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Design and Development of the Pediatric Urology Recovery After Surgery Endeavor (PURSUE) Multi-Center Pilot and Exploratory Study

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Abstract

Introduction:

Lower urinary tract reconstruction in pediatric urology represent a physiologiclly-stressful event that is associated with high complication rates, including readmissions and emergency room visits. Enhanced Recovery After Surgery (ERAS) protocol is a set of multidisciplinary, perioperative strategies designed to expedite surgical recovery wihtout adversely impacting readmission or reoperation rates. Early pediatric urology data demonstrated ERAS reduced complications in this population.

Methods and Analysis:

In 2016, a working group of pediatric urologists and anesthesiologists convened to develop an ERAS protocol suitable for patients undergoing lower urinary tract reconstruction and define study process measures, patient-reported outcomes, and clinically-relevant outcomes in pediatric and adolescent/young adult patients.

A multicenter, prospective, propensity-matched, case control study design was chosen. Each center will enroll five pilot patients to verify implementation. Subsequent enrolled patients will be propensity matched to historical controls. Eligible patients must be aged 4 to 25 years and undergoing planned operations (bladder augmentation, continent ileovesicostomy or appendicovesicostomy, or urinary diversion). 64 ERAS patients and 128 controls will be needed to detect a decrease in mean length of stay by two days.

Pilot phase outcomes include attainment of ≥70% mean protocol adherence per patient and reasons for protocol deviations. Exploratory phase primary outcome is ERAS protocol adherence, with secondary outcomes including length of stay, readmissions, reoperations, emergency room visits, 90-day complications, pain scores, opioid usage, and differences in Quality of Recovery 9 scores.

Ethics and Dissemination:

This study has been registered with authors' respective institution review boards and will be published in peer-reviewed journals. It will provide robust insight into the feasibility of ERAS in pediatric urology, determine patient outcomes, and allow for iteration of ERAS implementations as new best practices and evidence for pediatric surgical care arise. We anticipate this study will take 4 years to fully accrue with completed follow up.

Registration Details:

Pediatric Urology Recovery After Surgery Endeavor (PURSUE, ClinicalTrials.gov NCT03245242) is a multicenter, prospective, case-control study that will examine outcomes in pediatric and adolescent/young adult patients undergoing lower urinary tract reconstructive operations who receive care under an ERAS pathway.

Article Summary

Strengths and Limitations of This Study

- This protocol outlines a multicenter, prospective propensity score-matched cohort study of an Enhanced Recovery After Surgery (ERAS) protocol applied to pediatric and adolescent/young adult patients undergoing lower urinary tract reconstructive surgery.

- Each participating free-standing pediatric center will take part in a pilot phase to understand barriers to implementation, protocol compliance, and protocol uptake and an exploratory phase to demonstrate clinical outcomes related to the ERAS care pathway as compared to propensity matched recent historical controls.

- Primary and secondary outcomes of interest are relevant to the underlying quality improvement initiative to implement a standardized care pathway (ERAS), reflect clinical outcomes, and include patient-reported outcome measures to understand the patient and family perspective.

- The comparator group will be recent historical patients who have undergone the same operations. Propensity score matching based on *a priori* identified covariates will be used to reduce confounding based on non-random assignment of perioperative care (e.g., routine care versus ERAS protocol). Time-series analysis will provide insight into any ongoing changes occurring over time with regards to either process, clinical, or balancing measures.

Introduction

Background

Lower urinary tract reconstruction represents some of the most challenging surgical operations performed by pediatric urologists. These operations can be long, complex, and often involve a bowel resection and anastomosis. Patients undergoing these operations are at high risk for postoperative complications, including nausea and vomiting, ileus, surgical site infection, urinary tract infection, and pyelonephritis.[1] To date, the optimal perioperative care for these patients has not been well-defined, with practices varying widely from institution to institution.[2,3]

Relevance

Since its initial description in the late 1990s, enhanced recovery after surgery (ERAS) has emerged as an innovative tool in the care of adult surgical patients. ERAS represents a multidisciplinary protocol with a strong implementation framework that targets all phases of care for the surgical patient.[4] ERAS has been shown in various adult surgical populations to maintain adequate pain control and facilitate earlier return to baseline function without adverse impact on complication or readmission rate through evidence-based care.[5-7] A large multicenter ERAS study of adult colorectal resection and hip fracture repairs demonstrated clinically-significant reductions in length of stay (0.4–0.9 days), postoperative major complications (rate ratio 0.28 compared to pre-ERAS controls [95% confidence interval 0.12–0.68]), and decreased opioid use (by 31–42%).[7] Data audits function as an essential part of an ERAS protocol, allowing teams to review compliance and use continuous quality improvement methodology to iterate and target areas requiring amelioration, further improving clinical outcomes.[8] Standardizing perioperative care of complex pediatric urology patients using an

approach like ERAS has potential to reduce undesirable variations in care, optimize recovery, and lead to improvements in surgical outcomes.[9]

To date, experience with ERAS in pediatric patients has been limited. Published studies have methodological limitations including retrospective nature, lack of specified inclusion and exclusion criteria, poorly defined ERAS protocol elements, small sample size, lack of audits, and/or limited follow up.[10,11] A single-center, prospective pilot trial of 13 pediatric urology patients undergoing procedures with ERAS, compared to 26 historical controls, demonstrated fewer complications and reduced length of stay from 8 to 5.7 days.[12] Another group studying a similar population retrospectively reported even greater improvements in length of stay.[13] These small experiences reflect that some pediatric operations occur with far less frequency than common adult operations, increasing variability in postoperative care and overall experience from center to center and surgeon to surgeon. The evidence base for perioperative practices are not necessarily well developed or even valid in a pediatric population. Additionally, parents, guardians and families are integral to the care of pediatric surgical patients and their involvement in a pathway should be considered.[11]

Anticipated Impact

To address these issues, a collaborative multicenter effort was initiated by the study authors with goals of defining and implementing an ERAS protocol adapted for pediatric urology patients and studying both implementation and outcomes prospectively. Centers will gain valuable experience in implementation, which requires stakeholder engagement and multidisciplinary participation, while the study group seeks to understand system, provider, and patient-level barriers to protocolized surgical care.

Furthermore, study of ERAS in a pediatric and emerging young adult population undergoing metabolically stressful operations has the potential to demonstrate the value of standardized care similar to gains seen in adult counterparts.

Objectives

Pediatric Urology Recovery After Surgery Endeavor (PURSUE) study has two primary objectives: 1, to determine if an ERAS protocol can decrease variation in care for complex pediatric patients while simultaneously improving recovery time from surgery without any change in balancing measures, and 2, to broaden exposure of the pediatric urology community to ERAS by engaging study centers in ERAS protocol implementation at geographically-diverse medical centers. In this report, we describe study design considerations, ERAS protocol definitions, and rationale for the PURSUE study.

