A Multi Center Randomized Trial to Study Tamsulosin for Urolithiasis in the Emergency Department STONE

Protocol

Sponsored by:

National Institute of Diabetes and Digestive and Kidney Diseases

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1 Introduction

1.1 Introduction and Objectives

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) has sponsored a collaborative agreement to conduct a multi-center randomized **S**tudy **T**amsul**O**si**N** for urolithiasis in the **E**mergency Department (STONE study). This protocol describes the background, design, and organization of the multi-center phase of the trial which follows the vanguard phase performed at George Washington University Medical Center only.

1.2 Primary Hypothesis

The primary objective of this study is to determine the effect of tamsulosin on the proportion of patients passing a kidney stone as determined by patient report.

1.3 Purpose of the Study Protocol

This protocol describes the background, design and organization of the multi-center phase of the randomized clinical trial and may be viewed as a written agreement among the study investigators. Before recruitment begins, the protocol is approved by the Steering Committee and the Institutional Review Board (IRB) of each clinical center. Any changes to the protocol during the study period require the approval of the Steering Committee and the IRBs.

2 Background

2.1 Background and Significance

Kidney stones affect up to 15% of men and 7% of women in the United States.[1] The incidence is variable according to geographical location and season, and the concept of the "stone belt" -geographical locations with unusually high incidences of urinary calculi- is well accepted. The highest incidence of stone disease occurs in the south-eastern United States in the summer months. The incidence of stone disease is twice as common in whites as in African-Americans and Asians, and is twice as common in males as in females. The highest incidence seems to be the fourth decade of life.[1] The economic impact of urolithiasis is enormous; in 1986, more than $2 billion was spent on the treatment of kidney stones, mostly for removal and fragmentation, even before widespread use of shock-wave lithotripsy.[2] Until the 1980s, urinary stones were a major health problem, with a significant proportion of patients requiring extensive surgical procedures and a sizable minority losing a kidney. One study showed that about 20% of patients with recurrent stone disease who underwent surgery for obstruction and infection went on to develop mild renal insufficiency.[3] The advent of extracorporeal techniques for stone destruction and the refinements in endoscopic surgery have greatly decreased the morbidity associated with stone surgery. One unfortunate result of this technologic success is that advances in the medical management of stone disease and research in prevention have languished.[3] The current standard of care for acute ureterolithiasis includes only pain medication. When this fails, the patient moves on to procedural therapy with its inherent risks and expense. There is no currently accepted or practiced medical treatment for these patients.

The goals of medical conservative therapy are to prevent modifiable factors and control painful symptoms until stone expulsion. The stone size and the site, as well as the internal anatomical structure of the ureter and a history of spontaneous stone expulsion all affect the likelihood of stone expulsion and are unmodifiable factors.[4-6] Factors which encourage stone retention are spasm, edema and ureteral infection, which are modifiable.[7] Therefore the administration of spasmolytic drugs, anti-edemics and antibiotics are recommended by several groups, even in the absence of current specific guidelines.[7-10]

Nifedipine, steroids, and tamsulosin have been studied as potential medical treatments for nephrolithiasis. Each of the three has shown promise and safety in small studies. We propose to study tamsulosin alone rather than nifedipine and steroids. We believe that tamsulosin has a more favorable safety profile and is therefore a better choice than nifedipine for an extensive study.

2.1.1 The Pharmacology of Tamsulosin

Tamsulosin is an antagonist of alpha-1 adrenoceptors. The empirical formula of tamsulosin hydrochloride is $C_{20}H_{28}N_2O_5S \bullet HCl$. It is readily absorbed from the gastrointestinal tract and exhibits linear kinetics following single and multiple dosing. Steady state concentrations are achieved by the fifth day of once-a-day dosing. The effects of food on the pharmacokinetics of tamsulosin are consistent. Tamsulosin HCL is metabolized in the liver by cytochrome P450 enzymes and less than 10% is excreted unchanged in the urine. The half-life of tamsulosin HCL in healthy volunteers is 9-13 hours.

Mechanism of Action

In 1970 Malin, et al noted adrenergic receptors in the human ureter[11], and several studies have focused on the role of the adrenergic system in ureteral physiology. In general, the induction of ureteral contraction by alpha-adrenergic agonists is dose dependent.[12] The main alpha-adrenergic agonist noradrenaline induces a positive ionotropic effect, increasing muscle tone until causing complete ureteral obstruction from spasm at high doses. Hence alpha-adrenergic stimulation decreases the volume of urine flow

through the ureter. The blockade of alpha-adrenergic receptors by a specific antagonist results in decreased ureteral peristaltic amplitude and frequency with a consequent loss of intra-ureteral pressure and, therefore, an increase in fluid transport ability.[13] Further study revealed a prevalence of the alpha-1d-adrenoceptor subtype in the human ureter.[14] Tamsulosin is a combined alpha-1a and alpha-1d selective antagonist, and it is most likely that its effect on the obstructed ureter is to induce an increase in the intra-ureteral pressure gradient around the stone, by increasing the urine bolus (and consequently increasing intra-ureteral pressure) above the stone, as well as decreasing peristalsis below the ureter (and consequently decreasing intra-ureteral pressure below the stone), in association with a decrease in basal and micturition pressures at the bladder neck.[15, 16]

Safety Profile

The first empirical use of α1-adrenoceptor antagonists in urology occurred about 25 years ago in patients with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hypertrophy (BPH), or LUTS/BPH.[17] The subselectivity and pharmacodynamic properties of tamsulosin may provide advantages in safety, tolerability, and administration compared with other alpha blockers, such as terazosin and doxazosin. Unlike other alpha blockers, tamsulosin does not require titration to be efficacious. Studies have shown that it has a minimal and usually clinically insignificant effect on blood pressure in normotensive and hypertensive patients.[18, 19] Dizziness and abnormal ejaculation are stated to be the most common adverse events, with asthenia, postural hypotension and palpitations being seen less frequently (1 to 2% incidence).[20] Studies vary in the frequency of symptomatic postural hypotension, with reports ranging from 0-2.5%.[19, 21]

A recent study reported safety experience with 1784 patients receiving 0.4 mg tamsulosin for six months (with a total drug exposure time of 811 patient years).[22] The most frequent adverse events are shown below in Table 1. Intraoperative floppy iris syndrome has been reported frequently in patients on tamsulosin undergoing cataract surgery. Complications from this syndrome can be minimized as long as the ophthalmologist is aware that the patient is taking tamsulosin.[23] In logistic regression analysis alpha-blockers, converting enzyme inhibitors, diabetic medications and diuretics did not significantly affect the odds ratio for having an adverse event. However, concomitant alpha-antagonists (a protocol violation) and treatment with verapamil (which also has alpha-antagonist activity) significantly enhanced the odds ratio for having an adverse event to 3.87 (CI 1.52-9.85) and 3.17 (CI 1.52-6.58), respectively. Minor increases in the odds ratio, which did not reach statistical significance, were also observed for Ca^{2+} antagonists other than verapamil and for nitrates. In a study of 756 patients with benign prostatic hypertrophy randomized to tamsulosin (0.4 and 0.8mg/day) or placebo, the incidence of positive orthostatic test results in the tamsulosin groups was comparable to that observed in the placebo group.[24]

While there are differences in the incidence of various side effects among alfuzosin, doxazosin, tamsulosin and terazosin, the overall side-effect profiles of these agents have been characterized as "very similar" by the Alpha-Blocker Committee at the 4th International Consultation on BPH.[25] The results of seventeen trials examining the safety and efficacy of various alpha- blockers were reviewed by Lowe, who concluded that therapy with these agents is "…well tolerated, and the majority of side effects with alpha-blockers are mild to moderate, seldom causing patients to prematurely discontinue therapy".[26] The blood pressure effects of tamsulosin are comparable to those of either terazosin[27] or doxazosin,[28] although tamsulosin was associated with a lower level of nocturnal orthostatic hypotension.[27]

Table 1 Most frequent adverse events during a 6 months treatment with 0.4 mg tamsulosin o.d.[22]			
Adverse Event	**N**	**%**	**(95% CI)**
Dizziness	45	2.5	(1.85, 3.36)
Abnormal ejaculation	29	1.6	(1.09, 2.33)
Headache	29	1.6	(1.09, 2.33)
Hypotension	26	1.5	(0.95, 2.13)
Gastrointestinal disorder	18	1.0	(0.60, 1.59)
Nausea	17	1.0	(0.56, 1.52)
Cardiovascular disorder	11	0.6	(0.31, 1.10)
Impotence	10	0.6	(0.27, 1.03)
Dry mouth	9	0.5	(0.23, 0.96)
Sweating	9	0.5	(0.23, 0.96)
Arrhythmia	8	0.4	(0.19, 0.88)
Postural hypotension	7	0.4	(0.16, 0.81)
Pruritus	7	0.4	(0.16, 0.81)

