
<tr>
<td>Problems with charger</td>
<td>1</td>
<td>1</td>
<td>1.2%</td>
</tr>
<tr>
<td>Explantation of Alfapump®</td>
<td>9</td>
<td>9</td>
<td>11.1%</td>
</tr>
<tr>
<td>Reimplantation of Alfapump®</td>
<td>6</td>
<td>6</td>
<td>7.4%</td>
</tr>
<tr>
<td>Ascitic fluid leakage – hole in bladder catheter</td>
<td>1</td>
<td></td>
<td>1.2%</td>
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</table>
Relevant Guidance

A NICE Interventional procedure guidance IPG479 published in February 2014 makes the following recommendations on the use of a subcutaneous implanted battery-powered catheter drainage system such as the Alfapump® for managing refractory and recurrent ascites:15

- Current evidence on the safety and efficacy of subcutaneous implantation of a battery-powered catheter drainage system for managing refractory and recurrent ascites is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research.
- Research (which may include observational studies) should clearly document the indications for use of the procedure and details of patient selection. Reported outcomes should include quality of life, overall survival and paracentesis-free survival, duration of function of the drainage system, nutritional parameters and any complications associated with its implantation or use.

The British Society of Gastroenterology Guidelines on the Management of Ascites in Cirrhosis from 2006 makes no mention of the use of the Alfapump® device.16 But these guidelines were written before the Alfapump® device was available. The guidelines make the following treatment recommendations for the management of ascites:

- Therapeutic paracentesis is the first line treatment for patients with large or refractory ascites.
- TIPSS could be used for the treatment of refractory ascites requiring frequent therapeutic paracentesis or hepatic hydrothorax with appropriate assessment of risk benefit ratio.
- Liver transplantation should be considered in patients

The European Association for the Study of the Liver Guidelines from 2010 on the Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome in Cirrhosis also make no mention of the use of the Alfapump® device.2 But these guidelines were also written before the Alfapump® device was available. The guidelines make the following treatment recommendations for the management of ascites:

- Methods for treatment of refractory ascites include large volume paracentesis with albumin administration, continuing diuretic therapy (if effective in inducing natriuresis), insertion of transjugular intrahepatic portosystemic shunt (TIPSS), and liver transplantation.
- Repeated large-volume paracentesis plus albumin (8 g/L of ascites removed) is the first line of treatment for refractory ascites (Level A1).
- TIPSS is effective in the management of refractory ascites but is associated with a high risk of hepatic encephalopathy and studies have not been shown to convincingly improve survival compared to repeated large-volume paracentesis (Level A1). TIPSS should be considered in patients with very frequent requirement of large-volume paracentesis, or in those in whom paracentesis is ineffective (e.g. due to the presence of loculated ascites) (Level B1).
- Once ascites becomes refractory to medical treatment, the median survival of patients is approximately 6 months. As a consequence, patients with refractory ascites should be considered for liver transplantation.

An online search found three NHS commissioning groups that have issued advice or a policy decisions and recommendation regarding the Alfapump® system. These are presented in table 3.