Methods and Analysis

ERAS Protocol Development

The study group first met to discuss the proposal for a multicenter study at The Societies for Pediatric Urology Fall Congress in September 2016 in Dallas, Texas, USA. Follow up phone conferences were held several times over the following year. The participants at the initial meeting included attendings, fellows, and residents from pediatric urology and pediatric anesthesiology. Six institutions participated in the original discussions and committed to the study (represented by the authors).

Prior to this work, the study group was only aware of a single pediatric urology ERAS protocol that was adapted for use in patients predominantly with neurogenic bowel and bladder (e.g., myelomeningocele).[12] This was used as a starting point and was similar

to existing adult urology ERAS protocols for radical cystectomy.[14] Modification and addition to this protocol were arrived at by literature review and group consensus. Highlights of the original protocol include omission of formal preoperative bowel preparation, multimodal analgesia with regional blocks for all, no nasogastric tube postoperatively, early feeding (clear liquids in evening after leaving operating room, regular diet following day), and early discontinuation of intravenous fluids by postoperative day 2. **Table 1** lists all 20 ERAS protocol elements defined for the purpose of this study.

The authors identified several important components to add to the original pilot protocol, including ensuring a preoperative clear liquid complex carbohydrate load up to 2 hours prior to surgery and encouraging patients to eat a regular diet the night before surgery. Minimizing *nil per os* duration is crucial to limit metabolic stress, minimize catabolic response from surgery, reduce risk of short term atrophy of the gastrointestinal villi, and protect patients against developing insulin resistance, which has been associated with postoperative complications.[5] Specifically, the study group sought to avoid situations where patients drink only clear liquids for several days prior to the operation, nullifying the intentions of ERAS precepts.

Venous thromboembolism (VTE) prophylaxis was added with the caveat that it should apply only to those patients with certain risk factors (age ≥ 14 years, BMI ≥ 30 kg/m^2, history of VTE, history of malignancy, history of coagulation disorder). The primary recommendation was for sequential compression devices to be placed on the patient prior to induction. No recommendation was made for pharmacologic prophylaxis on the basis that the risk/benefit profile may not make sense in children.[15,16] Since creating

this clinical pathway, there have been new reports regarding clarification of pediatric risk factors for VTE.[16,17] Future revisions of the protocol will require adjustment to match newer evidence.

Normothermia was also added and defined as a core body temperature between 36–38˚C from incision to close time. Any value outside this range nullifies the measure. Maintaining normal temperatures may minimize risk of wound infection in adults.[18,19] Notably, normothermia promotes normal metabolic demands on the body (including pharmacokinetics of anesthetics) and minimizes stress from hypo- or hyperthermic conditions.[20] This was a Surgical Care Improvement Project core measure (SCIP-INF-10).[21] The evidence underlying this measure is not level I, but the study group included it for its importance from a physiologic perspective and to match existing published ERAS principles.

Minimizing surgical drains is another ERAS goal. To adapt this to lower urinary tract reconstruction, it was defined as avoiding placement of intraperitoneal or subcutaneous drains. This measure does not include urinary drains, as the group felt these to be important to protect and maximize drainage of the urinary tract postoperatively as a matter of urologic principle. To account for those patients in whom a clinical decision has been made to leave an intraperitoneal or subcutaneous drain, a postoperative measure was added that any such drains should be removed on or by postoperative day four. This day was proposed on the basis of pilot data showing that many patients are ready to go home and that these drains are rarely helpful.

The remainder of the measures from the pilot study were adopted and definitions updated to be internally consistent and account for most foreseeable scenarios. Refer to **Appendix Table 1** for complete definitions of all 20 ERAS protocol measures. Importantly, the ERAS protocol as defined was to be adopted by all participating centers as standard of care for treatment of patients undergoing urologic reconstructive surgery.

Study Design

Several study designs were debated and discussed, including randomized controlled trials (RCT) of various permutations as well as prospective observational studies. Important characteristics discussed included ensuring both implementation and study design were feasible with minimal overhead, robust data collection through the use of a shared REDCap database, *a priori* defined ERAS protocol definitions and outcomes, inclusion of both pediatric (ages 4-17 years) and emerging young adult (18-25) patients undergoing lower urinary tract reconstruction, and identification of an adequate control group to demonstrate clinically meaningful differences.

Several centers (Children's Hospital Colorado, St. Louis Children's Hospital, and Cincinnati Children's Hospital Medical Center) already had ERAS protocols in place (or started them concurrently during study startup) and randomization by patient was felt to lack equipoise on the basis of pilot data showing substantial patient benefit. Randomization by protocol item was deemed too complex and not feasible. Randomization by surgeon was also felt to lack equipoise, although this is debatable from the standpoint that opposing views on ERAS implementation details may represent unknowable qualities of the intervention. Randomization by center would suffer similar pitfalls identified above. Blinding and allocation concealment are staples of RCTs, but

are not possible in the setting of implementation of a complex protocol involving tens of interventions that touch nearly every aspect of the diffuse perioperative space. Furthermore, ERAS relies on standardization of perioperative care, and having patients on either an ERAS protocol or ad hoc care would necessarily create an unwelcome opportunity for cross contamination issues. A stepped wedge cluster randomized trial design was also considered and is being planned for a separate large multicenter effort in pediatric bowel resection for inflammatory bowel disease.[22] Because two centers in this study group already had existing ERAS protocols, this was not compatible with this option.

The notion that RCT may not be appropriate in all circumstances, particularly within the realm of surgical procedures, is not new and has been discussed previously.[23] There is an applicable framework for advancing surgical care through research and creation of evidence-based practices called the Idea, Development, Exploration, Assessment, and Long-term study (IDEAL) framework.[24] In this classification, surgical innovation passes through several different stages. ERAS in pediatric urology is in the beginning stages and falls under stages 2 (Development) or stage 3 (Exploration), given the ground work shown in two small early studies.[12,13] The IDEAL framework defines goals and methods that are best suited to each stage. At stage 3, prospective study is carried out in either an uncontrolled manner or in smaller size than a full-blown controlled trial. Because of the limitations posed by ERAS, equipoise, and surgeon experience, the study group determined the best study would be a case-control study, with ERAS patients making up a prospective observational arm and propensity-matched controls coming from recent patients not exposed to the ERAS protocol.