Tamsulosin in women

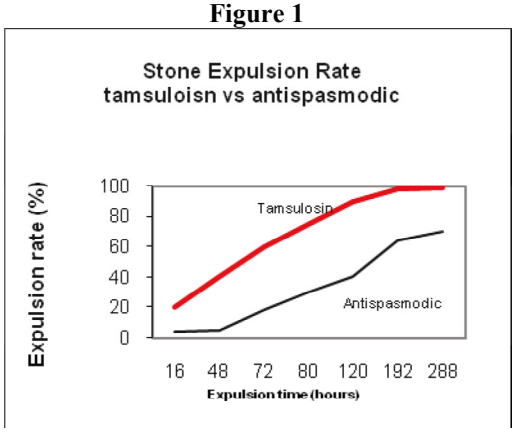
The current approved indication for tamsulosin is in the treatment of benign prostatic hypertrophy. Because of this, the drug has not been as widely studied in women. Acute renal colic is approximately twice as common in men as it is in women. However, it is a disease of both sexes, and any medication that is to find a wide application for the treatment of renal colic must be safe in both men and women. In recent years there have been studies on the effects of tamsulosin in females, and it has been shown to be safe and effective. Animal studies have demonstrated that the female canine and pig urethra has alpha-1a adrenoreceptors and binds tamsulosin.[29, 30] In a study of eleven healthy women volunteers, tamsulosin significantly reduced the mean and maximal uretheral pressure over the entire urethra.[31] There was no effect on systemic blood pressure. A small trial of the effect of tamsulosin on urodynamic voiding parameters in patients with neurogenic bladder recently published has shown the medication is safe and effective in both men and women.[32] The preliminary studies looking at tamsulosin as a treatment for urolithiasis included both men and women, and reported no complications specific to women.[16, 33] We believe that the evidence from animal and human studies supports the hypothesis that tamsulosin should be equally as safe and effective in women as it is in men.

2.1.2 Tamsulosin and other α-1 blockers in the Medical Management of Urolithiasis

Since 2002 there have been a number of trials evaluating the medical management of nephrolithiasis. Among the first was a study of tamsulosin with floroglucine-trimetossibenzene, (an antispasmodic agent),[16] In addition, all patients received 30mg deflezacort daily for ten days, in addition to cotrimazole twice daily for eight days. The study was limited to those with a unilateral juxtavesical stone and patients were followed for a maximum of one month. The tamsulosin group had a significantly quicker time for stone expulsion (a mean of 66 hours versus 111 hours, p=.020, see below Figure 1) and a significant reduction in analgesia requirements as measured by the need for intramuscular diclofenac (a mean of 2.83

versus 0.13 injections, p<0.0001). The tamsulosin group had no hospitalizations, compared with ten in the antispasmodic arm, nine of whom underwent ureteroscopy (p<0.001).

Figure 1



These results strongly suggest a benefit from tamsulosin, but there are a number of methodological problems with this study. Non-concealed allocation assignment rather than blinded randomization was used. Furthermore, neither the patients, their treating clinicians, nor the individuals assessing outcomes were blinded to treatment group assignment. A brief anonymous review of this study in the British Medical Journal concluded that "even though this study is fraught with methodological shortcomings, it seems highly likely that tamsulosin (Flomax) is effective in hastening the passage of juxtavesical ureteral stones and decreasing both the severity and duration of renal colic".[34]

A study by Červenàkov et al. from the Slovak Republic was published in 2002. The authors reported improved outcomes in 51 patients treated with tamsulosin (0.4mg/day), when compared to a control group.[35] After one week of therapy, stone elimination was 80% in the tamsulosin group and 63% in the control group. There are however, a number of methodological concerns and differences in treatment approaches which make data from this trial difficult to generalize to the population in the United States. For example, although the authors report this as a double blind study, it was not placebo controlled. All the patients were hospitalized, and the treatment regimen included intravenous diazepam, although the frequency is not specified. The authors fail to give a single confidence interval or p-value for their results. All of this leads to the conclusion that while the study lends support to our hypothesis, it would be inappropriate to treat patients in this country based on the Slovak approach. To our knowledge however, this is only one of two small studies that has used tamsulosin without steroids for the treatment of nephrolithiasis.

In 2005 Yilmaz published a study from Turkey which evaluated the effects of three different alpha-1 adrenergic blockers on the passage rate of distal ureteral stones.[36] All three agents (tamsulosin, terazosin, and doxazosin) were equally efficacious at increasing the frequency of spontaneous passage of distal ureteral calculi. Moreover, the authors noted that there were no side-effects that led to a study subject dropping from the study, and equally important, not one of the 114 patients in elected to have a surgical intervention during the one month study period. Another interesting aspect of this study is that the average stone size was 6.0 mm. In a study of American patients, Miller reported that 67% of patients have a stone size less than 4 mm (see above section B3).[5] While this difference in the two populations cannot be easily explained, the results do add still further support to the hypothesis that tamsulosin will be effective for stones even larger than 4 mm in diameter. Unfortunately the authors failed to provide a power analysis, so the results cannot be easily generalized, and there was no study of the effect on those

patients with more proximal stones, which make up a sizeable minority of all patients with ureterolithiasis.

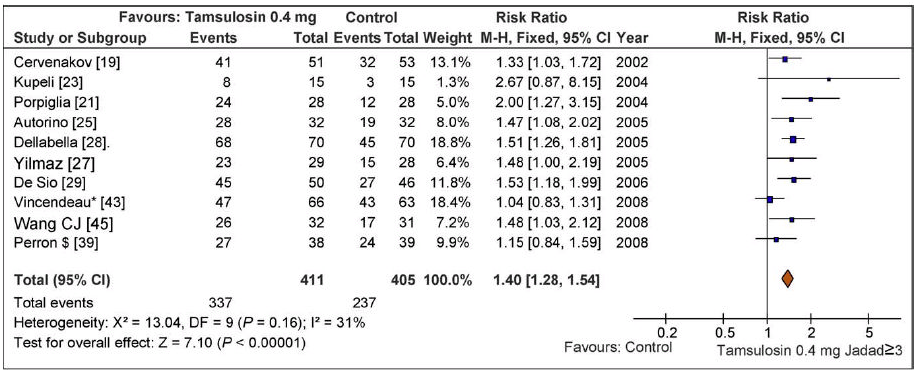
In 2006, Hollingsworth reviewed nine randomized controlled trials (693 patients) which assessed the efficacy of calcium-channel blockers or alpha blockers to treat urinary stone disease. [37] Patients given calcium-channel or alpha blockers had a 65% greater likelihood of stone passage than those not given such treatment. The pooled risk ratio in favor of the treatment group was 1.65 (95% CI: 1.45, 1.88, $p<0.0001$); the absolute risk reduction was 0.31 (95% CI: 0.25, 0.38) and the number needed to treat (NNT) was 4. In all trials the primary outcome of interest (the proportion of patients who passed stones) occurred more often in the treatment group than in the control group. In 5 out of 6 trials the treatment groups had shorter mean times to stone expulsion than the control groups. Of importance for our work are the authors' conclusions that despite these promising results, a definitive high-quality randomized controlled trial is necessary to confirm the efficacy of alpha-blockers in patients with urolithiasis. Hollingsworth suggested that such a study would involve 113 patients in each treatment arm to show a significant effect (using the lower CI limit of the pooled relative risk 1.45, a background occurrence of stone passage of 0.47, a two-sided alpha error of 0.05 and a power of 0.90); if the occurrence of stone passage in the controls was lower (30%), the required sample would be 532 patients in total. This suggested sample size is very similar to that initially calculated for our own study (see sample size section 5.4.1).