**Table 3: A selection of local NHS policies for the Alfapump®.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Recommendation</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td>Bristol CCG</td>
<td>Alfa Pumps for the Removal of Ascites due to Liver Disease is not routinely funded by the CCG and is subject to this restricted policy.</td>
<td>September 2016</td>
</tr>
</tbody>
</table>
| South Gloucestershire CCG    | PRIOR APPROVAL REQUIRED<br>The CCG will commission the use of the Alfa Pump system only when the following criteria have been met:<br>Patients must have the ability to operate the device.<br>AND<br>Patients must have cirrhosis of the liver - defined by histological and/or clinical, and/or radiological criteria<br>AND<br>Patients must present with refractory ascites* and require periodic large volume paracentesis (large volume defined as ≥ 5 L to accord with the clinical guidance of EASL, European Association for the Study of the Liver, which recommends withdrawal of 5 L should precipitate administration of albumin).<br>*Definition of refractory ascites [Moore and Aithal, Gut 2006 Oct; 55 Suppl 6:v1-12] Ascites that cannot be mobilised or early recurrence of which (that is, after therapeutic paracentesis) cannot be satisfactorily prevented by medical therapy.<br>This includes two different subgroups:<br>1. Diuretic resistant ascites - ascites that are refractory to dietary sodium restriction and intensive diuretic treatment (spironolactone 400 mg/day and frusemide 160 mg/day for at least one week, and a salt restricted diet of less than 90 mmol/day (5.2 g of salt)/day).<br>2. Diuretic intractable ascites - ascites that is refractory to therapy due to the development of diuretic induced complications that preclude the use of an effective diuretic dosage.<br>Alfa Pumps will not be commissioned on ANY the following grounds: |}
| North Somerset CCG           |                                                                               |                |
- Patient has had a Gastrointestinal haemorrhage over the last 7 days
- Renal failure defined as serum creatinine higher than or equal to 2 mg/dl
- Severe coagulopathy defined as prothrombin time greater than 40% more than Upper Limit of Normal (as determined locally)
- Platelet count of less than 40,000/μL unless platelet therapy is given at the time of surgery
- Clinical Evidence of recurring bacterial peritonitis, defined as 2 or more episodes over the last 6 months or a single episode within the last 2 weeks
- Clinical evidence of recurring urinary infections, defined as 2 or more episodes over the last 6 months or a single episode within the last 2 weeks
- Clinical evidence of loculated ascites
- Advanced hepatocarcinoma, defined as one which exceeds Milan criteria
- Obstructive uropathy, residual urinary volume exceeding 100ml, or any bladder anomaly which might contraindicate implantation of the device
- Other concomitant disease or condition likely to significantly decrease life expectancy or present anaesthetic risk (e.g., moderate to severe congestive heart failure)
- Immuno-modulatory treatment (including azothiaprine, methotrexate, anti-TNF therapies) used within last 4 months
- Known or suspected hepatic or extra hepatic malignancy, unless adequately treated or in complete remission for ≥ 3 years
- BMI>40 presenting a risk for surgery and tunnelled lines
- Patients with contraindications for general anaesthesia

Patients who are not eligible for treatment under this policy may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy.
Specialist application

Specialists at the Freeman Hospital who have experience in the using the Alfapump® system have indicated they would only consider its use in patients who have no other treatment options for refractory ascites, such as liver transplant or TIPSS. If TIPSS or transplant is not contraindicated then either of these would be used to treat refractory ascites rather than an Alfapump®. Generally they consider use of the Alfapump® for patients with an expected survival of >6 months and who are having very regular paracentesis (e.g. every 2 weeks). They estimate that the Alfapump® becomes cost effective in this group of patients. In their experience to date patients with severe liver synthetic function dysfunction (low albumin and high prothrombin time and bilirubin) do not do well on the Alfapump® and so it would not be considered a viable option in these patients. The “ideal” patient for use of the Alfapump® is one who has refractory ascites due portal hypertension with preserved liver synthetic function who has a contraindication to TIPSS and liver transplant. Relatively few patients are therefore realistic candidates for the Alfapump®, perhaps 5 per year for the North East region. The numbers could increase with increased awareness of the Alfapump®, but are likely to remain low.
Cost Analysis

There is no robust, published information on how many patients would be eligible for the Alfapump® system in the NTAG region.

Between April 2013 and August 2016 there were 8 requests to IFR panels across Sunderland, DDES, North Tyneside, Newcastle and South Tees CCGs. Five of these requests were approved, one is awaiting a decision, and one was declined as the patient died. The liver unit at the Freeman hospital has identified a further five patients in which it would consider use of the Alfapump® system.

Published information regarding new cases (incidence) and total number (prevalence) of people living with cirrhosis is limited. A study reported the average incidence and prevalence of liver cirrhosis between 1992 and 2001, and estimated the number of new cases of cirrhosis to be in the region of 20 per 100,000 population per year. This equates to approximately 8,000 new cases per year in England and Wales.\(^1\)

Although it is not possible to make exact predictions, the National Horizon Scanning Centre estimate that 4,000 people with cirrhosis will develop ascites within 10 years and in the region of 400 people will subsequently develop refractory ascites. The timing of clinical progression to refractory ascites is variable; therefore calculating a reasonable estimate of total number of cases of cirrhosis with refractory ascites is difficult.\(^1\)

The population of the NE&C is 3,239,890 according to the UKMi Prescribing Outlook Cost Calculator 2015, which equates to 640 new cases of cirrhosis in the NE&C per year.