After discussion, the study group defined two study phases. First, a pilot phase will assess study recruitment across sites, ERAS implementation, protocol adherence, and study procedures. Second, an exploration phase will prospectively compare all patients on the ERAS protocol to recent historical controls matched on propensity to undergo surgery with utilization of an ERAS protocol, should they have been treated presently, using clinically-important covariates deemed most likely to affect recovery. Data from the pilot study will be fed forward into the exploratory study. The decision for a built-in pilot study allows each center to build comfort level with study procedures along with maturation of the ERAS protocol. From a methodological standpoint, a pilot study is setup like a smaller version of the larger study without the need to define sample size or demonstrate clinically important outcomes but rather examine outcomes related to the setup of the study itself.[25] A built-in pilot component at each center (first five patients) will allow ascertainment of treatment team perceptions of ERAS and barriers to protocol implementation. While five is a small number, high-volume centers only perform 10–15 of these cases per year.[26]

Center Eligibility and Patient Selection

Centers will be allowed to enroll patients in the study if the center performed a minimum of five lower urinary tract reconstructive operations in the year prior to center enrollment. This constitutes a baseline measure of quality and familiarity with the care of these complex patients perioperatively.

Surgeons and research assistants at each respective center will be responsible for subject identification and recruitment through existing clinical relationships. Patients aged of 4–25 years old undergoing the following lower urinary tract reconstructive

operations may be enrolled after providing informed consent (and assent, when applicable): augmentation enterocystoplasty, creation of continent urinary channel (appendicovesicostomy, ileovesicostomy, or colovesicostomy), creation of an antegrade continence enema channel, and incontinent urinary diversions (ileal conduit with or without cystectomy or ileovesicostomy). Because some of these operations may be done with or without a bowel anastomosis—which is a major risk factor for surgical stress, increased operative time, and risk of ileus—bowel anastomosis will be tracked and used for matching cases to controls as it is a strong effect modifier. Some providers noted patients with neurogenic bowel not on a bowel management program (retrograde enemas, oral stool softeners, or rectal suppositories) may be at increased risk prolonged return of bowel function, ileus, bowel obstruction, or anastomotic bowel leak. For this reason, clinically constipated patients defined as Bristol 1 or 2 stools more than once per week, bowel movement interval greater than every other day, or palpable stool in > 50% of colon on physical preoperative exam will be excluded from the study. Patients with these findings become eligible if their stooling pattern is addressed at least 4 weeks in advance of surgery with implementation of a bowel management program continued up to the night before surgery.

The use of historical controls has long been felt to be controversial, secondary to the retrospective nature of their identification and data collection and potential biases. Using quality improvement methodology, in which historical controls are often used to compare outcomes to an intervention cohort, run diagrams and interrupted time-series analysis can provide insight into changes occurring over time with regards to either process, clinical outcome, or balancing measures.[27] This has the benefit of ensuring

that the prospectively enrolled patient outcomes are attributed to the intervention (ERAS) and not to changes in patient care that were already underway prior to implementation. While use of prospective controls from non-ERAS institutions might serve as a better comparison (reduced bias, prospective data collection, parallel comparison of modern surgical patients undergoing similar operations), the study group felt that observational bias (Hawthorne effect) might influence malleable outcomes such as length of stay.

Outcome Measures

The pilot phase outcomes of interest include enrolling a minimum of two patients per center in first six months, and completing at least 90 days follow up on the first five enrolled patients (**Figure 1**). A goal of ≥ 70% protocol item adherence (out of 20) at ≥ 75% of study centers was set. Finally, barriers to implementation will be identified and may determine if there is a need to optimize the protocol for wider application.

The primary outcome of the exploratory phase is adherence to the ERAS protocol with number of items achieved (out of 20). Secondary outcomes include length of stay, 30-day readmissions, 90-day reoperations, 90-day returns to the emergency room, 90-day complications by Clavien-Dindo classification (see **Table 2** for full list of defined complications), number of long-term complications within 1 year (**Table 3**), minimum, median, maximum daily pain score during first 7 days after surgery, and mean daily IV morphine equivalents (mg/kg) usage during first 3 days after surgery.[28] It is important to clarify that because this is an observational trial and the ERAS protocol is

implemented as standard of care at each center, the collection of complications here is a clinical outcome measure rather than one seen as a result of study intervention.

In addition to the objective clinical outcomes listed, patient- and family-reported outcome measures will be administered to assess the impact of surgery on work and school (e.g., missed days of each) and adjustment time at home needed to return to "normal" (i.e., daily routines not impacted heavily by having had surgery). These instruments include open-ended, non-validated parent and child surveys to be given pre- and postoperatively, and a Quality of Recovery 9 questionnaire to assess overall return of function (given before and after surgery, and again at clinic follow up).[29] **Figure 2** demonstrates which outcome measures will be tracked over time with respect to the index surgery. Patients will be followed for one year, specifically to ensure that patients with a ventriculoperitoneal (VP) shunt do not experience increased rates of externalization, infection, or revision which has long been a concern of the community.[30]

Data Collection

A shared REDCap database has been designed, tested, and implemented for use for this study. Data use agreements have been executed between centers and data sharing language was incorporated into patient consent to allow sharing of de-identified data sets maintaining patient confidentiality. The majority of perioperative process, outcome, and balancing measures are charted within the medical record as part of standard of care. Where possible, these will be automatically abstracted electronically as five out of the six study centers use the Epic electronic health record system. In cases where data is not normative or where it requires clincal interpretation or cannot be abstracted

electroncially, manual chart review by research assistants trained by the study team will be done. Continuous data quality checks will be completed quarterly, including analysis of missing required data and any discrepancies.

After primary accrual is completed, the study committee plans to transition the shared database into a shared clinical registry for ongoing data collection to continue to study ERAS and further refinements to the care pathway.

Statistical Analysis

A total of 64 ERAS patients will be needed to detect a decrease in mean overall LOS by 2 days, with type I error of 5% (false positive) and type II error of 20% (false negative) based on data from the pilot study showing mean LOS of 8.0 days (SD 7.3) for historical patients versus 5.7 days (SD 5.1) for patients who were treated under the ERAS protocol. Patients will be propensity score-matched on likelihood to have been treated under an ERAS protocol 1:2 to recent historical controls from 5 years prior to the initiation of the ERAS protocol. Propensity matching controls for measured baseline covariates before analysis of the outcomes to reduce confounding. Based on pilot data (mean 2.1 complications/patient [SD 1.9] historically and versus 1.3 complications/patient [SD 1.2] under ERAS), this study will also be powered to detect a decrease in any grade complications per patient by 50%. Patients will be divided into two strata: those who underwent and did not undergo a bowel anastomosis as part of the index operation. Propensity score-matching within the two strata using nearest-neighbor algorithm (also referred to as greedy matching) will occur on the following variables: age, sex, chronic kidney disease, presence of VP shunt, planned bladder augmentation, history of prior abdominal surgery (other than VP shunt), diagnosis of

myelomeningocele, ambulatory status, and center. Bowel anastomosis was determined by the study group to be a strong effect modifier and thus patients will be exactly matched on that variable (creating two strata) and propensity matched on remaining covariates to avoid overfitting.

Because of the nature of propensity-matched data, care must be taken for comparison of historical controls and ERAS cases. Differences in baseline characteristics between matched groups will be assessed using methods that are not influenced by sample size and that do not refer to a hypothetical population (i.e., standardized differences).[31] The Mantel-Haenszel test will be used to compare proportions, and generalized linear modelling with generalized estimating equations to adjust for the matching design will be used to assess association of outcomes and predictors.[32] Two-tailed p-values < 0.05 will be considered significant. No interim analyses are planned.