Singh performed a similar review in 2007, using a pooled analysis of 16 studies using an alpha blocker and 9 using a calcium channel antagonist.[38] He concluded that compared to standard therapy these agents significantly improved spontaneous stone expulsion (alpha-antagonist RR 1.59; 95% CI 1.44 to 1.75; NNT of 3.3 [95% CI 2.1 to 4.5]). Singh's review concluded that because of the limitations of methodological quality within the studies reviewed, a large, well-done, randomized, clinical trial is needed to confirm these results before uniform adoption can be recommended. A similar call for a randomized controlled trial was made in a Best Available Evidence review in the same issue of Annals of Emergency Medicine as Singh's paper.[39] In a review of the cost effectiveness of medical expulsive therapy (MET) using alpha-antagonists in a decision tree analysis, Bensalah calculated that using tamsulosin would result in a cost advantage of $1,100 over observation alone.[40] As such it was recommended as a cost-effective strategy.

Parsons, who reviewed 11 trials, reported a meta-analysis of alpha blockers for ureteral stones in 2007.[41] This analysis showed that compared to patients receiving conservative therapy only, patients receiving conservative therapy plus alpha-blockers were 44% more likely to spontaneously expel the stones (RR 1.44, 95% CI 1.31 to 1.59, $p<0.001$), and stone expulsion incidence increased significantly (RD 0.28, 95% CI 0.22 to 0.34, $p<0.001$).

In 2009 Seitz performed a systematic review of 47 randomized control trials.[42] Pooling of studies of alpha-blockers and calcium channel blockers studies demonstrated a higher and faster expulsion rate compared to a control group (risk ratio [RR]: 1.45 vs. 1.49; 95% confidence interval [CI]: 1.34–1.57 vs. 1.33–1.66). Additionally, lower analgesic requirements, fewer colic episodes, and fewer hospitalizations were observed within treatment groups. Their forest plot for tamsulosin 0.4 mg. is shown below.

Table 2 Seitz's Forest Plot



In an attempt to better understand why some studies did not show a significant benefit with respect to chance of stone expulsion, they broke the trials down by mean stone size. Only 4 of 9 studies where this was <5mm showed a significant benefit for alpha-blocker use whereas 19 of 20 where the mean stone size was ≥ 5mm showed an advantage. It was hypothesized that since smaller stones are more likely to pass in general, there was less chance of seeing a treatment effect. Interestingly, the studies that failed to show an increased chance of stone expulsion still found more rapid and less painful stone passage.

Further analysis of the pooled data showed consistent decreases in time to stone passage, analgesic requirement, need for hospitalization and days of work lost in patients treated with and alpha-blocker. Safety of the various medications was noted to be excellent across all trials with minimal drop-out rates due to adverse drug events.

The authors commented on the significant limitations of their meta-analysis primarily due to the fact that most studies were small, single-institution trials typically lacking prior power calculation and proper allocation concealment. In addition, the adjunctive usage of varying other medications (steroids, NSAIDs), different durations of treatment and variability in radiographic study all led to moderate heterogeneity of the data. A mild publication bias toward positive studies was noted. In conclusion, Seitz too called for multicenter, randomized, placebo-controlled trials.

Negative studies

In 2009 Hermanns reported no difference in a study which compared tamsulosin to placebo for 21 days. [43] This study looked for a "clinically relevant difference in expulsion rate of 25%" and assumed that 65% of patients would pass the stone without MET within 21 days. A total of 45 patients were allocated in each of the two arms of the study. The primary end point (stone expulsion by day 21) was confirmed with low-dose abdominal CT. The authors note that this study was the first randomized double blind placebo-controlled study to evaluate MET, and it failed to find any difference in the rate of stone expulsion between the two arms (placebo rate=88.9%, tamsulosin rate=86.7%). Although there was no difference in the rate of expulsion, there was a *trend* to faster expulsion in the tamsulosin group, (median 7 days) than in the placebo group (median 10 days), although this difference was not significant (p=0.36). There was, however a significant difference in the number of analgesics required with patients in the tamsulosin arm requiring less than those in the placebo arm (3 vs. 7, p=0.011). Of note was the large number of patients (32%) in whom the time of stone passage was not known. It should also be noted that Hermanns used a baseline passage rate at 21 days of 65%. In contrast to this passage rate, in Hollingsworth's meta-analysis the baseline expulsion rate across nine studies was 47%, with rates ranging from 20% to 73%. Thus the baseline expulsion rate of 65% at 21 days seems high, and this may contribute to the negative findings.

Another negative study was published in 2009 by Ferre, in which the primary outcome was stone expulsion at 14 days.[44] The study was randomized *but not placebo-controlled*, and was powered to detect a 30% difference between the study groups. It found no difference between the two treatment arms to which 40 patients each had been randomized. The authors note that this 30% difference was "rather large", it is therefore of little surprise that the study failed to detect this difference.

Vincendeau published the most recent negative study in 2010.[45] This study was a multi center randomized placebo controlled trial in which the primary outcome was a reduction in the mean length of stone expulsion by 50% - from 16 to 8 days. The study randomized 129 patients, and failed to detect any difference between the placebo and tamsulosin arms. We are not surprised at the negative finding, since the study was looking for a very large clinical difference between the two groups – a difference even larger than that in the study by Ferre. Furthermore and for an unexplained reason, the rate for stone passage in the *control* group the study was substantially higher than the mean for the alpha-blocker studies in the meta-analysis by Hollingsworth noted above. In addition all study patients were initially hospitalized and all were given phloroglucinol, neither of which is standard practice in the US.

2.1.3 Dosing

The European pilot studies that have used tamsulosin for urolithiasis used a dose of 0.4 mg/day.[16, 46] This is also the recommended starting dose of tamsulosin when used for the treatment of benign prostatic hypertrophy. Using this dose rather than 0.8 mg/day which is sometimes used in the treatment of BPH will also minimize the risks of side effects from the medication.[24]

2.2 Rationale for the Proposed Study

The earlier work on the medical management of urolithiasis involved nifedipine and steroids, and was performed in Europe on patients all of whom were admitted.[8] Admission is not routine in the United States unless there are complications (such as a solitary kidney, inability to manage pain, or superimposed infection). Another European study performed on outpatients was not a placebo-controlled double blind study, and involved weekly x-ray exposure and expensive ultrasound examination.[7] Furthermore, the studies have tended to be small, involving less than 50 patients in each arm. The most recently published trial[47] comparing an antispasmodic with tamsulosin or nifedipine was neither blinded or placebo controlled, and did not examine any independent effect of steroids. The outpatient regimen involved routine antibiotics, and intramuscular analgesia, which are not a routine part of patient management in the USA.

A single US trial involving the use of steroids and nifedipine was published in 2000.[9] However this trial looked at these agents as part of an intensive medical management program, and other agents used included routine antibiotics. This trial was not blinded and was performed in the private offices of urologists. It involved on 35 patients in each arm of the trial, and there was no IRB oversight. It also had no placebo arm. Although the addition of nifedipine and steroids resulted in a higher rate of stone passage and fewer lost work days, the lack of appropriate blinding and the confounding addition of antibiotics make it difficult to generalize from this study.

A European study involving tamsulosin and steroids was published in 2003.[16] This was a very small pilot study, with only thirty patients in each treatment arm, and non-concealed allocation assignment rather than blinded randomization was used. Furthermore, neither the patients, their treating clinicians, nor the individuals assessing outcomes were blinded to treatment group assignment. The authors concluded that tamsulosin and steroids increased stone expulsion rate and reduced the need for surgical intervention.

A second small European study was recently published by Porpiglia.[46] This compared nifedipine and tamsulosin (each with steroids) to a control group. The three treatment arms were small (thirty patients or

less) and neither physician nor patients were blinded to treatment allocation. No placebo was used. The authors concluded that both tamsulosin and nifedipine with steroids were safe and improved outcomes, but that tamsulosin with steroids was a superior therapy. There has been no attempt in any of the previous studies to evaluate the role of steroids separately from that of either tamsulosin or nifedipine.

To date there has been only one published study looking at the effects of tamsulosin alone.[35] Although this study showed improved outcomes in the treatment group, the methodological approach (hospitalizing all the patients, and the use of IV diazepam in all) and lack of statistical rigor (including a lack of confidence intervals and p-value) prevent it from being used as a basis for urologists in the USA to change their treatment stratagems. A second and much more recent study from Turkey compare the events of three different alpha-1 adrenergic blockers. The study found all three medications tested to be equally efficacious.[36] This study however, only looked at the effect of tamsulosin on distal ureteral stones (defined by the researchers as those in the juxtavesical tract and ureterovesical junction), and did not compare this treatment group to a steroid alone group. This study was not blinded or placebo controlled, and there was no power analysis.

