**Retrograde versus antegrade placement of a double-J catheter in patients with extrinsic ureter obstruction**

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<th>Dossiernummer</th>
<th>NL49696.098.14</th>
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<tr>
<td>Short title</td>
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<td>Version</td>
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<td>Date</td>
<td>12/11/2014</td>
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# PROTOCOL SIGNATURE SHEET

<table>
<thead>
<tr>
<th>Name</th>
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<tr>
<td>Head of Department:</td>
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<td>Coordinating investigator:</td>
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<td>Drs. Joanne Verdult</td>
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<td>Interventional radiologist</td>
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<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ABR</td>
<td>General assessment and registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene beoordeling en registratie)</td>
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<tr>
<td>AE(s)</td>
<td>Adverse event(s)</td>
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<tr>
<td>CCMO</td>
<td>Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek</td>
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<tr>
<td>CRF</td>
<td>Case record form</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
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<td>FU</td>
<td>Follow up</td>
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<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
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<tr>
<td>INR</td>
<td>International normalized ratio</td>
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<tr>
<td>ITT</td>
<td>Intention to treat</td>
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<tr>
<td>JJ</td>
<td>Double J catheter</td>
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<tr>
<td>LUTS</td>
<td>Lower urinary tract symptoms</td>
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<tr>
<td>METC</td>
<td>Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>PCN</td>
<td>Percutaneous nephrostomy</td>
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<tr>
<td>PUJ</td>
<td>Pelviureteric junction</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>SAE</td>
<td>Serious adverse event</td>
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<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
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<tr>
<td>WMO</td>
<td>Medical research involving human subjects act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)</td>
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**SUMMARY**

**Rationale and Aim**

Percutaneous nephrostomy is common treatment for acute hydronephrosis. However, the external drainage catheter shows a high incidence of complications in long-term management, such as infection and dislocation. For the long-term treatment of ureter obstruction an internal nephro-ureteral catheter can be used (double J catheter). These catheters are generally inserted by a retrograde approach under cystoscopic guidance, often under general anaesthesia. Insertion however may be difficult, or in some cases even impossible. The alternative is then insertion in an antegrade fashion through percutaneous access.

The purpose of this study is to compare the technical success rates, scores on the visual analogue scale (VAS) and complications after retrograde and antegrade double J catheter insertion in patients with extrinsic urinary tract obstruction.

**Study design**

Randomized controlled trial.

**Study population**

Patient population consist of adults (18 years of age or older) with a CT or MRI diagnosis of extrinsic ureter obstruction by a mass surrounding the urinary tract. Patients with a renal transplant, ileal conduit urinary diversion or horseshoe kidney are excluded from the study. Patients may not have signs of acute infection, macroscopic haematuria, coagulation abnormalities or known allergy to contrast media or be pregnant.

**Intervention**

Subjects will be randomized to receive a double J catheter inserted by a retrograde or an antegrade approach

**Main study endpoints**

The primary endpoint is the immediate technical success rate. Secondary study endpoints are VAS score immediately after the procedure, technical success rate at 30 days, mortality within 30 days, major complications (i.e. transfusion required retroperitoneal bleeding, perforation, sepsis) and minor complications (i.e. urinary tract infection, macroscopic haematuria, inflammation of the skin) within 30 days, renal function at 7 days and 30 days and EQ5D questionnaire scores at 30 days after intervention.

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness**

Burden to the patient resulting from participation in this study consists of 2 follow-up visits; at 7 days and 30 days after primary intervention for clinical follow-up and laboratory blood tests. Subjects will be seen for ultrasound of the kidney(s) and abdominal X-ray at 30 days. They will receive the EQ5D questionnaire personally or by mail at 30 days after treatment.
1. INTRODUCTION AND RATIONALE

Dilatation of the renal pelvis and calices as a result of urinary tract obstruction can be intrinsic or extrinsic and can result from both benign and malignant aetiologies. Extrinsic obstruction is most often caused by compression or mural infiltration of the ureter wall by a surrounding pelvic mass, for instance a urologic, gynaecologic or colorectal tumour. Furthermore, extrinsic obstruction can be caused by benign aetiologies such as retroperitoneal fibrosis, scar tissue, endometriosis, inflammation or, in rare circumstances, by anatomic variants. In order to prevent irreversible damage to the kidney early recognition of ureter obstruction is important.