Study Committee

Given the importantance of a strong implementation serving as a foundation for success, the study group has created several committees, including an organizing committee and audit committee. The organizing committee is charged with overseeing data collecion, arranging study conference calls and meetings and adjudicating authorship for subsequent papers laid out through a set of bylaws. The organizing committee serves as a backstop to proper trial conduct under the purview of study (KOR) and site primary investigators (ACS, GJV, RC, DIC, CDAH). The audit committee arguably serves a more important role, overseeing regular clinical audits of ERAS protocol compliance. The committee is charged with meeting after each center's pilot phase (5 patients) and ad hoc thereafter, and they will review overall compliance and

serve as an external study group as part of plan/do/study/act (PDSA) quality improvement methodology to identify challenging areas and suggest solutions that may be novel for that center. This highlights the point that the ERAS clinical pathway sets high-level goals, but leaves implementation details and specifics to each center. This creates heterogeneity that mirrors real-world quality improvement projects, improving the generalizability of the project, but can lead to maladaptive internal center processes. The audit committee's goal is to help each center identify issues early in the implementation and aid with finding creative solutions.

Stengths and Limitations of the Study Design

Strengths of this study design include its multicenter nature, which the authors aim to use to demonstrate feasibility of ERAS implementation in a variety of geographically-diverse pediatric-focused settings. Prospective data collection, *a priori* definitions of protocol elements, and an exhaustive list of potential short and long-term complications also lend strengths to its design. The SPIRIT checklist was used when preparing this report.[33] Potential limitations of this study include variation in protocol implementation, unsuccessful attempts at protocol implementation, unobserved patient characteristics or other biases affecting outcome measures, and use of historical, retrospective controls. The study group notes that there is very little level I evidence for protocol items in pediatric patients. Some are extrapolated from adult evidence and may not hold true. Additionally, patient-reported outcomes in this population are lacking. Pain interference and validated general function measures are available but were not designed nor tested expressly to measure recovery after surgery. When examining clinical outcomes, propensity matching on clinically-relevant patient characteristics will allow meaningful

comparison, and run charts of patient care variables over time will shed light on any changes in care patterns or outcomes that may have already been underway.

Ethics and Dissemination

This study was approved by each free-standing tiertiary care children's hospital respective institutional review board (St. Louis Children's Hospital 201703081, Children's Hospital of Pittsburgh 17070089, Children's Hospital Colorado 17-0746, Cincinnati Children's Hospital Medical Center 2017-3322, Ann & Robert H. Lurie Children's Hospital 2019-2566, and Children's Hospital of Richmond at VCU HM20015891). Prospectively enrolled patients who meet inclusion criteria will be approached for inclusion by either a urologist or research assistant prior to the day of surgery. Study protocol does not allow for patients to be approached in the preoperative area to avoid patient or family coersion. No study activites will occur prior to obtaining consent. Patients under 18 years age (and over specific ages that vary by center) will assent to enrollment. Participants retain the right to withdraw at any point for any reason. Importantly, non-adherence to the ERAS protocol or ERAS protocol deviation is not grounds for removal from the study. Not every patient will necessarily meet clinical standards for every protocol item. Rather, the goal of the ERAS protocol is to maximize evidence-based strategies to return the patient to normal function. ERAS protocol changes will only be made after completing primary accural and analysis of results in conjuction with a thorough literature review by the study committee. Patient and families will be engaged in future revisions of the underlying ERAS clinical pathway that result from evidence gathered through this study.

In conclusion, Pediatric Urology Recovery After Surgery Endeavor (PURSUE, ClinicalTrials.gov NCT03245242) is a multicenter, prospective propensity-matched case-control cohort study that will examine outcomes in pediatric and emerging young adult patients undergoing lower urinary tract reconstruction who receive care under an ERAS pathway.[34] Results will be published in peer-reviewed journals by study group members. This protocol marks the first phase of a collaborative quality improvement effort within the pediatric urology community to improve and standardize care of patients undergoing urologic reconstructive surgery.

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PURSUE study group members: Douglas E. Coplen (St. Louis Children's Hospital, St. Louis, MO, USA), Paul F. Austin (Texas Children's Hospital, Houston, TX, USA), Erica J. Traxel (St. Louis Children's Hospital, St. Louis, MO, USA), Jacob AuBuchon (St. Louis Children's Hospital, St. Louis, MO, USA), Robert P. Moore (St. Louis Children's Hospital, St. Louis, MO, USA), Vijaya M. Vemulakonda (Children's Hospital Colorado, Aurora, CO, USA), Brian T. Caldwell (Children's Hospital Colorado, Aurora, CO, USA), Carter J. Sevick (Children's Hospital Colorado, Aurora, CO, USA), Nicholas Burjek (Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA), Elizabeth B. Yerkes (Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA), Yvonne Y. Chan (Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA), C.D. Anthony Herndon (Children's Hospital of Richmond at VCU, Richmond, VA, USA)

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Conflict of Interest

None

Author Statement

KOR, BTC, and DTW organized the initial meeting to discuss study protocol concepts in Dallas, TX, USA in 2016. KOR, MAB, TPW, DIC, DTW, and GJV developed and refined

the 20-protocol ERAS pathway used in the study based on literature searches, screening and review. KOR led protocol development and created patient recruitment tools. KOR, MAB and ACS chair the PURSUE organizing committee that oversees study activities. KOR is the study primary investigator. KOR, ACS, CDAH, RC, DIC, GJV serve as site primary investigators. KOR performed the power analysis and statistical analysis plans with additional input, oversight and revision by DIC. KOR, ACS, DTW, GJV, TPW, BV, DIC, RC, RZ, PURSUE Study Group and MAB were involved in the study conception, design, protocol manuscript drafting and critical revision. All authors approve the final version.

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Figure Legends

Figure 1. Overview of study conception, implementation, center eligibility, patient inclusion and exclusion criteria, and design methodology arrived at through group consensus.

Figure 2. Timeline of patient enrollment, data collection including process and balancing measures, clinical outcomes, and patient-reported outcome measures during the PURSUE study.

Tables

Table 1. Comprehensive list of pre-, intra-, and post-operative ERAS protocol items targeted by the care pathway, customized for pediatric urology patients. The definitions for these items were arrived at through multidisciplinary consensus of the study group.