In contrast, we will investigate the role of tamsulosin in a randomized and placebo-controlled study, to enable the efficacy and optimum treatment regimen to be determined. We believe that a federally-funded study will provide both the objectivity and publicity to ensure that results are widely disseminated. This will ensure that if a benefit from the study medications is demonstrated, both emergency physicians and urologists will feel comfortable in prescribing the medications, a situation which is not the case for nifedipine and steroids.

3 Study Design

The study is a multi-center randomized, placebo-controlled, double-blind clinical trial. Participants are randomized to one of two treatment groups, placebo or active tamsulosin. The primary objectives of this study are to test the hypothesis that tamsulosin is clinically useful in the treatment of acute urolithiasis. If tamsulosin achieves similar results in a properly conducted placebo controlled trial to those noted in previous smaller pilot studies, we expect to see a significant reduction in days lost from work and decreased morbidity, as well as cost savings resulting from a decreased number of patients referred for the surgical management of retained stones.

3.1 Primary Research Question

Does the administration of tamsulosin after the clinical and radiographic diagnosis of acute urolithiasis produces an increase in the proportion of patients passing their stone at 28 days by patient report?

3.2 Secondary Research Questions

The secondary research questions are whether tamsulosin produces a reduction in each of the following:

- Time to passage of stone
- Length of time in pain
- Number of days lost from work
- Need for surgical intervention or lithotripsy
- Overall costs
- Stone passage confirmation on CT scan
- Crossover to open label tamsulosin/Flomax

3.3 Design Summary

The multi-center trial will be conducted in the Departments of Emergency Medicine (ED) at The George Washington University Hospital in Washington D.C, Mercy Hospital of Pittsburgh and Presbyterian-University Hospital, both part of the University of Pittsburgh Medical Center, and Thomas Jefferson University Hospital. It is a continuation of the vanguard phase of the study performed solely at The George Washington University Hospital.

This research study is a blinded randomized controlled clinical trial of 400 patients in addition to the 109 enrolled in the vanguard phase. Patients diagnosed with kidney stones via radiographic imaging are approached for screening. Patients who satisfy the eligibility criteria and consent to randomization will be centrally randomized to one of the following two medical protocols, each to be taken once a day for 30 days:

- The active group who receive 30 tablets of 0.4 mg tamsulosin.
- The placebo group who receive 30 similar inactive tablets.

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

1. Age ≥ 18 years

2. Evidence of ureterolithiasis (i.e. stone is located in ureter) as demonstrated on CT with confident diagnosis. This does not include stones located in the bladder or solely in the kidney.
3. Willingness to participate and able to proceed with standard outpatient management (no personal or job-related issues, e.g. airline pilot).
4. Has a telephone in order to be contacted for follow-up.

3.4.2 Exclusion Criteria

1. Patient desiring or requiring immediate surgical intervention making them not a candidate for outpatient kidney stone management. (This includes prior surgery for the same stone).
2. Current urinary tract infection based on urine dipstick or micro urinanalysis as admission and urgent procedural management are likely indicated.
3. Known anatomical genitourinary abnormalities or prior GU surgeries. (Shockwave lithotripsy and ureteroscopy for prior stone(s) are not exclusionary.)
4. Positive pregnancy test making proper radiological imaging contraindicated.
5. Breastfeeding mothers.
6. History of hypersensitivity to tamsulosin.
7. Current use of alpha blockers or calcium channel blockers.
8. Current use of steroids which may have an independent effect on stone expulsion.
9. Spontaneous stone expulsion prior to enrollment.
10. Largest stone dimension ≥ 9mm assessed using radiologic imaging, being very unlikely to pass spontaneously.
11. Previous treatment for the current ureteral stone not elsewhere classified (including shockwave lithotripsy, ureteroscopy and medications not currently being taken).
12. Current use of vardenafil which is tamsulosin contraindicated.
13. Ipsilateral, transplanted or solitary kidney as hospitalization may be necessary.
14. Known renal insufficiency (by patient history).
15. Fever defined as >101.5°F which may indicate infection.
16. Floppy iris syndrome which is tamsulosin contraindicated.
17. Planned cataract surgery in the next 60 days which is tamsulosin contraindicated.
18. Prisoners /wards of state.
19. Prior enrollment in STONE (Candidates who are screened and found ineligible may be rescreened at a later date.)

3.5 Randomization Method and Masking

Consenting patients will be assigned to one of the two treatment groups with a randomization sequence prepared and maintained centrally by the Biostatistical Coordinating Center (BCC). The active and placebo study medication will be packaged according to the randomization sequence, so that the patient is randomized when he or she is assigned to the next available individual supply of study medication. The study is double masked; neither the patient nor the clinical staff will be aware of the treatment assignment.

The simple urn method will be used to generate the randomization sequences because it provides a high probability of balance in treatment assignments, it is unpredictable, and it allows an explicit randomization analysis,[48, 49] to be conducted with relative ease. Randomization will be stratified by clinical site to assure balance between the two treatment groups with respect to anticipated differences within the clinic populations and possible differences in patient management.

4 Study Procedures

4.1 Screening and Randomization

Potential study subjects will be identified while present in the Emergency Department. While the patient is in the ED, a member of the research team will be notified. This researcher will determine if the patient meets the inclusion and exclusion criteria. If the patient meets enrollment criteria, the study protocol will be explained to the patient. If they express interest in participation, informed consent will be obtained, randomization will take place, study medications will be dispensed, and urological follow-up will be arranged before the patient is discharged from the ED.

4.2 Medical Treatment Protocol

The placebo group will receive placebo plus active analgesia, and the active treatment groups will receive analgesia together with a thirty day course of tamsulosin. Standard follow-up care will be offered. Other than administration of tamsulosin or placebo, there will be no differences in the approach to treatment. Any treating physicians will be blinded to treatment group. A one-page guideline for enrolled patients to bring to their physician to help further standardize treatment has been designed.

4.3 Study Outcomes and Ascertainment

4.3.1 Primary Outcome

The administration of tamsulosin after the clinical and radiographic diagnosis of acute urolithiasis produces an increase in the proportion of patients passing their stone within 28 days.

Determination of the symptomatic stone

In cases in which there is more than one stone noted on the CT scan, the physician treating the patient will determine the likely location and dimensions of the stone causing symptoms by reviewing the patient's ED record.

Multiple stones

If the physician believes that the symptomatic stone has not yet reached the bladder the patient may be offered enrollment. If there are multiple stones and the physician believes that the stone causing symptoms has reached the bladder, the patient will not be eligible for enrollment.

Definition of stone expulsion

Stone expulsion will be defined as a report by the patient that the stone was noted to have passed by visualization or capture after urination and that the pain has been relieved.

4.3.2 Secondary Outcomes

The secondary outcomes are:

- Length of time in pain
- Surgical intervention or lithotripsy
- Cost savings based on days of work lost, surgical interventions, hospitalizations, etc.
- Time until stone expulsion
- Total amounts of analgesia taken
- Days of work lost

- Complications including repeat ED visits or other hospitalizations
- Stone passage confirmation on CT scan
- Crossover to open-label tamsulosin/Flomax

Together with these secondary hypotheses, a secondary objective is to identify the most appropriate clinical subgroup(s) for treatment.

4.4 Baseline Procedures

In this randomized clinical trial, the following data and procedures will be performed at screening:

- Informed consent
- Eligibility
- Medical history
- Physical exam
- Labs: dipstick urinalysis
- Labs: pregnancy test for females
- Labs: hematology and/or serum chemistry, *if clinically indicated*
- Result of CT scan

4.5 Patient Management and Follow-up

After randomization, patients are contacted on days 2 and 7, and then on days 15, 20, 29 (to capture status through Day 28), and finally on day 90, as outlined below along with the procedures to be completed in this study and frequency that they will be performed. All the interventions and clinical follow-up in this study are those normally performed in the treatment of patients diagnosed with nephrolithiasis. The only treatment that is not routine is taking tamsulosin or placebo. Follow–up data will be collected in one of three ways: telephone follow-up is the most preferred method, but email communication or texting to the patient's cell-phone can also be used in the case that a telephone call is not feasible.

