RCT
Potential PURL Review Form
PURL Jam Version
Version #11 October 29, 2009

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

1. Citation	McClinton S, Starr K, Thomas R, McLennan G, McPherson G, McDonald A, Lam T, N'Dow J, Kilonzo M, Pickard R, Anson K, Burr J; SUSPEND Study Group. Use of drug therapy in the management of symptomatic ureteric stones in hospitalized adults (SUSPEND), a multicentre, placebo-controlled, randomized trial of a calcium-channel blocker (nifedipine) and an α-blocker (tamsulosin): study protocol for a randomized controlled trial. Trials. 2014 Jun 20;15:238.
2. Hypertext link to PDF of full article	http://www.ncbi.nlm.nih.gov/pubmed/?term=24947817
3. First date published study available to readers	06/20/2014
4. PubMed ID	24947817
5. Nominated By	Jim Stevermer Other:
6. Institutional Affiliation of Nominator	University of Missouri Other:
7. Date Nominated	09/13/2015
8. Identified Through	InfoPOEMs Other:
9. PURLS Editor Reviewing Nominated Potential PURL	Kate Rowland Other:
10. Nomination Decision Date	09/29/2015
11. Potential PURL Review Form (PPRF) Type	RCT
12. Other comments, materials or discussion	
13. Assigned Potential PURL Reviewer	Jennie Broders
14. Reviewer Affiliation	Other Other: St. Margaret's
15. Date Review Due	10/06/2015
16. Abstract	BACKGROUND: Urinary stone disease is common, with an estimated prevalence among the general population of 2% to 3%. Ureteric stones can cause severe pain and have a significant impact on quality of life, accounting for over 15,000 hospital admissions in England annually. Uncomplicated cases of smaller stones in the lower ureter are traditionally treated expectantly. Those who fail standard

care or develop complications undergo active treatment, such as extracorporeal shock wave lithotripsy or ureteroscopy with stone retrieval. Such interventions are expensive, require urological expertise and carry a risk of complications.Growing understanding of ureteric function and pathophysiology has led to the hypothesis that drugs causing relaxation of ureteric smooth muscle, such as the selective α-blocker tamsulosin and the calcium-channel blocker nifedipine, can enhance the spontaneous passage of ureteric stones. The use of drugs in augmenting stone passage, reducing the morbidity and costs associated with ureteric stone disease, is promising. However, the majority of clinical trials conducted to date have been small, poor to moderate quality and lacking in comprehensive economic evaluation.This trial aims to determine the clinical and cost-effectiveness of tamsulosin and nifedipine in the management of symptomatic urinary stones.
METHODS/DESIGN:
The SUSPEND (Spontaneous Urinary Stone Passage ENabled by Drugs) trial is a multicentre, double-blind, randomized controlled trial evaluating two medical expulsive therapy strategies (nifedipine or tamsulosin) versus placebo.Patients aged 18 to 65 with a ureteric stone confirmed by non-contrast computed tomography of the kidney, ureter and bladder will be randomized to receive nifedipine, tamsulosin or placebo (400 participants per arm) for a maximum of 28 days. The primary clinical outcome is spontaneous passage of ureteric stones at 4 weeks (defined as no further intervention required to facilitate stone passage). The primary economic outcome is a reduction in the incremental cost per quality-adjusted life years, determined at 12 weeks. The analysis will be based on all participants as randomized (intention to treat). The trial has 90% power with a type I error rate of 5% to detect a 10% increase in primary outcome between the tamsulosin and nifedipine treatment groups.

17. Pending PURL Review Date

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer if needed]