Pre-operative	Intra-operative	Post-operative
Counsel about ERAS	Regional anesthesia (catheter-based block)	Nausea/vomiting prevention
Clear-liquid carbohydrate load (10 mL/kg up to 350 mL)	Avoiding excess drains (intraperitoneal or subcutaneous)	Early feeding (clears POD 0, regular POD 1)
Avoid prolonged fasting (eat regular diet and avoid prolonged clears-only diet day prior to surgery)	Euvolemia (4–7 mL/kg/hr crystalloid)	Early mobilization (out of bed POD 1)
No bowel preparation (continue bowel regimen if on one)	Normothermia (36–38˚C during skin-to-skin time)	Adjunctive pain medication (acetaminophen and NSAID)
Antibiotic prophylaxis per AUA guidelines	Minimizing opioids (< 0.15 mg/kg IV morphine equivalents)	Early stoppage of intravenous fluids (either discontinue or lower rate to keep vein open [TKO] by POD 2)
DVT prophylaxis (≥ age 14 or risk factors)	Minimally-invasive assistance (at surgeon discretion)	Early removal of extra drains/catheters (non-urinary drain removal by POD 4)
	No nasogastric tube on leaving OR	Minimizing opioids (< 0.30 mg/kg/day IV morphine equivalents)

Table 2. List of pre-defined postoperative short-term complications.

90-Day Short-Term Complications
Clavien Grade I
electrolyte disturbance
fever (≥ 38˚C)
IV complication (infiltration)
nausea / vomiting
neuropraxia (positioning complication)
transient elevation in Cr (acute kidney injury)
wound dehiscence
incisional seroma
other grade I
Clavien Grade II
blood transfusion
catheter manipulation, ACE
catheter manipulation, Mitrofanoff / Monti / urethral / SPT ± urinary retention
ileus requiring NG tube ± TPN + nausea / vomiting
infection / bacteremia treated with Abx ± fever
infection / pyelonephritis treated with Abx ± fever
infection / superficial wound treated with bedside drainage, Abx ± fever
infection / UTI treated with Abx ± fever
infection / GI infection with Abx ± fever ± diarrhea
venous thromboembolism
lymphocele or chylous ascites treated conservatively with diet changes
other grade II
Clavien Grade III
abdominal abscess requiring IR / OR drainage
catheter malfunction / loss requiring placement in OR
fascial dehiscence / evisceration treated in OR
hemorrhage requiring embolization or OR
small bowel obstruction treated surgically in OR
urinoma requiring IR / OR drainage
ureteral obstruction requiring PNT by IR / OR
lymphocele or chyle leak requiring IR / OR drainage or intervention
other grade III
Clavien Grade IV
respiratory failure requiring ventilation
renal failure
multiorgan failure
sepsis
other grade IV
Clavien Grade V
death

Table 3. List of pre-defined postoperative long-term complications.

1-Year Long-Term Complications
channel stenosis (any level) requiring revision
channel false passage
bowel obstruction
bladder stone formation
bladder perforation
incisional hernia
new onset metabolic acidosis
new onset chronic kidney disease
new onset renal scarring
VP shunt externalization
VP shunt infection (positive shunt tip and cerebral spinous fluid cultures)

Appendix Table 1. Specific definitions of 20 ERAS process measures for pediatric lower urinary tract reconstructive operations.

Phase of case	Measure	Definition
Preoperative	Counseling about ERAS	This will typically be done as part of the consent process. Patients/families should not have their sole counseling occur in the preoperative area. Patients/families will be provided a standardized handout on ERAS and what to expect from surgery throughout the process from preoperative all the way through follow up.
	Clear-liquid carbohydrate load	Patients will be provided a commercially-available complex clear liquid carbohydrate liquid preoperatively. Patients will drink 10 mL/kg up to maximum of 350 mL (1 bottle) in the 3 to 2 hours prior to surgery in concert with American Society of Anesthesiologists (ASA) guidelines. If not available, other carbohydrate-rich clear liquids are also permissible on protocol, including Gatorade, PowerAde, Pedialyte. If the patient has a G-tube, these liquids can be administered per G-tube. Water should not be used. Other liquids outside this list are not permissible as part of the protocol.

Phase of case	Measure	Definition
	Avoid prolonged fasting	Patients will remain adherent to ASA guidelines for pediatric patients. These include: solids up to 8 hours, non-human milk up to 6 hours, breast milk up to 4 hours, and clear liquids up to 2 hours prior to surgery. Patients should not be placed on an extended clear liquid diet prior to surgery. Patients should be encouraged to eat and drink normally up to the scheduled *nil per os* (NPO) guidelines stated above. If the patient does not eat > 24 hours prior to surgery or was placed on an extended clear liquid diet (no solid food on day before surgery) or did not receive normal G-tube feedings, if applicable, patient will not meet this criterion.
	No bowel preparation	Patients will not receive oral laxatives, suppositories, oral antibiotic agents or other bowel prep agents outside of the patient's normal regimen (if on one). Many patients undergoing urology reconstruction have concomitant neurogenic bowel and are already on bowel programs which may include daily antegrade or retrograde enemas or oral laxatives. These should be maintained up to the day prior to surgery. Patients should be evaluated adequately (clinical history) well in advance of surgery to ensure they are not constipated. Clinical judgement should be used to modify any bowel regimen program at least 4 weeks prior to scheduled OR date.
	Antibiotic prophylaxis	Perioperative antibiotics should be administered within the guidelines of the American Urological Association and best hospital practices. AUA guidelines state that prophylaxis should consist of a weight-based dose of 2nd/3rd generation cephalosporin (e.g., cefoxitin) or alternatively an aminoglycoside + metronidazole or clindamycin (e.g. gentamycin + metronidazole) to be administered within 60 minutes of procedure start time (cut time). If patients have allergies or clinical conditions that preclude these, alternatives include ampicillin/sulbactam, ticarcillin/clavulanate, piperacillin/tazobactam or a fluoroquinolone. If patient is felt to have a UTI pre-operatively or has colonization, alternative antibiotic regimens tailored to recent culture results may be used. Antibiotics in most cases should be re-dosed in the operating room according to local standard and be discontinued within 24 hours of surgery per guidelines, but may be continued at the discretion of the surgeon based on clinical circumstance.
	DVT prophylaxis	Patients with one or more risk factors should have sequential compression devices (SCDs) placed on the lower extremities prior to induction of anesthesia. This will be verified by intraoperative nursing documentation. Risk factors include obesity (BMI ≥ 30), age ≥ 14, history of malignancy, or history of venous thromboembolic event. Patients who do not have any risk factors may safely omit any prophylaxis per standard of care. SCDs should be removed at the end of the case to encourage early mobility once reaching the surgical floor.