In general, the treatment of choice in acute hydronephrosis is insertion of a percutaneous nephrostomy catheter (PCN). However, this external drainage catheter shows a high incidence of complications in long-term management, such as infection and dislocation, which may eventually decrease the quality of life. Therefore, for the long-term management of ureteral obstruction placement of a double J catheter is an alternative. In most institutions retrograde stent insertion is attempted first. Retrograde stent insertion is typically performed under cystoscopic guidance with patients occasionally under general anaesthesia. In patients with malignant obstruction the retrograde approach may be difficult, or even impossible. In these cases, catheter insertion using an antegrade fashion by means of a percutaneous route is an alternative, often as a two-step procedure. During the first procedure a PCN is inserted and during the second procedure an antegrade double J.

The major complication of the antegrade technique is retroperitoneal bleeding. Transfusion-demanding bleeding ranges between 1% and 4% in case of standard PCN. The retrograde approach avoids the potential complications of PCN, which is the prerequisite for antegrade stent placement. Potential complications of a double J catheter, and thus for both techniques, are perforation, infection, haematuria, malposition, migration, inadequate relief of obstruction and ureteral erosion or fistulisation.

Several studies report on the results of retrograde internal stent placement, sometimes in comparison with PCN. These studies show that retrograde stent insertion is technically successful in more or less 75% of cases. Only two studies compare retrograde and antegrade double-J catheter placement, however not in randomized fashion. In a series of 65 patients Chitale et al. retrospectively compare technical success rates of retrograde stent insertion with PCN followed by antegrade stent placement in patients with malignant obstruction. The retrograde approach had a success rate of only 21%. On the other hand, antegrade stent insertion was successful in 98% cases. They conclude that obstruction of the pelvic ureter is best managed by two-stage antegrade ureteric stenting. In a series of 50 obstructed ureters (in 30 patients) Uthappa et al. report success rates of 50% and 96%, of respectively retrograde and antegrade stent insertion.
A review of our own experience in the management of obstructed ureters using antegrade ureteral stenting showed a high technical success rate of 96% and a low morbidity rate. An additional advantage of an antegrade approach compared to a retrograde approach is that it can be performed using local analgetics only, thus obviating the need for general anaesthesia.

To the best of our knowledge, no RCT has yet been performed comparing the outcome of antegrade versus retrograde approach of ureteral stent insertion. An overview of the literature does show that retrograde or antegrade stent insertion in patients with extrinsic ureteral obstruction have moderate to high technical success rates and low morbidity rates. An antegrade approach seems to be associated with a higher technical success rates than a retrograde approach, however a retrograde approach is more commonly used.

2. OBJECTIVES

2.1. Primary objective
The primary objective is to compare the immediate technical success rate after retrograde and antegrade stent insertion in patients with extrinsic urinary tract obstruction.

2.2. Secondary objectives

- To compare VAS scores after retrograde and antegrade stent insertion in patients with extrinsic urinary tract obstruction.
- To compare the complications after retrograde and antegrade stent insertion in patients with extrinsic urinary tract obstruction.
- To compare technical success rates at 30 days after retrograde and antegrade stent insertion in patients with extrinsic urinary tract obstruction.
- To compare scores on EQ5D questionnaire at 30 days after retrograde and antegrade stent insertion in patients with extrinsic urinary tract obstruction.
- To assess possible predictive factors for immediate technical success.
- To assess possible predictive factors for technical success at 30 days.
- To assess possible predictive factors for the evolvement of major and minor complications.
- To assess possible predictive factors for the outcome on the EQ5D questionnaire.

3. STUDY DESIGN
The study is a multicentre randomized non-blinded clinical trial with two-armed treatment allocation. The study will run in at least 2 large hospitals in the Netherlands. The study will start in 2014 and end when the inclusion of subjects is completed.
4. STUDY POPULATION

4.1. Population
Patients, 18 years of age or older, with extrinsic urinary tract obstruction are eligible for participation in this trial.

Patients who are asked to participate in this study are entitled to choose whether or not to take part. Participation is entirely voluntary and eligible subjects should be competent to understand the implications of participation in the study. Informed consent forms are designed to assure the protection of patient’s rights.