1. Number of patients starting each arm of the study?	391 patients tamsulosin, 387 nifedipine, 389 placebo
2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?	Recruited patients presenting to 24 UK National Health Service hospitals with ureteric colic. Adults aged 18–65 years with one stone of 10 mm or less (at the largest dimension) in either ureter identified on CT KUB were included. Patients who were ineligible included those needing immediate intervention decided by clinical assessment, those with sepsis, those with an estimated glomerular filtration rate of less than 30 mL/min, and those already taking or unable to take anαblockerorcalciumchannelstabiliser.Weexcluded people older than 65 years because nifedipine dose titration is recommended for this age group. Full details of all inclusion and exclusion criteria are available in our published protocol.11
3. Intervention(s) being investigated?	Utilization of medical expulsion therapy with tamsulosin or nifedipine
4. Comparison treatment(s), placebo, or nothing?	Participants self-administered tamsulosin 400 μg, nifedipine 30 mg, or placebo orally once daily until spontaneous stone passage occurred, the need for inter- vention was agreed, or until 4 weeks had passed since randomisation, whichever came first. We did not verify adherence to trial medication.
5. Length of follow up? Note specified end points e.g. death, cure, etc.	Participants self-administered tamsulosin 400 μg, nifedipine 30 mg, or placebo orally once daily until spontaneous stone passage occurred, the need for inter- vention was agreed, or until 4 weeks had passed since randomisation, whichever came first. We did not verify adherence to trial medication.
6. What outcome measures are used? List all that assess effectiveness.	The primary outcome was spontaneous stone passage in 4 weeks, defined as the absence of need for additional interventions to assist stone passage at 4 weeks after randomisation. Other outcomes were pain assessed by participant-reported number of days of analgesic use and visual analogue scale at 4 weeks, time to stone passage assessed by the date of imaging showing no stone at up to 4 weeks, health status

assessed by the Short Form (SF)-36 questionnaire, and safety assessed by participant report of discontinuation of medication due to adverse effects and by serious adverse events monitoring. We also assessed health outcomes with the EQ-5D questionnaire, and heath-care resource use and participant costs (health economic components), the results of which will be reported elsewhere. Safety outcomes were reported as and when they happened (via the case report form, patient questionnaires, and patient and clinician report). Suspected serious adverse events were graded at site by the local principal investigator, reported to the trial office to be confirmed by the chief investigator. Safety events were monitored by the sponsor, research ethics committee, and MHRA. Non-serious adverse events were not collected or reported.

7. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, p-values, etc.

Spontaneous stone passage, defined by absence of need for intervention to assist stone passage during the 4 weeks after randomisation, did not differ between groups (table 2). 307 (81%) of 378 participants in the tamsulosin group needed no further intervention compared with 304 (80%) of 379 in the nifedipine group, and 303 (80%) of 379 in the placebo group. These findings were consistent across the predefined subgroups of sex, stone size, and stone location (figure 2). We also noted no difference in stone passage at up to 12 weeks (data not shown), by which time an additional 27 (7%) participants in the tamsulosin group, 25 (6%) in the nifedipine group, and 28 (7%) in the placebo group had an intervention planned. Table 2 for the CI

8. What are the adverse effects of intervention compared with no intervention?

Serious adverse events were reported in three participants allocated to nifedipine (one had right loin pain, diarrhoea, and vomiting; one had malaise, headache, and chest pain; and one had severe chest pain, difficulty breathing, and left arm pain) and in one participant in the placebo group (headache, dizziness, lightheadedness, and chronic abdominal pain). No deaths were reported.

9. Study addresses an appropriate and clearly focused question - ***select one***

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable

Comments: We sought to establish whether tamsulosin or nifedipine increased the likelihood of spontaneous stone passage measured by the absence of need for further intervention and, if so, which was the better drug.

10. Random allocation to comparison groups

☐ Well covered
☒ Adequately addressed
☐ Poorly addressed
☐ Not applicable

Comments: Trained site personnel (research nurses and clinicians) enrolled participants at each site. Participants were allocated in a 1:1:1 ratio to either tamsulosin, nifedipine, or placebo by a remote randomisation system hosted at the Centre for Healthcare Randomised Trials (CHaRT) in Aberdeen, UK, using an algorithm with centre, stone size (≤5 mm or >5 mm), and stone location (upper, mid, or lower ureter) as minimisation covariates.

11. Concealed allocation to comparison groups

☐ Well covered
☒ Adequately addressed
☐ Poorly addressed
☐ Not applicable

Comments: Each randomly assigned participant was given 28 capsules of trial medication (over-encapsulated tamsulosin or nifedipine, or placebo) supplied by an independent source (Tayside Pharmaceuticals, Ninewells Hospital, Dundee, UK) who had no further involvement in the trial, ensuring that participants, clinicians, and trial personnel remained unaware of the allocated group.