Phase of case	Measure	Definition
Intraoperative	Regional anesthesia	Standard clinical judgement of the multidisciplinary team (urologists, anesthesia) in concert with patient/family wishes should be used to offer regional catheter-based anesthesia to all patients. Options include wound soakers, transversus abdominus plane (TAP) catheters, quadratus lumborum (QL) catheters, erector spinae plane (ESP) catheters, or epidural. If planning wound soakers, TAP/QL/ESP catheters at the end of the case, preoperative TAP blocks performed by anesthesia using 0.2 mL/kg of 0.2–0.5% Ropivacaine should be injected on each side under ultrasound guidance. Wound soakers, TAP catheters, quadratus lumborum catheters or wound catheter pain pumps should be filled with 0.2% ropivacaine and connected to an epidural infusion pump to provide a continuous rate determined by the patient's weight (0.05 mL/kg/hr, maximum 0.5 mg/kg/hr). The infusion rate can be adjusted or stopped to monitor alternative analgesics prior to catheter removal. Epidurals can be run according to standard of care at each institution, although by protocol should not include a narcotic/opioid. Initial concentrations and rates for all regional anesthetic regimens will be documented. Duration of therapy will be documented. Wound soakers, TAP/QL/ESP catheters, and epidural catheters are to be left in place up to 5 days post-operatively or at clinical discretion of treating physicians within standard of care. They can be removed on day of discharge. Those left in longer than day 5 should have documented reason. Drainage around pain catheters can occur. This is normal. Dressings should be reinforced prior to scheduled removal. The risk of infection of pain catheters is generally small, but if concern exists, clinical judgement should be used as to the disposition of the pain catheters and documented. If none of the above are deemed clinically appropriate, bilateral transversus abdominis plane (TAP) blocks, caudal blocks or paravertebral blocks can be performed by the surgical or anesthesia team either through the surgical field or ultrasound guided. These do not count, however, for this protocol item given their limited duration of effectiveness for the patient. Blocks (as opposed to catheter-based postoperative therapies) do not provide continuous post-operative anesthesia to the wound beyond 6-12 hours. Justification of the use of blocks over other continuous regional options should be documented.
	Avoiding excess drains	There is wide variability in the use of surgical drains by surgeons, according to local practice, experience and clinical scenario. Urologic reconstruction, though, typically requires drains in the form of catheters across newly-constructed catheterizable channels or catheters to drain the urinary tract to keep it under low pressure during healing. To meet this criterion, patients should not have a drain placed intraabdominally, in the space of Retzius, or subcutaneously. Acceptable catheters include: suprapubic tube, antegrade continence enema channel, appendicovesicostomy/ileovesicostomy/colovesicostomy, and/or urethral catheters. The duration of therapy will be according to surgeon preference.

Phase of case	Measure	Definition
	Euvolemia	Hydration statuses of patients can vary greatly and are highly dependent on pre-operative fasting conditions, concomitant medical diagnoses like diabetes insipidus, and intraoperative fluid shifts related to insensible losses from an open abdomen, urine output and blood loss. Surgery involving the genitourinary tract can often be difficult because urine output cannot be recorded accurately throughout the case, which is often an indicator of fluid status and response to intraoperative intravenous fluid resuscitation. The goal is to maintain euvolemia and avoid bowel edema and subsequent ileus while maintaining safe cardiopulmonary function, end organ perfusion and offsetting bodily fluid and insensible losses. To meet this criterion, a goal of an average intravenous fluid volume between 3 and 7 mL/kg/hr as calculated according to the patient's preoperative weight and time from in room time to out of room time. Blood loss not requiring transfusion can be replenished in a 3:1 ratio of crystalloid to blood or 1:1 ratio of colloid to blood. Intravenous pressors should be considered to improve hemodynamics as opposed to fluid boluses. Some patients with preexisting comorbidities like diabetes insipidus may require greater than usual fluid volumes to maintain euvolemia. Such instances should be well-documented and justified.
	Normothermia	Patient's temperature should be maintained between 36°C to 38°C throughout the intraoperative period (skin-to-skin time). This can be done with a combination of warming blanket and/or alteration of the operating room environmental controls. To minimize variability, esophageal temperature monitoring should be used. Anesthesia record will be used to verify this item. Any value outside this range will not count.
	Minimizing opioids	There is no well-accepted clinical standard for minimizing intraoperative opioids. Data gathered during a pilot study were used as a basis for this definition. Patients will have met this criterion if they receive < 0.3 mg/kg IV morphine equivalents intraoperatively. This is equivalent to a total of 3.6 mcg/kg fentanyl IV. As a guideline for intraoperative opioid usage, providers may opt for no intraoperative opioids so long as the patient has some form of regional anesthesia on board starting at the beginning of the case and they show no signs of pain response. Alternatively, we recommend fentanyl may be administered in 1-2 mcg/kg doses with induction, prior to incision, and as deemed appropriate throughout the procedure by the anesthesiologist for analgesia. Opioids should only be used if clinically indicated. This total dosage equates to about 75% of mean post-operative day 0 IV morphine equivalent usage across all patients in the Phase I/II study. The last 25% of mean post-operative day 0 IV morphine equivalent is allocated toward post-operative pain control in the recovery unit or hospital ward. Patients should have their pain adequately controlled as necessary in accordance with standard of care. If pain assessments determine there is inadequate pain control, all pain pathway items should be reassessed by nursing, surgical and anesthesia teams to maximize pain control as best as possible in accordance to the ERAS pathway where possible.
	Minimally-invasive assistance	Where technically and clinically feasible, surgeons should endeavor to perform part of the surgery with either laparoscopic or robotic assistance. In many cases, the cecum, appendix and terminal ileum can be mobilized into the pelvis to allow for reconstruction through a smaller muscle-splitting Pfannenstiel incision with minimization of time the peritoneum is open. This minimizes insensible fluid losses and fluid shifts. Surgeon judgement and experience will heavily influence this part of the pathway, but should be given consideration. If laparoscopic or robotic assistance is used in any part, this criterion will be met. Of note, this item is not meant to indicate that the entire operation need be done laparoscopically or robotically. Surgeon judgement is paramount.