4.2. Inclusion criteria
- Legally capable and written informed consent
- 18 years or older
- A CT or MRI diagnosis of extrinsic ureter obstruction by visible or non-visible mass surrounding the urinary tract
- Possible dorsal percutaneous approach to kidney
- Possible transvesical approach
- Possible treatment by an urologist and intervention radiologist with sufficient experience
- Patient is willing and able to comply with the specified follow-up evaluation

4.3. Exclusion criteria
- Active infection, defined as temperature >38,0 °C
- Macroscopic haematuria
- INR > 2,0
- Thrombocytes < 50 10⁹/l
- Ileal conduit urinary diversion
- Kidney transplantation
- Horseshoe kidney
- Known allergy to contrast media
- Pregnancy

Patients with intrinsic ureteral obstruction or obstruction caused by ligation are not included in the study. Anatomical abnormalities i.e. PUJ stenosis, partial duplicated or duplicated urinary system, ectopic ureter are no exclusion criteria. In addition, the presence of only one kidney is not an exclusion criterion.

4.4. Reassessment
If a patient fails to meet the above-mentioned criteria for a reason thought to be reversible, the patient may be reassessed for entry on a later date.

### 4.5. Calculation sample size

 Primary outcome: immediate technical success rate.

Results from recent studies (later than 2000) show that retrograde insertion of a stent has been technically successful in an average of 75% of the cases. The success rates of the antegrade approach are reported in an average of 97%. Results of the studies on retrograde and antegrade stent insertion for extrinsic urinary obstruction are reported in respectively table 1 and 2.

**Table 1. Results of the studies on retrograde stent insertion for extrinsic urinary obstruction**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Aetiology</th>
<th>Number of patients</th>
<th>Technical success rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yossepowitch (2001)**</td>
<td>Prospective</td>
<td>Extrinsic UO</td>
<td>39</td>
<td>73%</td>
</tr>
<tr>
<td>Chitale (2002)*</td>
<td>Retrospective</td>
<td>Malignant pelvic disease</td>
<td>24</td>
<td>21%</td>
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<tr>
<td>Chung (2004)**</td>
<td>Retrospective</td>
<td>Extrinsic UO</td>
<td>90</td>
<td>95%</td>
</tr>
<tr>
<td>Uthappa (2004)†</td>
<td>Prospective</td>
<td>Malignant UO</td>
<td>50</td>
<td>50%</td>
</tr>
<tr>
<td>Rosenberg (2005)†</td>
<td>Retrospective</td>
<td>Malignant UO</td>
<td>28</td>
<td>92%</td>
</tr>
<tr>
<td>Ganatra (2005)††</td>
<td>Retrospective</td>
<td>Malignant UO</td>
<td>157</td>
<td>85%</td>
</tr>
<tr>
<td>Kanou (2007)**</td>
<td>Prospective</td>
<td>Extrinsic malignant UO</td>
<td>75</td>
<td>73%</td>
</tr>
<tr>
<td>Rosevaer (2007)**</td>
<td>Retrospective</td>
<td>Extrinsic UO</td>
<td>54</td>
<td>84%</td>
</tr>
<tr>
<td>Jeong (2007)††</td>
<td>Retrospective</td>
<td>Extrinsic malignant UO</td>
<td>86</td>
<td>85%</td>
</tr>
<tr>
<td>McCullough (2007)††</td>
<td>Retrospective</td>
<td>Malignant pelvic disease</td>
<td>57</td>
<td>54%</td>
</tr>
<tr>
<td>Ku (2008)*</td>
<td>Retrospective</td>
<td>Extrinsic malignant UO</td>
<td>68</td>
<td>85%</td>
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<tr>
<td>Kamiyama (2011)††</td>
<td>Retrospective</td>
<td>Extrinsic UO</td>
<td>53</td>
<td>96%</td>
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<tr>
<td>Song (2011)††</td>
<td>Retrospective</td>
<td>Gynaecologic malignancy</td>
<td>75</td>
<td>67%</td>
</tr>
</tbody>
</table>

UO = ureteral obstruction

**Table 2. Results of the studies on antegrade stent insertion for extrinsic urinary obstruction**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Aetiology of obstruction</th>
<th>Number of patients</th>
<th>Technical success rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chitale (2002)*</td>
<td>Retrospective</td>
<td>Malignant pelvic disease</td>
<td>60</td>
<td>95%</td>
</tr>
<tr>
<td>Uthappa (2004)†</td>
<td>Prospective</td>
<td>Malignant UO</td>
<td>50</td>
<td>96%</td>
</tr>
<tr>
<td>Carrafielo (2007)**</td>
<td>Prospective</td>
<td>Malignant UO</td>
<td>45</td>
<td>99%</td>
</tr>
</tbody>
</table>

UO = ureteral obstruction
A review of our experience in the management of the obstructed ureter using antegrade ureteral stenting shows technical success of 96%.