12. Subjects and investigators kept "blind" to comparison group allocation	☐ Well covered ☒ Adequately addressed ☐ Poorly addressed ☐ Not applicable Comments: Each randomly assigned participant was given 28 capsules of trial medication (over-encapsulated tamsulosin or nifedipine, or placebo) supplied by an independent source (Tayside Pharmaceuticals, Ninewells Hospital, Dundee, UK) who had no further involvement in the trial, ensuring that participants, clinicians, and trial personnel remained unaware of the allocated group.
12. Comparison groups are similar at the start of the trial	☒ Well covered ☐ Adequately addressed ☐ Poorly addressed ☐ Not applicable Comments: Baseline characteristics were similar for the three groups (table 1).
14. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias.	☒ Well covered ☐ Adequately addressed ☐ Poorly addressed ☐ Not applicable Comments: Baseline characteristics were similar for the three groups (table 1).
15. Were all relevant outcomes measured in a standardized, valid, and reliable way?	☐ Well covered ☒ Adequately addressed ☐ Poorly addressed ☐ Not applicable Comments:
16. Are patient oriented outcomes included? If yes, what are they?	Yes they were patient oriented outcomes. The primary outcome was spontaneous stone passage in 4 weeks, defined as the absence of need for additional interventions to assist stone passage at 4 weeks after randomisation. Other outcomes were pain assessed by participant-reported number of days of analgesic use and visual analogue scale at 4 weeks, time to stone passage assessed by the date of imaging showing no stone at up to 4 weeks, health status assessed by the Short Form (SF)-36 questionnaire, and safety assessed by participant report of discontinuation of medication due to adverse effects and by serious adverse events monitoring. We also assessed health outcomes with the EQ-5D questionnaire, and heath-care resource use and participant costs (health economic components), the results of which will be reported elsewhere.
17. What percent dropped out, and were lost to follow up? Could this bias the results? How?	Between Jan 11, 2011, and Dec 20, 2013, 1167 participants were randomly assigned (391 to tamsulosin, 387 to nifedipine, and 389 to placebo; figure 1). Of these, 17 were subsequently excluded because of ineligibility and 14 participants were lost to follow-up, and were not included in the primary outcome analysis. We were able to ascertain the primary outcome for 1136 (97%) participants in the final analysis. 719 (62%) of 1150 eligible participants completed the 4-week questionnaire and 564 (49%) of 1150 eligible participants completed the 12-week questionnaire, with no differences in the proportion returned between groups (data not shown). This is a small proportion of the patients and does not likely bias the results.
18. Was there an intention-to-treat analysis? If not, could this bias the results? How?	We analysed data for the primary outcome from the modified intention-to-treat population, which included all randomly assigned participants apart from those with missing primary outcome data and those who were found to be ineligible after randomisation.
19. If a multi-site study, are results comparable for all sites?	We recruited patients presenting to 24 UK National Health Service hospitals with ureteric colic.

20. Is the funding for the trial a potential source of bias? If yes, what measures were taken to insure scientific integrity?	The funder (through their peer and funding board review process) approved the study proposal but had no role in the collection, analysis, or interpretation of data, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.
21. To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized.	all adult patients presenting with kidney stones
22. In what care settings might the findings apply, or not apply?	most inpatient patients admitted for kidney stones, likely for a short admission
23. To which clinicians or policy makers might the findings be relevant?	FM, hospitalist, urologists, hospital administrators for cost analysis.

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions

For UpTo Date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS as editor & current year as publication year.