Table 3: Phone call follow-up Days 2-90

	Day 2	Day 7	Day 15	Day 20	Day 29	Day 90
Study drug taken	X	X	X	X	X	
Total NSAIDs taken	X	X	X	X	X	-
Total Percocet taken	X	X	X	X	X	-
Other analgesics taken?	X	X	X	X	X	-
Stone captured?	X	X	X	X	X	X
Returned to work?	X	X	X	X	X	X
Side effects: Dizzy/nausea/other	X	X	X	X	X	-
Seen PCP for follow-up?	X	X	X	X	X	X
Seen urologist for follow-up?**	X	X	X	X	X	X
Any return ED visits?	X	X	X	X	X	X
Hospitalizations?	X	X	X	X	X	X
Surgical interventions for the stone?	X	X	X	X	X	X
Stone seen on any repeat CT/KUB?	-	-	X	X	X	-
CT scan	-	-	-	-	X	-

**if the patient was seen for urology follow-up, data regarding repeat urinalysis and blood pressure will be collected.

4.5.1 CT scan at 29 days

A follow-up low dose CT scan of the abdomen and pelvis will be performed at day 29 (with a window to day 36). If a documented CT was done outside the study before 29 days that shows passage, it will be

reviewed by the PI who will determine if the information is comparable and sufficient. If so, the study CT will not be performed. This scan will be used in conjunction with the follow-up data to confirm stone passage.

4.6 Adverse Event Reporting

Detailed information concerning adverse events will be collected and evaluated throughout the conduct of the protocol. Results of clinical observations, laboratory tests, and reported events form the basis for evaluating the safety profile of this therapy. At all contacts, patients will be questioned regarding side effects or symptoms associated with the study medication which are as follows:

- Dizziness at rest
- Dizziness on standing (postural hypotension)
- Abnormal ejaculation (in men)
- Gastrointestinal disorder
- Peptic ulcer disease
- Gastrointestinal bleeding
- Urinary tract infections
- Facial flushing
- Headache
- Tachycardia
- Other side effects

The clinical center will report adverse events to the coordinating center in a timely fashion. The coordinating center will summarize and report adverse events to the DSMB.

Additional procedures are warranted for cases of serious adverse events which is defined by the FDA as a patient outcome that is: (1) death; (2) life-threatening, i.e., the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death; (3) hospitalization (initial or prolonged); (4) disability, i.e., resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life; (5) congenital anomaly, i.e., there are suspicions that exposure to a medical product prior to conception or during pregnancy resulted in an adverse outcome in the child; (6) requires intervention to prevent permanent impairment or damage. Serious adverse events will be reported immediately to the NIDDK project office, the BCC and the local IRB. The BCC will notify the DSMB chair; and the entire DSMB will confer if needed.

The only indication for breaking the randomization code is when it is medically necessary to unmask the study drug assignment to be able to treat the patient, such as an allergic reaction or severe side effect that appears to be related to the medication.

5 Statistical Considerations

Our data analysis is designed to evaluate the following goals of the study: 1) to determine the efficacy of tamsulosin with respect to primary and secondary outcomes in patients with urolithiasis, 2) to ensure that such treatment is safe 3) to determine if benefit is equally evident across a range of clinically relevant subgroups. The principal analyses of primary and secondary outcomes employ the intent-to-treat (ITT) approach. Although data may be missing at points in time, all relevant data available from each participant will be employed in all analyses. An ITT analysis more closely reflects actual conditions and experiences of clinical practice than analyses based on the subset of 'complete' or 'totally compliant' participation and, therefore, does not overestimate the impact of an intervention. Treatment group assignments are not altered based on adherence to the assigned treatment regimen. Furthermore, applying ITT maintains the benefits of randomization; if dropouts and non-compliers are ignored, then the study design becomes more observational and bias due to post-randomization subset selection is introduced. All significance tests will be 2-sided, with alpha=0.05.

5.1 Data Relevant to the Primary Outcome

A power analysis was conducted for the primary outcome measure, reduction in time to stone passage. Two published studies[6, 9] provide data on the time from diagnosis to either passage of the kidney stone or complete relief of pain under current standard treatment procedures. Although this time interval varies directly by stone size and location at time of diagnosis, a weighted average of the patient groups in Miller's work[6] showed an overall mean time interval of about 14 days, and a 30 day passage rate of 90%. In recent Italian studies[16, 46] using tamsulosin and nifedipine in urolithiasis, the overall passage rate of the control arm is much lower. In the control arm of these studies, the 30 day expulsion rate was only 35-43%. We cannot account for this wide variation in overall passage rate between the American and Italian data sets. In order to perform a reliable power analysis, we have used an estimated passage rate of 70% in the placebo group.

As mentioned above in the Background section 2.1.2, in his meta review in 2006, Hollingsworth suggested the need for a definitive clinical study which suggested a sample size very similar to that calculated for our own study.

5.2 Interim Analysis

Interim statistical analyses of clinical trials are a requirement of all National Institutes of Health (NIH) sponsored clinical trials. The Data and Safety Monitoring Committee (DSMC) meets at least once a year to review trial results; however, the exact timing of the interim analyses is at the discretion of the committee. Before each meeting, a formal detailed statistical report will be written by the Biostatistical Coordinating Center (BCC) which presents the results of every aspect of the study, including all baseline variables, protocol adherence, all outcome variables, adverse events reported and center performance in terms of recruitment, data quality, loss to follow-up and protocol violations. However, the main emphasis is on the primary outcome. For this evaluation, a cohort of patients is chosen consisting of all patients randomized before a certain date so that the analysis cohort does not depend on time to stone expulsion.

The main statistical issue relevant to interim analysis is the problem of performing multiple tests of significance on accumulating data. A number of procedures have been developed to handle this situation[50, 51] Most techniques[52, 53] entail adjusting the nominal significance level at the interim evaluations to some value less than α, such that the overall probability of committing a type-I error is maintained at α. For this trial, the group sequential method of Lan and DeMets[54] will be used to characterize the rate at which the type I error is spent. This method is flexible with regard to the timing of

the interim analyses. Asymmetric stopping boundaries will be used for the Lan-DeMets procedure. The upper boundary which describes the stopping rule for benefit will be based on 1-sided type I error of .025 and the Lan-DeMets generalization of the O'Brien-Fleming boundary. The lower boundary will be based on a less stringent stopping rule: 1-sided type 1 error of .05 and the Lan-DeMets generalization of the Pocock type boundary. However, this should not preclude the Data and Safety Monitoring Committee recommending termination earlier if there is evidence of harm.

Sometimes, a surprising development may lead to extra looks or even continuous monitoring of the data, such as on a monthly basis. The Lan-DeMets procedure is flexible, in that one can switch from occasional to continuous monitoring of the data, with negligible effect on the type I error level. [55] In some instances the Lan-DeMets boundary for statistical significance may be crossed, but due to other considerations the DSMC decides that the trial should continue. In this case, the type I error previously spent under by the α spending function can be retrieved to be distributed over future looks without inflating the total type I error probability.[56]

It is often useful to calculate conditional power given the observed data to date, and conditional on the future data showing the originally assumed design effect.[57] If this conditional power is low (under 10 percent) the DSMC may consider termination for futility if the accrual rate is slow with confidence that the Type II error is not greatly inflated.)

It is recognized that any decision to terminate the study would not be reached solely on statistical grounds but on a number of complex clinical and statistical considerations.[58]

5.3 Analysis Plan

5.3.1 Preliminary Analyses

To assess the efficacy of tamsulosin for the treatment of urolithiasis, the BCC will employ a systemic statistical analysis strategy. The first analytic step will be to compile descriptive statistics (e.g. mean, standard deviation, range, proportion) of patient demographics. This activity, while not directly addressing any of the study hypotheses, will serve to describe central tendencies and the variability of outcome variables and co-variables.

Then a series of interactive data analyses will be conducted, which will be used to characterize data distributions, detect any missing data patterns, examine associations and redundancies among independent variables, and generally watch for unusual or unexpected data patterns. This will help verify whether the assumptions of the proposed statistical models are reasonably met and if necessary to choose alternative analytic methods such as non-parametric tests or transformations.

The second step will be to compare treatment groups with respect to important suspected covariates, specifically age, gender, stone location and size, and the number of prior episodes of renal colic. Any variables found to have substantial imbalance (either statistically significant or large in magnitude) between the study groups will be included as covariates. The third step will be to analyze the data according to our specific aims.

5.3.2 Testing of efficacy and safety outcomes

One of the secondary endpoints is whether the patient requires a more complicated treatment within 90 days of the index emergency visit. This would be evidenced by the need for surgical intervention or lithotripsy. Based on the practice characteristics of the research site we expect a low number of these cases. In addition, work by Yilmaz[36] described above lends strong evidence to our expectation that the

surgical intervention rate will be low. These cases will be described descriptively. The two study groups will be compared using the Pearson chi-square test or the Mantel-Haenszel procedure if covariate adjustment is necessary. An additional secondary outcome is the number of days of work missed. These will be tested by t-test or (or ANCOVA with covariates), or if necessary because of distributions requirements, by the Wilcoxon test.