Basic assumptions:
• The primary outcome is estimated 75% in the retrograde group.
• The primary outcome is estimated 90% in the antegrade group.

The sample size is calculated using the two-group $\chi^2$ test for equal proportions and equal group size (software: PASS) With the power fixed to 80% and a two-sided significance of $\alpha = 5\%$ the required sample size is calculated to be 97 patients per group. With an estimated loss to follow-up of 10%, the total study population will be a least 214 patients.

4.6. Participating centres and centre eligibility
To be fully eligible for participation in the trial and to include patients in the trial, centres should meet the following minimum criteria:
• At least one radiologist/radiology resident of the intervening team should have sufficient experience with placement of antegrade double J catheters.
• At least one urologist/urology resident of the intervening team should have sufficient experience with placement of retrograde double J catheters.

Sufficient experience is defined as the completion of a least 10 full procedures. Procedures that have been carried out by two operators (for example, in training setting) do count. Procedures do not need to be successful, nor uncomplicated.

Note that patients may only be included in the trial when the intervention team that will treat the patient includes at least one member with sufficient experience (defined above). For this reason, the possibility of treatment by an urologist/radiologist with sufficient experience is listed as an inclusion criterion.

5. TREATMENT OF SUBJECTS
5.1. Screening
Patients with ureter obstruction are screened for participation in the study by the urologist or oncologist to whom they are referred. Patients may be randomized prior to or after PCN.

Screening consist of:
• CT or MRI with features of extrinsic ureter obstruction by visible or non-visible mass surrounding the urinary tract.
• Evaluation of inclusion and exclusion criteria

If screening conditions are met, written informed consent (IC) is obtained.
5.2. Investigational treatments

5.2.1. Randomisation to retrograde arm

A urologist performs the retrograde placement of a double J catheter. The procedure is performed in either the outpatient clinic or in the operating room, under local or general anaesthesia. The patient is in the lithotomic position. In some procedures fluoroscopy is used. The bladder is accessed with a cystoscope with an Albarran deflector. A "nitinol" or Terumo guide wire is placed through the Albarran deflector into the ureteral orifice. The ureter is catheterized up towards the pyelocaliceal system. The draining catheter is placed over the guidewire. The position is checked using fluoroscopy.

5.2.2. Randomisation to antegrade arm

The antegrade placement of a double J catheter is performed under ultrasound and fluoroscopic guidance by an intervention radiologist. The procedure is performed in either one or two procedures, with local and on indication intravenous anaesthesia (Fentanyl 0.05 - 0.15 mg intravenous). Exceptionally the procedure will be performed with the patient under general anaesthesia. After sonographic localisation the renal pelvis is accessed with a fine needle (22 gauge). For all antegrade ureter manipulations it is preferable to have access by means of a middle calyx by a dorsal approach. Once a catheter is placed a stiff guide wire (Amplatz) is inserted. With an Amplatz wire in safe position, the parenchymal tract is dilated by means of a dilator and sheath. When presence of a nephrostomy catheter prior to the procedure an Amplatz is inserted and the nephrostomy catheter is changed for a sheath. The ureter is catheterized down in to the bladder by a hydrophilic-coated glide wire (0.0035 inch) and a catheter. If the glide wire passes the obstruction but the catheter does not follow, balloon dilation is an option. When the glide wire and the catheter have reached the bladder an Amplatz guide wire is inserted and the double J catheter can be inserted into the right position.

The supportive treatment, such as use and dosage of antibiotic prophylaxis, use and dosage of analgesics, sedative or pain medication prior to or during intervention, the location of treatment within the hospital (angiosuite, operating room or outpatient clinic) and the choice of equipment used during intervention will be left to the discretion of each participating centre.

5.3. End of the procedure

Correct position and patency of the double J catheter will be ensured under fluoroscopy. In some cases, for instance in patients with severe kidney failure or substantial hydronephrosis, the treating physician will choose to leave a PCN catheter or an urinary catheter behind temporarily to achieve optimal drainage.
6. METHODS

6.1. Study parameters

6.1.1. Main study endpoint
Immediate technical success rate, defined as correct position of the double-J catheter with the proximal loop within the renal pelvis or a calix above the obstruction and distal loop in the urinary bladder with fluoroscopy. Antegrade contrast studies should show patency of the double J catheter.