Phase of case	Measure	Definition
	No nasogastric tube on leaving operating room	No nasogastric (NG) tube shall be placed intraoperatively by the anesthesia team. An orogastric (OG) tube may be placed temporarily to drain stomach contents if felt necessary, but should be otherwise avoided. Placement of OG intraoperatively by definition must be removed at the end of surgery. Placement of NG tube on leaving the OR shall be documented and not qualify for this item. Patients who develop ileus and clinically require NG tube during the post-operative period still qualify for this item if no NG tube was used on leaving the OR. Such patients will require documentation of circumstances of secondary NG tube placement.
Postoperative	Nausea/vomiting prevention	Patients without clinical contraindications shall be written for weight-based antinausea prophylaxis, typically ondansetron to be given as needed on admission to the PACU or floor. Orders wills be used to verify this item. Alternatives to ondansetron such as promethazine, diphenhydramine or a scopolamine patch may be used at the discretion of the ordering physician. Regimen will be documented.
	Early feeding	Patients should receive clear liquids on the evening of surgery (counted as postoperative day 0) and regular diet starting on day after surgery (postoperative day 1). Regular diet should have no restrictions outside of clinically-indicated patient needs (e.g., soft, bland, purée, etc.). Presence of orders to this effect on the specified days will be used to verify this item.
	Early mobilization	Patients should be out of bed in some fashion on post-operative day 1. This may include transfer to a chair, ambulation with or without assistance as deemed clinically safe and feasible by the surgical team and nursing staff. Patients who do not get out of bed will not have met this criterion. Similarly, sitting on the edge of the hospital bed is not considered sufficient to meet this criterion. Activity should be encouraged and increased each subsequent hospital day. Nursing documentation of activity will be used to verify this item.
	Adjunctive pain medication	Patients should be scheduled initially (not written prn or as needed) to receive a weight-based based dose of acetaminophen and/or NSAID therapy. These may be given orally or parenterally. To meet this item, these should be scheduled after surgery for 24 hours and can then be transitioned to as needed at the discretion of the care team. If these are written as needed on leaving the operating room, patient will not receive credit for this item. In accordance with clinical standard of care, patients who have contraindications to receiving either medication (e.g. allergy, liver disease, chronic kidney disease, etc.) should not be written for them. Patients should have their pain adequately controlled as necessary in accordance with standard of care. If pain assessments determine there is inadequate pain control, all pain pathway items should be reassessed by nursing, surgical and anesthesia teams to maximize pain control as best as possible in accordance to the ERAS pathway where possible.
	Early stoppage of intravenous fluids	Patients who have tolerated oral intake (no prerequisite amount is defined) and who are clinically stable according to standard of care should have their intravenous maintenance fluids turned off (saline locked) by post-operative day 2. “To Keep Open” or TKO rates are permissible. Patients who are not well, are vomiting, have ileus or have an NG tube should not have their IV fluids removed and will not meet this criterion.
	Early removal of extra drains/catheters	If no drain was left outside the urinary tract at the time of surgery, then the patient will automatically qualify for this ERAS protocol item. If a drain was left intentionally outside the urinary tract, then it should be removed by or on post-operative day 4. If there are clinical circumstances that require the drain be continued, then the clinical team should keep it in place and document reasoning.

Phase of case	Measure	Definition
	Minimizing opioids	There is no well-accepted clinical standard for minimizing postoperative opioids. Data gathered during a pilot study were used as a basis for this definition in addition to prior study data regarding the decreased need for postoperative opioids in the setting of wound soakers. Patients will have met this criterion if they receive < 0.15 mg/kg/day IV morphine equivalents averaged over the first 3 post-operative days. This equates to less than all the postoperative IV morphine equivalent usage for 11 of 13 patients in the pilot study, where nurses were informed to use opioids only for breakthrough pain control. This is equivalent to an average of 3 weight-appropriate doses of IV morphine, IV hydromorphone or oxycodone per day. Communication with nursing staff (day and night shift nurses) and anesthesia team is key to minimizing opioid usage. Patients should have their pain adequately controlled as necessary in accordance with standard of care. If pain assessments determine there is inadequate pain control, all pain pathway items should be reassessed by nursing, surgical and anesthesia teams to maximize pain control as best as possible in accordance to the ERAS pathway where possible.

Planning

Initial meeting at SPU Fall Congress 2016 (Dallas, TX)
Study designs debated
ERAS protocol defined
Power analysis and statistical planning

IRB

Shared REDCap database
Multicenter design with data use agreements
ERAS programs implemented as standard of care
Study is observational, no medical interventions
Prospective ERAS arm with matched historical controls
All patients / families consent prior to enrollment
Register with ClinicalTrials.gov (NCT03245242)

Pilot

Enroll 2 patients in first 6 months per center
Pilot phase ends after 5th patient at center
Outside process measure compliance audit
Goal = ≥ 70% protocol adherence
Provider surveys (before and after pilot)
Patient / Family survey pre- and post-op
Quality of Recovery 9 instrument

Exploratory

Enroll 64 ERAS patients (across all centers)
Compare to 128 propensity-matched historical controls
- matched on age, sex, diagnosis, prior surgery, center, type of operation, ambulatory status, VP shunt

1 year follow up
Primary outcome: protocol adherence
Secondary outcomes: LOS
re-admissions within 30 days
re-operations within 90 days
ED visits within 90 days
Clavien-Dindo complications
max/mean pain scores
opioid usage (mg/kg IV morphine equivalents)
patient-reported outcome measures
VP shunt infections, other surgical complications after reconstruction to 1 year

Center eligibility:

- must have performed 5 or more target operations in the last year

Inclusion criteria:

- 4 to 25 years old
- undergoing urologic reconstructive operation that includes one or more of the following:
  - bladder augmentation
  - appendicovesicostomy (Mitrofanoff)
  - ileo- or colovesicostomy (Monti)
  - ileocecostomy (Monti-MACE)
  - urinary diversion requiring a bowel anastomosis

Exclusion criteria:

- **clinically constipated** (Bristol 1 or 2 stools more than once per week, bowel movement interval > every other day, or palpable stool in > 50% of colon on pre-operative physical exam)

Figure 1. Overview of study conception, implementation, center eligibility, patient inclusion and exclusion criteria, and design methodology arrived at through group consensus.