To examine whether the treatment groups experience comparable rates of complications we will monitor patients for several unlikely but potential complications of tamsulosin as outlined above. Events not typically associated with patients with acute urolithiasis will be classified as adverse effects. Adverse and serious adverse events are expected to occur at a very low rate in both study conditions. These will be analyzed descriptively.

5.3.3 Exploratory Analyses

It is possible that the beneficial effects of the study drug, if observed, will be more evident in one subset of patients than another. To assess this possibility, we will conduct a series of analyses, categorizing patients into a variety of clinical sub-groups: first episode vs. recurrent episode of ureterolithiasis; small stones (<1.9mm) vs. moderate stones (2-5.9mm) vs. large stones (>6mm); location of stone; male patients vs. female patients; age. These will be tested as interactions with treatment group, using cross-product terms, in a Cox proportional hazards model to assess the duration of symptoms.

5.3.4 Statistical Complications

Because of the brief treatment and follow-up period and the expected very low rate of side effects, it is anticipated that the attrition rate will be low. However, if any patients end their treatment early while still providing outcome information, the primary outcome will be analyzed according to the intention-to-treat principle. It is possible that some outcome data may be missing for some patients. For example, some patients may not be reachable by telephone, may refuse to provide follow-up information or may have unreliable recall. If the number missing is low these patients will be dropped from the analysis; otherwise multiple imputation methodology[59] will be employed to reduce statistical bias and make efficient use of all of the data.

5.4 Sample Size and Power

5.4.1 Sample size

The primary outcome for the STONE study is the proportion of patients who pass stones within 28 days. Data on stone passage rates is summarized in a meta-analysis by Hollingsworth et al[37] who found the baseline occurrence of stone passage in the control group across nine studies to be 47% with rates ranging from 20% to 73%. The lower confidence limit of the passage rate in the treatment group across the nine studies was 68%. A two group chi-squared test with a 0.05 two-sided significance level will have 90% power to detect the difference between a placebo proportion of 0.45 and a tamsulosin proportion of 0.60 when the sample size in each group is 250 accounting for losses to follow-up.

Due to concerns that the passage rate might be inappropriate, this sample size will be achieved in a two-stage approach. After the outcomes of the treatment of the first 100 patients were obtained, the passage rate in the placebo group was calculated by the BCC. The DSMB reviewed the data and agreed that the total sample size of 500 was accurate. Therefore, the remainder of the sample will be collected in a multi-center trial. There will be approximately 200 more patients randomized to each treatment group along with the 109 patients randomized in the pilot study, would achieve the total sample size of 500 patients.

5.5 Statistical Analyses

The principal analyses of primary and secondary outcomes employ the "intent-to-treat" approach as described by Peduzzi.[60] The intent-to-treat analyses include all randomized patients with all patients included in their randomly assigned treatment group; treatment group assignment is not altered based on the patient's adherence to the assigned treatment regimen. All statistical tests are two-sided with the overall significance level of the primary outcome α=0.05. However, the significance levels used in the interim and final analyses of the primary outcome are adjusted to account for the interim analyses.

- *Baseline characteristics:* Comparison of the baseline characteristics (e.g., age, gender, stone location and size) between the two treatment groups uses standard parametric and nonparametric statistical techniques, such as the Pearson chi-square test and Fisher's exact test for categorical data and ANOVA and the Kruskal-Wallis test for continuous data.

- *Primary outcome:* The principal analysis of STONE will be a comparison of the proportion passing stones in the two groups using the Pearson chi-square test. Logistic regression will be used if covariate adjustment is necessary.

- *Secondary outcomes:* Secondary time to event outcomes (e.g., time to passage of stone; time to pain relief) are analyzed using life-table analysis of the time to event. A proportional-hazards regression model is used to evaluate potential covariates that may modify the secondary time to event outcomes (e.g., size and location of stone). Graphical procedures are used to assess the proportionality assumption. If the proportionality assumption is found to be unreasonable, then other models such as the accelerated failure time model or the proportional odds model are used to evaluate the covariates.

- Secondary dichotomous outcomes (e.g., need for surgical intervention or lithotripsy) are analyzed using the same methods as described for the primary outcome. Ordinal outcomes (e.g., number of days lost from work) are analyzed using Poisson regression with adjustment for covariates if necessary. Continuous variables will be analyzed using general linear models.

- *Subset analysis*: It is possible that the beneficial effects of the study drug, if observed, are stronger in one subset of patients than another. Subsets based on sex, age, stone size, stone location and stone recurrence may receive differential benefit. To assess this possibility, these groups are tested as interactions with treatment group, using cross-product terms, in the appropriate model (e.g., Cox proportional hazards, logistic regression, Poisson regression).

  If the two groups show a difference in the incidence of the primary outcome, interactions will be evaluated and subgroup analyses conducted to determine whether the effect prevails throughout particular subgroups of patients. Indeed, NIH guidelines require investigators to evaluate consistency between the genders and across racial subgroups. It should be noted, however, that subgroup analyses have been greatly abused,[61] particularly when there is no overall treatment difference. There is a strong temptation to search for a specific subpopulation in which the therapy is nevertheless effective. Yusuf et al[62] concluded "*the overall 'average' result of a randomized clinical trial is usually a more reliable estimate of the treatment effect in the various subgroups examined than are the observed effects in individual subgroups*." Thus subgroup analyses will be interpreted with care.

- *Interim analysis:* The Lan-DeMets[55] spending function approach is used to adjust the probability of a type I error for testing the primary outcome when interim 'looks' of the data are taken by the

Data Safety Monitoring Board. The spending function corresponding to an O'Brien - Fleming boundary is used. The Lan-DeMets procedure is flexible, in that the number of looks does not have to be specified in advance and the time interval between looks does not have to be the same throughout the study. The rate at which the type I error is spent is a function of the fraction of total information available at the time of the interim analysis (i.e., information time).[63] Prior to taking any 'looks' at the data, the study Steering Committee and the DSMB will develop study-specific procedures for interim analyses and stopping rules.

6 Data Collection and Management

6.1 Data Collection Forms

Data will be collected on standardized forms on which nearly all responses have been pre-coded. Each form is briefly described below:

- Screening Log lists all patients screened for the study and some demographic data.
- Eligibility and Randomization Form is completed for all randomized patients and records assigned study drug code number, and information on the study drug administration.
- Screening Form is completed for all randomized patients. This form includes detailed medical data obtained during screening for the study.
- Adverse Event Form records adverse events.
- Follow-up Form for all contact calls for follow-up of randomized patients.
- Radiologic Imaging Forms for radiologic imagining at screening and at follow-up.

6.2 Web Data Entry System

For this protocol, web data entry screens corresponding to the study forms listed above will be developed and maintained by the staff of the BCC. Clinical center staff will enter data into the MySQL database located at the BCC through a web data management system (MIDAS). The data are edited on-line for missing, out of range and inconsistent values. A Users' Manual documenting this system is provided to the centers by the BCC.

6.3 Centralized Data Management System

Daily data conversions from the MySQL database create up-to-date SAS datasets. Data are reviewed weekly using edit routines similar to those implemented on-line during data entry, as well as additional checks for data consistency within or across forms. A database of resulting potential data problems is generated in MIDAS for initial review by BCC staff, who then evaluate the comments keyed in association with edits on missing or unusual values. Valid edits will be flagged in MIDAS for resolution at the clinical centers.

At regular intervals, specialized data reviews comparing data availability and consistency across forms are run by the BCC staff on the entire database or on a specific subset of data. These reports are also submitted to the centers for correction or clarification.

An audit trail, consisting of all prior versions of each data form as entered in the computer for each patient, is maintained so that the succession of corrections can be monitored.

6.4 Performance Monitoring

The BCC will present regular reports to the Steering Committee, and the Data and Safety Monitoring Board. These include:

- Monthly Recruitment Reports - reports of the number of people screened and enrolled by month and by clinical center are provided monthly to the Steering Committee.
- Steering Committee Reports - reports detailing recruitment, baseline patient characteristics, data quality, incidence of missing data and adherence to study protocol by clinical center, are provided the Steering Committee.

- Data and Safety Monitoring Board Reports - for every meeting of the DSMB a report is prepared which includes patient recruitment, baseline patient characteristics, center performance information with respect to data quality, timeliness of data submission and protocol adherence (in addition to safety and efficacy data). The reports also include adverse events, loss to follow-up and all outcome variables as described previously in this protocol.