6.1.2. Secondary study endpoints

- **VAS scores retrieved directly after the procedure.** VAS will be scored after each PCN procedure in patients with extrinsic ureteral obstruction. When a double J catheter is inserted as a 2-step procedure after PCN, the highest VAS score of either part of the procedure will be counted.
- **Technical success rate at 30 days,** defined as correct position double-J stent with proximal loop in renal pelvis and distal loop in the urinary bladder on abdominal X-ray, non-dilated renal collecting system with ultrasound and stable or improved renal function.
- **Death within 30 days**
- **Major complications:**
  - Transfusion required retroperitoneal bleeding or bleeding into the renal pelvis
  - Perforation of the urinary tract with clinical signs of retroperitoneal urine leakage
  - Perforation of the bowel
  - Sepsis, defined as clinical signs of an urinary tract infection and a positive urine and blood culture
- **Minor complications:**
  - Urinary tract infection, defined as clinical signs of an urinary tract infection and a positive urine culture
  - Macroscopic haematuria
  - Inflammation of the skin
  - Lower urinary tract symptoms (LUTS)
  - Other
- **Score on the EQ5D questionnaire at 30 days**

6.1.3. Other study parameters

- **General participant demographics**
  - Date of birth
  - Gender
  - BMI
- **Side of obstructed system:**
- Level of obstruction:
  - Proximal 1/3 ureter
  - Mid segment ureter
  - Distal 1/3 ureter
- Anatomical abnormalities:
  - Duplicated collecting system
  - (Partial) duplicated collecting system
  - PUJ stenosis
  - Ectopic ureter
  - Other
- Cause of obstruction:
  - Malignancy (i.e. colon, gynaecologic, bladder, prostate, other)
  - Retroperitoneal fibrosis
  - Scar tissue
  - Endometriosis
  - Lymphadenopathy
  - Other
- Laboratory blood tests:
  - Serum creatinine
  - GFR
  - Potassium
  - INR, on the day of treatment only in patients who use Coumarin derivatives
- Use and dosage of analgetics, sedative or pain medication prior to or during intervention
- Use and dosage of antibiotic prophylaxis
- Location of the procedure:
  - Intervention room
  - Outpatient clinic
  - Operating room
- Equipment used during the procedure
- Presence of external nephrostomy catheter prior to procedure (2-step procedure)
- Presence of external nephrostomy catheter after procedure
- Presence of an urinary catheter after procedure

6.2. Randomization and treatment allocation
The randomization procedure will be computer- and web-based. To achieve approximate balance randomisation will be stratified for each centre and for the presence of a PCN
catheter prior to treatment. Block randomization with random block sizes will be used to reduce bias and achieve balance in the allocation of participants to treatment arms. The block size will only be known to the statistician, to prevent investigator bias. When inclusion criteria are met and the informed consent is signed the patient will be randomised. It will not be possible to view the treatment allocation before the patient is registered in the study database, nor will it be possible to remove the patient from the study after treatment assignment has become known. Patients will be randomised on a 1:1 basis of retrograde stent insertion versus antegrade stent. Both patient and treating physician will be aware of the treatment.

If a patient has ureteral obstruction on both sides the patient will be randomized for one ureter. The other ureter will be treated in the same fashion.

If the randomized treatment fails, this will be noted as primary treatment failure. Only the technical success of this second treatment will be recorded.

If, during follow-up, a patient needs treatment of the other ureter, the patient will not be randomized but the other ureter will be treated in the same manner. Only the technical success and the VAS score direct after this procedure will be recorded. The patient will not start in a second follow-up schedule.

If, after follow-up, a patient needs treatment of the other ureter, and if eligible, the patient can be re-entered into the study and the second ureter is treated according to the new randomization. The patient will start in a second follow-up schedule.

If during or after follow up the double J catheter has migrated, blocked or dislocated and a new catheter needs to be placed, this will be done in the retrograde fashion.

6.3. Study procedures

6.3.1. Intervention
Subjects will be treated with retrograde or antegrade double J catheter as described above in chapter 5.