EXAMPLE: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert dated modified if given.} Accessed February 12, 2009. {whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:
Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at: http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert dated modified if given.} Accessed June 5, 2009.{search date}

1. DynaMed excerpts

Treatment overview:

- interventions for pain control
  - nonsteroidal anti-inflammatory drugs (NSAIDs) are drug of choice (EAU Grade A)
  - combination of IV morphine plus ketorolac is more effective than either monotherapy (level 1 [likely reliable] evidence)
  - local warming of abdomen and lower back may reduce pain in acute renal colic (level 2 [mid-level] evidence)
  - transcutaneous electrical nerve stimulation (TENS) may reduce pain caused by renal colic (level 2 [mid-level] evidence)
- if urinary tract infection (UTI)
  - UTIs must be treated or excluded prior to endourologic stone removal (EAU Grade A, Level 1b)
  - urgent decompression recommended for patients with possible UTI, signs of sepsis with obstructing stones (EAU Grade A, Level 1b)
  - give antibiotics (EAU Grade C, Level 3-4)
- first-line treatment of noncomplicated urolithiasis in pregnancy is conservative management with bed rest, hydration, and analgesia (EAU Grade A)(5)
- for ureteral stones
  - observation with periodic evaluation is option for newly diagnosed ureteral stones < 10 mm if active removal is not indicated (EAU Grade A, Level 1a)
- medications may be offered to facilitate stone

passage during observation period (EAU Grade A, Level 1a)
- alpha blockers or calcium channel blockers may facilitate passage of urinary stones (level 2 [mid-level] evidence)
  - choice of procedure for active stone removal depends on stone location, size, available equipment, and patient preference (EAU Grade A)
- extracorporal shock wave lithotripsy (ESWL) preferred for stones < 10 mm or in proximal ureter; ESWL may not be as effective as ureteroscopy for ureteral stones, but may be associated with fewer complications (level 2 [mid-level] evidence) and is contraindicated in pregnancy
- ureteroscopy is preferred for stones > 10 mm or in distal ureter; stenting after uncomplicated ureteroscopy may increase adverse effects without clear benefit (level 2 [mid-level] evidence)
- percutaneous nephrolithotomy is an alternative procedure
- laparoscopic or open surgical stone removal in rare cases where other procedures fail or are unlikely to be successful (EAU Grade C, Level 3)
- for renal stones
  - insufficient evidence regarding observation (annual follow-up) for asymptomatic caliceal stone which has been stable for 6 months (EAU Level 4)
  - choice of procedure for active renal stone removal depends on stone location, size, and other factors
- extracorporal shock wave lithotripsy (ESWL) preferred for stones < 2 cm (EAU Grade B)
  - not recommended for lower pole stones 1-2 cm as ESWL success rate less likely due to poor drainage
  - DynaMed commentary -- body habitus may preclude ESWL as option in obese patients, as skin-to-stone distance must be < 16 cm on most ESWL machines
- percutaneous nephrolithotomy (PNL) preferred for stones > 2 cm (EAU Grade B)
- flexible ureterorenoscopy is alternative procedure if PNL is not an option (EAU Grade B)
  - larger stones (> 2 cm) can be treated with flexible ureterorenoscopy, but associated with increased risk for follow-up procedure
  - placement of ureteral stent may be needed
- laparoscopic or open surgical stone removal in rare cases where other procedures fail or are unlikely to be successful (EAU Grade C, Level 3)
- Reference - European Association of Urology (EAU) guidelines on urolithiasis (EAU 2015 Mar)

2. DynaMed citation/access date

Title. Nephrolithiasis Author. In: DynaMed [database online]. Available at: www.DynamicMedical.com Last updated: 2015 Sep 03 01:13:00 PM. Accessed 10/07/15

3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)

alpha blockers or calcium channel blockers can be used to facilitate passage of urinary stones

4. UpToDate excerpts

Facilitating stone passage — Several different medical interventions increase the passage rate of ureteral stones, including antispasmodic agents, calcium channel blockers, and alpha blockers, which have been used in combination with or without steroids [85-94].

The benefits of medical therapy have been examined in meta-analyses, which have analyzed different agents [92,95]:

●In a 2014 meta-analysis of 32 trials that enrolled 5,864 patients, ureteral stone

passage was significantly more likely with alpha blocker therapy versus conservative treatment alone (77 versus 52 percent); in addition, stone passage occurred an average of three days faster with alpha blocker therapy [96].
●Another meta-analysis of nine controlled trials included 693 patients with mean stone size between 3.8 and 7.8 mm [92]. Compared with the control group, patients treated with a calcium channel blocker (usually nifedipine) or alpha blocker (usually tamsulosin) had a 65 percent greater likelihood of stone passage (95% CI 45-88 percent). In analyses of the individual agents, there was a 90 and 54 percent greater likelihood of stone passage with calcium channel blockers and alpha blockers, respectively, relative to controls.