Specialists at the at the Freeman Hospital have indicated that approximately five patients per year would be considered suitable for the Alfapump® system across the North East & Cumbria as an alternative to large volume paracentesis every 2 weeks or TIPSS.

The cost of the entire system including pump device, catheters and programmer is £20,000 plus VAT. This includes lifelong maintenance of the device and free replacement in the event of device failure.

There may be the potential for cost savings associated with the use of the Alfapump® as the number of hospital admissions for paracentesis will be reduced, and there would be reduction in the need for supplementation with IV albumin.

The PbR tariff for paracentesis is £815 (combined day case / elective tariff HRG FZ13Z including MFF). Therefore based on 16 hospital admissions per annum (3-4 weekly) the cost of paracentesis is £13000 per patient per annum.
The NICE Medical technologies guidance [MTG9] The PleurX peritoneal catheter drainage system for vacuum-assisted drainage of treatment-resistant, recurrent malignant ascites published in March 2012 estimated the cost per patient for inpatient and outpatient large-volume paracentesis to be £3146 and £1457 respectively.

The NHS National Innovation Centre (NIC) commissioned an independent economic assessment of the Alfapump® system. Sequana Medical issued a press release stating that this assessment suggests the device may save the NHS £50 million in ascites care annually. The independent economic assessment report, showing the underlying assumptions used, is not publically available for scrutiny.1

A cost-utility analysis model carried out by the manufacturer suggests that the Alfapump® system in comparison with large volume paracentesis (LVP) over a time horizon of 9 months had lower cost (£26 798 and £39 702 respectively) and produced more benefits (0.87 QALYs and 0.67 QALYs respectively). Alfapump® dominates over LVP from a UK NHS perspective with an incremental cost-effectiveness ratio (ICER) of (minus) -£64 841. This number falls well below the NICE willingness-to-pay threshold of £20,000.18
Points to consider

- There is currently insufficient evidence to identify groups of patients who are most likely to benefit from the Alfapump® system.
- Trial data comes from company sponsored trials. The majority of these trials are only available in conference abstracts. A Medline and Embase search only found one trial that had been fully published.
- There is limited safety data available on the use of the Alfapump® system.
- There is no robust, published information on how many patients would be eligible for the Alfapump® system in the NTAG region.
- NICE have produced an IPG which concludes that “Current evidence on the safety and efficacy of subcutaneous implantation of a battery-powered catheter drainage system for managing refractory and recurrent ascites is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research.”
- Recent IFR requests for treatment have been made on the basis of cost effectiveness (the subsequent reduction in paracentesis, improved quality of life, reduced infections from paracentesis etc.) however the economics have not been formally assessed or reviewed in clinical studies.
- Liver cirrhosis with refractory ascites is a condition which can significantly impact on an individual's quality of life. If the Alfapump® System proves to be effective and cost-effective, it may offer an alternative to repeated paracentesis or may reduce the need for these invasive hospital procedures.\(^1\)
- Studies are ongoing to look at improvements quality of life in patients with the Alfapump® device. Trials to data have not specifically included measures to look at the impact of the Alfapump® device on quality of life.
- Specialists at the Freeman Hospital who have experience in the using the Alfapump® system have indicated they would only consider its use in patients who have no other treatment options for refractory ascites, such as liver transplant or TIPSS. In their experience the “ideal” patient for is use of the Alfapump® is one who has refractory ascites due portal hypertension with preserved liver synthetic function who has a contraindication to TIPSS and liver transplant. Relatively few patients are therefore realistic candidates for the Alfapump®, perhaps 5 per year for the North East region.

Author's declaration: The author has no relevant interests to declare.
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7. Personal Communication with Sequana Medical AG.
15. NICE Interventional procedure guidance IPG479. Subcutaneous implantation of a battery-powered catheter drainage system for managing refractory and recurrent ascites. 23 February 2014.