6.3.2. Methods and/or tests to be used to assess the defined study endpoints
All patients will be followed during a 30 days follow-up period. Source documentation of clinical events (e.g. hospital record, catheterization reports, autopsy reports, etc.) will be obtained by the treating physician whenever possible.

Exams during follow-up that are extra, not as part of the medical treatment but for the study purposes, are listed below.
Day of treatment:
VAS score will be obtained by the treating physician direct after treatment

Follow-up period 30 days
Subjects will be asked to fill in the EQ5D questionnaire.

6.4. Withdrawal of individual subjects
Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. The reason for discontinuation must be recorded.

7. SAFETY REPORTING

7.1. Section 10 WMO event
In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal.

7.2. Interim safety analysis
For safety reasons an interim analysis will be performed by the statistician after the first 100 included patients in order to detect differences of 50% or more regarding major complications and/or treatment related death between the antegrade an retrograde treatment arm.

With respect to the number of patients receiving the double-J catheter we expect an annual inclusion of 100 patients.

7.3. AE and SAEs

7.3.1. Adverse events
Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the intervention. At each contact the treating physician will determine whether any AE has occurred. In addition, patients will be instructed to contact the treating physician if any adverse events occur between study evaluation moments. All adverse events reported spontaneously by the subject or observed by the treating physician or his staff will be reported.

7.3.2. Serious adverse events (SAEs)
A serious adverse event is any untoward medical occurrence or effect that:

- Results in death
- Is life threatening (at the time of the event)
• Requires hospitalisation or prolongation of existing inpatients’ hospitalisation
• Results in persistent or significant disability or incapacity
• Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

For the purpose of this study all serious adverse events reported spontaneously or observed by the treating physician during follow-up will be reported by the treating physician. These events are to be reported by mail to the coordinating investigator or primary investigator (j.verdult@hagaziekenhuis.nl or h.voverhagen@hagaziekenhuis.nl) within 48 hours. The coordinating investigator or primary investigator will report the SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 15 days after the primary investigator has first knowledge of the serious adverse events.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event. This is for a preliminary report with another 8 days for completion of the report.

7.4. Follow-up of AEs and SAEs
All AEs and SAEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study, as defined in the protocol.

8. STATISTICAL ANALYSIS
Analysis will be by intention to treat (ITT).

If there is disbalance between the two groups regarding certain baseline variables we will use regression models to compare the groups, with adjustment for these baseline characteristics. Certain baseline variables for which no stratification could be:
• Age
• Gender
• Cause of obstruction
• Level of ureter obstruction
• Use of general anaesthesia or sedation and local pain medication prior to or during intervention
Dichotomous outcomes (i.e. technical success rates and complications) will be compared between the groups using a chi-square test. Numerical outcomes (i.e. QoL, satisfaction scores) will be compared using unpaired t-tests.

Regression models (logistic regression) will be used to assess possible predictive factors for immediate technical success, technical success at 30 days and evolvement of major and minor complications.

9. ETHICAL CONSIDERATIONS

9.1. Regulation statement
The study will be performed in accordance with the spirit of the Declaration of Helsinki.

9.2. Recruitment and consent

10.2.1. Recruitment
All patients with extrinsic ureter obstruction will be considered for the study. A member of the Research team should review the patient for eligibility if all inclusion criteria are present, inform the patient about the purpose of the study and review all required baseline study data for that patient candidate. If applicable the informed consent process may be initiated.

9.2.2. Informed Consent
Before a patient participates in the study, a member of the research team will obtain his or her written informed consent. In most cases this will be an urologist. The subject will be asked to read a subject information section of the consent form approved by the responsible Medical Ethics Committee and sign it to indicate consent to participate in the study. If a patient is not capable of writing, informed consent can be given orally in the presence of at least one witness in accordance to the Medical Research Involving Human Subjects Act (article 6, subsection 2, altered WMO). Informed consent will be obtained after screening and before the start of the procedure. Patients will have time to consider participation up until the moment of treatment.

Patient Information Form and Informed Consent Form are attached in appendix D.

9.3. Benefits and risks assessment, group relatedness
The treatment for extrinsic urinary obstruction is placement of a percutaneous nephrostomy (PCN) or placement of a double J stent. In most institutions retrograde stent insertion is attempted first. Antegrade stent insertion is typically performed when failure of retrograde insertion or as a two-step procedure after PCN.