5. UpToDate citation/access date

Always use Basow DS as editor & current year as publication year.
Title. Diagnosis and acute management of suspected nephrolithiasis in adults
Author. Gary C Curhan, MD, ScD
Mark D Aronson, MD
Glenn M Preminger, MD In: UpToDate [database online]. Available at: http://www.uptodate.com. Last updated: Jun 02, 2015. Accessed 10/7/15

6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

Medical therapy may increase stone passage.

7. PEPID PCP excerpts
www.pepidonline.com
username: fpinauthor
pw: pepidpcp

Treatment
1. Acute Treatment
o Intervention depends on size, location, and infection risk
o Pain control
§ Oral NSAIDs/ ibuprofen: 600-800 mg tid
§ Indomethacin 50 mg qid
§ Ketorolac 30-60 mg IV/IM
§ IV meperidine: 50-100 mg, or morphine 10-15 mg every 3-4 hours
o Hydration:
§ Increase urine output to 2 L/day
o Speed stone passage and to avoid surgical intervention
§ Tamsulosin (typically 0.4 mg daily) or nifedipine (typically 30 mg daily) for pts with lower ureteral calculi
o Strain urine for stone
o Consider urologic consultation in or outpatient if:
§ Severe pain unresponsive to medication
§ Persistent fever or nausea
§ Significant impediment of urine flow
§ No movement of stone

8. PEPID citation/access data

Author. Title. Nephroliathiasis In: PEPID [database online]. Available at: http://www.pepidonline.com. Last updated: September 2012. Accessed10/7/15

9. PEPID content updating

1. Do you recommend that PEPID get updated on this topic?
☐ Yes, there is important evidence or recommendations that are missing
☒ No, this topic is current, accurate and up to date.
If yes, which PEPID Topic, Title(s):

2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (EB) that should be updated on the basis of the review?
☐ Yes, there is important evidence or recommendations that are missing
☒ No, this topic is current, accurate and up to date.
If yes, which Evidence Based Inquiry(HelpDesk Answer or Clinical Inquiry), Title(s):

10. Other excerpts (USPSTF; other guidelines; etc.)

11. Citations for other excerpts

12. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

Tamsulosin and nifedipine may be useful agents for stone passage in acute kidney stones.

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

1. Validity: How well does the study minimize sources of internal bias and maximize internal validity?

Give one number on a scale of 1 to 7
(1=extremely well; 4=neutral; 7=extremely poorly)
☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

3. Relevance: Are the results of this study generalizable to and relevant to the health care needs of patients cared for by "full scope" family physicians?

Give one number on a scale of 1 to 7
(1=extremely well; 4=neutral; 7=extremely poorly)
☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

4. If 4.3 was coded as 4, 5, 6, or 7, lease provide an explanation.

Acute kidney stone treatment is common in FM practice.

5. Practice changing potential: If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice?

Give one number on a scale of 1 to 7
(1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice)
☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

7. Applicability to a Family Medical Care Setting: Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising,

Give one number on a scale of 1 to 7
(1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)
☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

educating or counseling a patient; or creating a system for implementing an intervention?
8. If you coded 4.7 as a 4, 5, 6 or 7, please explain.

9. Immediacy of Implementation: Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market?
10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.

Give one number on a scale of 1 to 7
(1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)
☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

11. Clinical meaningful outcomes or patient oriented outcomes: Are the outcomes measured in the study clinically meaningful or patient oriented?
12. If you coded 4.11 as a 4, 5, 6, or 7 please explain why.

Give one number on a scale of 1 to 7
(1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)
☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

13. In your opinion, is this a Pending PURL?
Criteria for a Pending PURL:

- Valid: Strong internal scientific validity; the findings appears to be true.
- Relevant: Relevant to the practice of family medicine
- Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
- Applicability in medical setting:
- Immediacy of implementation

14. Comments on your response in 4.13

Give one number on a scale of 1 to 7
(1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL)
☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7