7 Study Administration

7.1 Organization and Funding

The trial management is composed of study staff from the NIDDK project office, the George Washington University Biostatistics Center, and the principal investigator. Organizationally:

- The clinical centers at the Emergency Departments of the George Washington University Hospital, the University of Pittsburgh and the Thomas Jefferson University Hospitalare responsible for recruiting and enrolling patients and for collecting and entering data.
- The NIDDK project office participates in all decision-making activities, has selected and will oversee the activities of the Data Safety Monitoring Board.
- The Biostatistical Coordinating Center (BCC) is responsible for statistical aspects of study design and conduct, designs and monitors quality control systems. The BCC produces performance reports, including periodic tracking reports and reports to the Steering Committee and Data Safety Monitoring Board.

7.2 Committees

7.2.1 Steering Committee

The Steering Committee is the primary decision making body for the study, and convenes periodic meetings and conference calls to review scientific issues and study progress. Members of the Steering Committee are the Principal Investigators from each of the clinical centers, the Principal Investigator at the Data Coordinating Center and the NIDDK project office representatives.

7.2.2 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) consisting of appropriately qualified independent experts has been appointed by the NIDDK to provide review of data on patient safety and study progress. The membership roster is maintained by NIDDK and is available from them as needed. The Data Coordinating Center will provide reports to the DSMB including adverse events. A summary of DSMB deliberations will be prepared by NIDDK and distributed to the clinical center to submit to their IRB.

8 Study Timetable

8.1 Training and Certification

Figure 2. Timeline

With funding beginning in September 2012 and the first 4 months will be spent on final preparations of the protocol, acquisition of study drugs and training and certification of study coordinators and staff. Screening will begin in April 2013.

8.2 Data Collection Period

The recruitment and follow-up period begins in April 2013 and continues through February 2016. Data queries are generated and resolved during this time period through April 2016. Data close-out will be performed during the final 6 months of funding starting in January 2016 through June 2016.

8.3 Final Analysis

After a period of approximately three and a half years for completion of data acquisition for the trial and close-out, the data set will be locked and ready for analysis. A few months will be required to complete the final report to the Steering Committee and to submit the study's primary report for publication.

Appendix A DESIGN SUMMARY

Study TamsulOsiN for urolithiasis in the Emergency Department (STONE)

OBJECTIVE

To determine if the administration of tamsulosin after the clinical and radiographic diagnosis of acute urolithiasis produces an increase in the proportion of patients passing their stone at 28 days.

ORGANIZATION

Clinical Centers:	George Washington University Hospital, Thomas Jefferson University Hospital, University of Pittsburgh Medical Center (Presbyterian Hospital and Mercy Hospital), University of Alabama at Birmingham Medical Center
Data Coordinating Center:	George Washington University Biostatistics Center
Steering Committee:	Clinical center PIs, data coordinating center PI and the NICHD Program Scientist

DESIGN

Type: Randomized clinical trial

Inclusion Criteria:
- Age >= 18 years
- Radiologic evidence of kidney stones
- Has telephone
- Informed consent

Major Eligibility Criteria:
- Require surgical intervention
- Pregnancy
- Hypersensitivity to tamsulosin or current use of medications which affect stone expulsion or contraindication to tamsulosin
- Renal insufficiency or kidney malformation
- Stone located in bladder only
- Current urinary tract infection

Groups:
- Experimental: Tamsulosin 0.4 mg
- Standard care: Placebo tamsulosin

Random Allocation: Standard urn design

Level of Masking: Double-blinded

Stratification: Clinical center

Sample Size: Trial goal = 500 (250/group)

Assumptions:

1) Type 1 error = 5% (2-sided); Power >= 90%

2) Outcome event = passage of symptomatic stone at 28 days post - randomization
   - Placebo group event rate = 45%
   - Tamsulosin group event rate = 60%

Interim Analysis: Group sequential method

SCHEDULED EVALUATIONS / DATA COLLECTION

Pre-randomization:
- Informed consent
- Eligibility
- Medical history
- Physical exam
- Labs: urinalysis
- Labs: hematology, serum chemistry*
- CT scan

Management Protocol
- Study medications are taken for 30 days post-randomization
- Stone passage documentation

Post-randomization Contacts on Days 2,7,15,20,29,90
- Medications taken including study drug
- Kidney stone passage
- Side effects
- Hospitalizations and doctor visits
- Return to work

OUTCOME MEASURES

Primary:
- Kidney stone passage <= 28 days

Secondary:
- Reduction in the length of time in pain
- Reduction in the number of days lost from work
- Reduction in the need for surgical intervention or lithotripsy
- Cost savings
- Crossover to open label tamsulosin/Flomax

TIMETABLE

Pilot Study	April 1, 2006 – December 31, 2010
Planning Grant	September 30, 2010 – August 31, 2012
Training/Certification	February 1, 2013 – March 30, 2013
Randomization:	April 1, 2013 –December 31, 2015
Data Processing:	April 2, 2013 – April 30, 2016
Closeout/final analysis:	January 1, 2016 – June 30, 2016

Appendix B Sample Informed Consent

Research Consent Form
Tamsulosin for Urolithiasis

IRB Reference number: _____
Principal Investigator: _____ Telephone number: _____
Sponsor: NIDDK

I. INTRODUCTION

You are invited to participate in a research study of tamsulosin for kidney stones because you have a kidney stone. Your participation is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. You do not have to take part in this study to receive care at (university/hospital). You may not receive any benefit from taking part in this study; however, the research may give us knowledge that may help people in the future.

This study is being conducted by the investigators listed above from the Department of Emergency Medicine at the (university/hospital). The costs of this research study are paid for by the National Institutes of Health.

Before you decide to participate, please take as much time as you need to ask any questions and discuss this study with anyone at (university/hospital), with family and friends, and your personal physician or other health professional. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

Please tell the Principal Investigator or study staff if you are participating in another research study.

II. WHY IS THIS STUDY BEING DONE?

The Department of Emergency Medicine at (the university/hospital) and the National Institutes of Health are carrying out a research study to find out if tamsulosin can reduce the time you are in pain with kidney stones, and possibly help the stones pass, which would reduce the need for surgery. The investigator (person in charge of this research study) is Dr. (local PI). About 400 patients will be enrolled. This research is funded by the government through the National Institutes of Health.

III. WHAT IS INVOLVED IN THIS STUDY?

The research will be conducted by giving you the medications and seeing how long it takes you to improve, and whether or not you required any surgery to remove the stone. The medication being studied is tamsulosin which used to relax the muscle in the ureters where the stone is. There will be no need to come back to the hospital for any special visits, other than the visits you would normally make because of your kidney stone. You have a 50-50 chance of getting either the medication or a sugar pill, called a placebo. There is no way of knowing whether or not you got the real medications or the sugar pill until the end of the study, unless there is an emergency in which case we can tell you immediately.
If you see a urologist, we may ask that doctor to share information about the visit with us.

HOW LONG WILL I BE IN THIS STUDY?
The total amount of time you will spend in connection with this study is three months. You will take the study medicines for 30 days and will be called by the researchers over the first thirty days and again after

three months to see how you are doing and to collect information about how many pain pills you have been taking.
You always can choose to stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first.

IV. WHAT ARE THE RISKS OF PARTICIPATING IN THIS STUDY?

The medication you may be given has been used for many years to treat other problems and has been shown to be very safe. It has been used for years to treat patients with prostate problems. The most common side effects are dizziness and abnormalities of ejaculation. Once you stop the medication any side effects rapidly end.

Reproductive Risks

Pregnant women may not take part in this research study because of the risk the fetus from radiation from the CT. To determine if you are pregnant, pregnancy testing will be performed on all women capable of becoming pregnant before and during participation in this study. Even if not sexually active, all female participants will be given a pregnancy test. The only exceptions are when female participants have stopped having menstrual periods at least one year after menopause (change of life); or have undergone sterilization surgery (tubes were tied or had a hysterectomy). The effect of the study drug on a child conceived (created) while a female participant is taking the study drug, are not known. If female participants become or suspect that they are pregnant during the study, the study doctor must be notified immediately. Also, breastfeeding mother may not take part in the study.

V. ARE THERE POTENTIAL BENEFITS TO TAKING PART IN THIS STUDY?

If you agree to take part in this study, there may be direct medical benefit to you. If you get the study pills and they work, you may get better much quicker than you would without them. This means that you will be in less pain for fewer days. In addition the pills may prevent you from needing surgery later. However we do not know if the treatment will work.
We hope the information learned from this study will benefit other individuals with kidney stones in the future.
We cannot and do not guarantee or promise that you will receive any benefits from this study.