Both procedures are performed in a weekly routine. To the best of our knowledge no RCT has been performed comparing the antegrade approach with the retrograde approach of
double J catheter insertion. Consequently, there is no evidence of better results after retrograde or antegrade double J catheter insertion.

The greatest risk of the antegrade approach is retroperitoneal bleeding. This risk is highest during the one step procedure when accessing the renal pelvis with a fine needle. The risk of significant retroperitoneal bleeding is comparable with the risk at PCN placement, about 3%\(^9\).

**9.4. Compensation for injury**

Each hospital will provide liability insurance concerning the treatment of every patient included in the study. This insurance coverage is available to the investigator and the patient. Damages to participating patients with exception of those related to the progression of the underlying disease, to genetic material, or those manifesting after 4 years of treatment, are covered by a clinical trial insurance taken by Haga Ziekenhuis, Leyenburg with:

Onderlinge Waarborgmaatschappij Centramed B.A.
Postbus 191
2270 AD Voorburg

The sponsor has a liability insurance, which is in accordance with article 7, subsection 8 - 11 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

In case of damage the patient is to contact the principle investigator, Dr. H. van Overhagen, by telephone and also the insurance company at the above-mentioned address. This information will be provided to the subject in Dutch by means of the Patient Information Form (Appendix B).
10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1. Handling and storage of data and documents

10.1.1. Case Record Form
All data of patients collected during the study will be recorded in the Case Record Forms (CRF). The CRF must be completed fully and legibly.

The investigator is responsible for the quality of the data recorded in the CRF. Where the investigator has not been responsible for completing the CRF an additional signature from the co-investigator overseeing the data entry of the study must be obtained.

10.1.2. Privacy
Patients will be identified in the CRFs by a unique code number. The code is not convertible to the subject. Only the coordinating investigator and the principal investigator of each centre will know the code.

The subject will be informed that the data will be stored in a computer, local regulations for the handling of computerized data will be followed as described in the written patient information/consent form and identification of individual patient data will only be possible for the investigators. Furthermore, the subjects will be informed about the possibility of inspections of relevant parts of the hospital records by health authorities or study monitor. These officials will be identified and have signed a confidentiality agreement.

10.1.3. Data processing
The CRF data will be collected and will be stored and processed in a computer database program. After processing the data will be transferred from the database to a statistical program. The data transfer to the statistician will take place at the end of the study after the database has been closed.

10.1.4. Data archiving
Patient identification log, hospital records, informed consent forms, case record forms and databases must be kept for at least 5 years after completing the study (EU- directive 2005/28/EG). If the investigator moves or retires, he/she must nominate someone in writing to be responsible for record keeping. Archived data may be held on microfiche or electronic record, provided that a backup exists and a hardcopy can be obtained from it if required.

10.2. Monitoring and Quality Assurance

10.2.1 Monitoring
All CRF’s will be checked for completeness within two months after inclusion by the coordinating investigator or the trial nurse. Data management (coordinating investigator Drs. J. Verdult and primary investigator Dr. H. van Overhagen) will be responsible for monitoring.
10.2.2. Quality assurance
For the purpose of compliance with Good Clinical Practice it may be necessary to conduct a site audit. This may occur at any time from the start to after conclusion of the study. The investigator signs the protocol and agrees to allow regulatory authorities and auditors to inspect his/her study records. The audits entail review of source documents supporting the adequacy and accuracy of CRFs.

10.3. Amendments
Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

10.4. Annual progress report
The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments.

10.5. End of study report
The coordinating investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient’s last visit. In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.6. Study publication policy
The principle investigator and coordinating investigator (i.e. H. van Overhagen and J. Verdult) will publish the results of the study in a peer reviewed medical journal as soon as appropriate. The primary investigator and coordinating investigator (i.e. H. van Overhagen and J. Verdult) have the first right to publication of the data and results of this study. Study-data may not be used without the written approval of the primary investigator.

The order of list of authors for publications resulting from this study will be composed as follows:
- First author: Joanne Verdult
- Co-authors: Dr. R. W. van der Meer, Dr. Hossain Roshani, Dr. Henk. W. Elzevier, Drs. Saskia Weltings and Prof. Dr. H. Putter.
- Co-authorship of additional institutes: one intervention radiologist and one urologist or oncologist per participating centre, each centre ranked by its contribution to the study (in patient numbers) starting with the highest contribution.
- Last author: Dr. Hans van Overhagen

11. REFERENCES