VI. WHAT ARE MY OPTIONS?

You do not have to take part in this study if you do not want to participate**.** Should you decide to take part and later change your mind, you can do so at anytime. There are no other medical alternatives that are currently offered for those patients who have kidney stones, other than pain relieving medications. If the stone does not pass within a few weeks, you may be offered interventions by urologists, such as lithotripsy (using shock waves to break up the stone) or removing the stone directly. These interventions are considered if the stone fails to pass despite medications. You may chose not to take part in this study. If you do not take part you will be offered all of the standard medications for this condition which are pain relieving medications (analgesics like Motrin or Percocet). You also have the right to refuse all treatment.
Your study doctor can explain these options in detail or refer you to the appropriate doctor for more information.

VII. WILL I RECEIVE PAYMENT FOR BEING IN THIS STUDY?

You will not be paid for taking part in this study.

VIII. WHAT WILL IT COST ME IF I DECIDE TO PARTICIPATE IN THIS STUDY?

There will be no additional costs to you as a result of taking part in this study. However, routine medical care for your condition (the care you would receive whether or not you were in this study) will be charged to you or your insurance company. You may be responsible for any co-payments and deductibles that are standard for your insurance coverage.

You will not be charged for the following that is part of this research study:

- Tamsulosin or placebo – the study medications

If you have any questions about your insurance coverage or the items you might be required to pay for, please call your insurance representative to discuss this further before making your decision about taking part in the study. You also may contact financial services for information. The contact information for financial services is:

_____

_____

IX. ARE THE RESEARCHERS BEING PAID FOR THE STUDY?

The sponsor of the study is paying (the university/hospital) and the (local PI) and his/her team for their work in this study.

X. WHO PAYS FOR MY MEDICAL CARE IF I BECOME ILL OR INJURED BECAUSE OF THE STUDY?

The researchers have taken steps to minimize the known or expected risks. In spite of all precautions, you still may experience medical complications or side effects from participating in this study. If you believe that you have been injured or have become ill from taking part in this study, you should seek medical treatment from (the university/hospital) or through your physician or treatment center of choice. Care for such injuries will be billed in the ordinary manner to you or your insurance company. You also should promptly notify the study doctor in the event of any illness or injury.

You will not receive any financial payments from (the university/hospital) for any injuries or illnesses. You do not waive any liability rights for personal injury by signing this form.

XI. WHAT ABOUT CONFIDENTIALITY?

Your records will be confidential. You will not be identified (e.g., name, social security number) in any reports or publications of this study. It is possible that representatives of regulatory agencies and from the study's sponsor may come to (the university/hospital) to review your information. In that situation, copies of the relevant parts of your records will be released with all identifying information removed. Except for these entities, research study records will be kept confidential unless you authorize their release or if the records are required by law (i.e. court subpoena).
Your information will be kept as confidential as possible. Access to study records will be limited to those who need the information for purposes of this study, as well as your health care providers should they need access to the information. All records are kept in a secure location and access is limited to research study personnel.

Except as required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, your identity will not be disclosed, unless you give the appropriate authorization.

XII. HOW WILL MY PRIVACY BE PROTECTED?

Federal law requires that hospitals, researchers and other healthcare providers (like physicians and labs) protect the privacy of health information that identifies you. This kind of information is known as "protected health information" or "PHI." This section tells you your rights about your protected health information in the study. This section also lists who you let use, release, and get your protected health information. You are free to not allow these uses and releases by not signing this form. If you do that though, you cannot participate in the study.
Protected health information that may be used and released (disclosed) in this study includes information such as:

- This consent form;
- Demographic information (like your name, address, date of birth, social security number, etc.);
- Information about your medical history from your medical records and your doctor's office;
- Information obtained from you to be used in the study as a result of tests or procedures;
- Results of physical examinations; laboratory results obtained on specimens collected from you (like blood, urine, tissue);
- Medical images like x-rays, CT scans, and MRIs;
- Admissions information;
- Health care expenses and health insurance coverage information;
- Questionnaires/surveys you complete;
- Interviews with you conducted by members of the Research Team;

By signing this form, you allow the use, sharing, copying, and release of your protected health information to carry out the study by: your healthcare providers (like doctors and hospitals) which are not part of the study, the study doctor and his or her research team, and other healthcare providers such as labs which are part of the study.

You also allow the study doctor and his or her research team, and other healthcare providers which are part of the study to release your health information to:

The (university/hospital) Institutional Review Board ("IRB") or its authorized representatives, as well as representatives of the Office of Human Research Protections (OHRP) who may review your records to ensure that your rights as a research subject are protected;

- The sponsor of the study and any contractors or partners it may have. (Research monitors and auditors)
- Research collaborators participating in this multi-site study at other institutions. (Data receiving center(s) responsible for collecting, monitoring and /or analyzing data from all the sites participating in this study)
- Regulatory agencies such as the U.S. Food and Drug Administration (FDA) to review data on the safety and effectiveness of the product that is being tested in this study and other Federal and state agencies that regulate research
- Clinical staff who are not involved in the study who may become involved in your care, if it might be relevant to your care; and (the university/hospital) workforce who are involved with the research;

You may request to review or have a copy of your personal health information collected during this study and placed in your medical record. This right to review and copy your personal health information only extends to information that is placed in your medical record; it does not extend to information that is placed in your research record.

This is a clinical trial and it is critical to the interpretation of the results that you not know which treatment group you are participating. Once the study is finished you may request to review and have a copy of your personal health information collected during this study and placed in your medical record. This right to review and copy your personal health information only extends to information that is placed in your medical record; it does not extend to information that is placed in your research record.

This permission does not end unless you cancel it, even if you leave the study. You can cancel this permission any time except where a healthcare provider has already used or released your health information, or relied on your permission to do something. Even if you cancel this authorization, the researchers may still use and disclose protected health information they already have obtained about you as necessary to maintain the integrity or reliability of the research. However, no new PHI or new biological specimens will be collected from you after you revoke your authorization.

To cancel your authorization, you will need to send a letter to (local PI) stating that you are canceling your authorization. This letter must be signed and dated and sent to this address:

_____

_____

A copy of this revocation will be provided to the study doctor and his or her research team. Not signing this form or later canceling your permission will not affect your health care treatment outside the study, payment for health care from a health plan, or ability to get health plan benefits.

Your protected health information will be treated confidentially to the extent permitted by applicable laws and regulations. Federal law may allow someone who gets your health information from this study to use or release it in some way not discussed in this section and no longer be protected by the HIPAA Privacy Rule.

By signing this form you authorize the study doctor and members of the research team to use and share with others (disclose) your PHI for the purpose of this study. If you do not wish to authorize the use or disclosure of your PHI, you cannot participate in this study because your PHI is necessary to conduct this study.

XIII. CAN I WITHDRAW FROM THE STUDY LATER?

You may withdraw from the study at any time. Leaving the study will not affect your current or future medical care at (the university/hospital). If you choose to no longer be in the study, you should call or write to the study doctor right away.

XIV. CAN I BE TAKEN OFF THE STUDY?

The study doctor or sponsor can decide to stop your participation in this study at any time. You could be taken off the study for reasons related solely to you (for example, not following study-related directions from the study doctor, circumstances that may develop and offer alternatives, or a serious reaction) or because the entire study is stopped. The sponsor may stop the study at any time. The sponsor may also decide to stop the study doctor's involvement in this study.

XV. WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

The Office of Human Research of (the university/hospital), at telephone number (phone number); can provide further information about your rights as a research subject. Research related injury should be reported to the Principal Investigator of this study. His/her telephone number is (phone number). For problems arising evenings or weekends, you may call (local PI) at (phone number).

XVI. CONSENT DOCUMENT

After you sign this Consent Form, the research team will provide you with a copy. Please keep a copy of this document in case you want to read it again.

If you agree to participate in this study, please sign below:

DOCUMENTATION OF CONSENT

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with ___(person obtaining consent)_____. All of my current questions have been answered. My signature below indicates my willingness to participate in this study and my understanding that I can withdraw at any time.

_____ _____
Participant's Name (printed) and Signature Date

_____ _____
Name (printed) and Signature of Person Obtaining Consent Date

_____ _____
(Local) Principal Investigator's Signature Date

DO NOT SIGN AFTER THE EXPIRATION DATE OF:

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