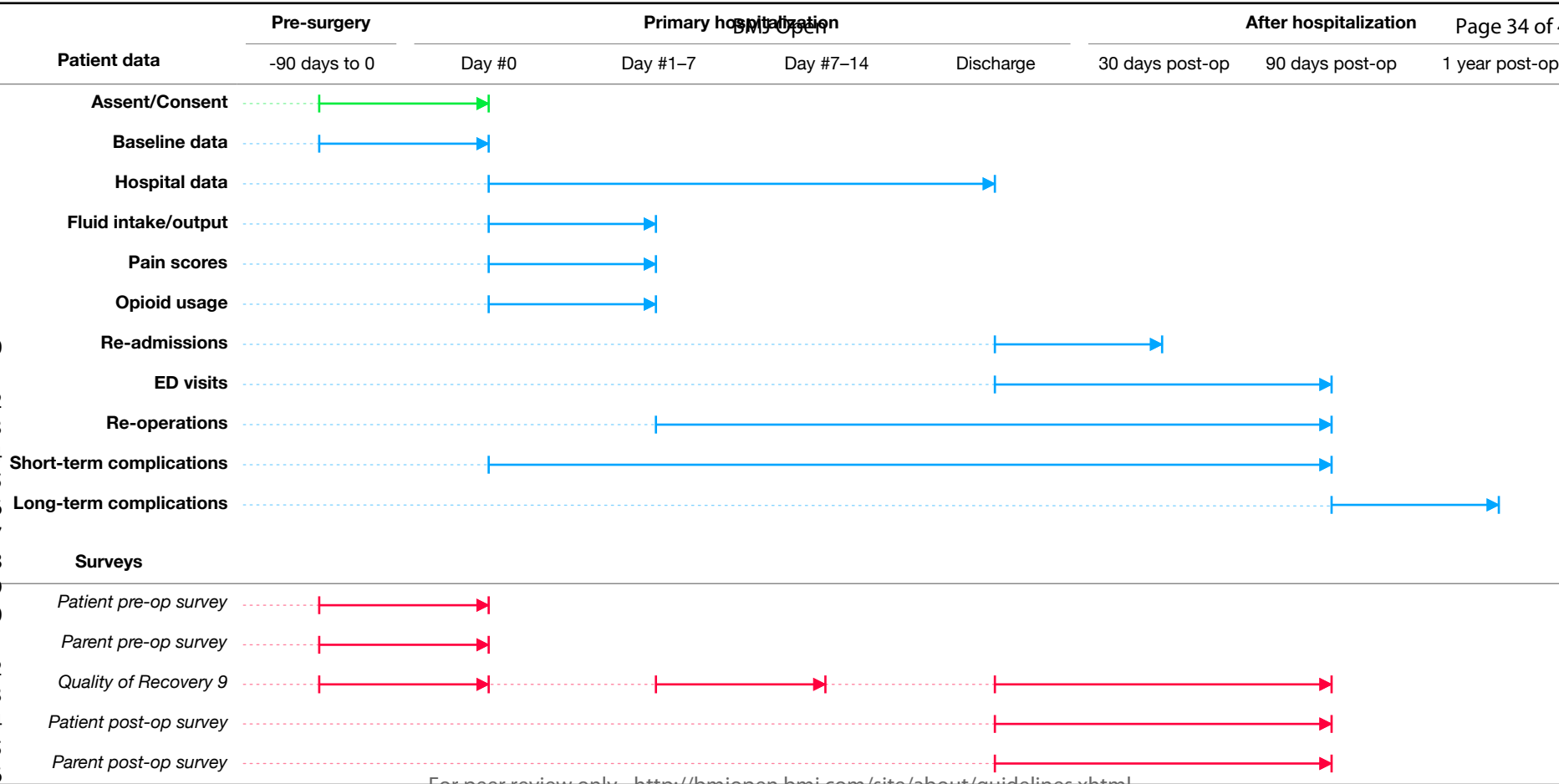

Figure 2. Timeline of patient enrollment, data collection including process and balancing measures, clinical outcomes, and patient-reported outcome measures during the PURSUE study.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 11, 16
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a - these are all listed on the clinicaltrials.gov website
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	16

contributorship			
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a - this is an investigator-initiated study
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	14
Objectives	#7	Specific objectives or hypotheses	9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants,			

interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	17-18
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	15-16
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a - this is an observational study
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)		14
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations		14
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size		11
Methods: Assignment of interventions (for controlled trials)				
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a - not a randomized controlled trial	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a - not a randomized controlled trial	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a - not a randomized controlled trial	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts),	n/a - not a randomized controlled trial	

		and how	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a - not a randomized controlled trial
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14-15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14-15

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15-16
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15-16
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial	17

		participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a - no additional collection of biological specimens is stipulated as part of this observational study
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a - given the observational nature of this study and implementation of ERAS as standard of care, any adverse clinical outcomes are deemed expected as part of the course of treatment and not the study itself
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
Dissemination	#31b	Authorship eligibility guidelines and any	17

policy: authorship		intended use of professional writers	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a - there are currently no plans for public sharing of the data set
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	17
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a - none are collected as part of the study

Notes:

- 2b: n/a - these are all listed on the clinicaltrials.gov website
- 5b: n/a - this is an investigator-initiated study
- 11d: n/a - this is an observational study
- 16a: n/a - not a randomized controlled trial
- 16b: n/a - not a randomized controlled trial
- 16c: n/a - not a randomized controlled trial
- 17a: n/a - not a randomized controlled trial
- 17b: n/a - not a randomized controlled trial
- 26b: n/a - no additional collection of biological specimens is stipulated as part of this observational study
- 30: n/a - given the observational nature of this study and implementation of ERAS as standard of care, any adverse clinical outcomes are deemed expected as part of the course of treatment and not the study itself
- 31c: n/a - there are currently no plans for public sharing of the data set
- 33: n/a - none are collected as part of the study This checklist was completed on 25. March 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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Design and Development of the Pediatric Urology Recovery After Surgery Endeavor (PURSUE) Multi-Center Pilot and Exploratory Study

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Design and Development of the Pediatric Urology Recovery After Surgery Endeavor (PURSUE) Multi-Center Pilot and Exploratory Study

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Abstract word count: 299 words (300 word limit)
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Abstract

Introduction:

Lower urinary tract reconstruction in pediatric urology represent a physiologiclly-stressful event that is associated with high complication rates, including readmissions and emergency room visits. Enhanced Recovery After Surgery (ERAS) protocol is a set of multidisciplinary, perioperative strategies designed to expedite surgical recovery wihtout adversely impacting readmission or reoperation rates. Early pediatric urology data demonstrated ERAS reduced complications in this population.

Methods and Analysis:

In 2016, a working group of pediatric urologists and anesthesiologists convened to develop an ERAS protocol suitable for patients undergoing lower urinary tract reconstruction and define study process measures, patient-reported outcomes, and clinically-relevant outcomes in pediatric and adolescent/young adult patients.

A multicenter, prospective, propensity-matched, case control study design was chosen. Each center will enroll five pilot patients to verify implementation. Subsequent enrolled patients will be propensity matched to historical controls. Eligible patients must be aged 4 to 25 years and undergoing planned operations (bladder augmentation, continent ileovesicostomy or appendicovesicostomy, or urinary diversion). 64 ERAS patients and 128 controls will be needed to detect a decrease in mean length of stay by two days.

Pilot phase outcomes include attainment of ≥70% mean protocol adherence per patient and reasons for protocol deviations. Exploratory phase primary outcome is ERAS protocol adherence, with secondary outcomes including length of stay, readmissions, reoperations, emergency room visits, 90-day complications, pain scores, opioid usage, and differences in Quality of Recovery 9 scores.

Ethics and Dissemination:

This study has been registered with authors' respective institution review boards and will be published in peer-reviewed journals. It will provide robust insight into the feasibility of ERAS in pediatric urology, determine patient outcomes, and allow for iteration of ERAS implementations as new best practices and evidence for pediatric surgical care arise. We anticipate this study will take 4 years to fully accrue with completed follow up.

Registration Details:

Pediatric Urology Recovery After Surgery Endeavor (PURSUE, ClinicalTrials.gov NCT03245242) is a multicenter, prospective, case-control study that will examine outcomes in pediatric and adolescent/young adult patients undergoing lower urinary tract reconstructive operations who receive care under an ERAS pathway.

Article Summary

Strengths and Limitations of This Study

- This protocol outlines a multicenter, prospective propensity score-matched cohort study of an Enhanced Recovery After Surgery (ERAS) protocol applied to pediatric and adolescent/young adult patients undergoing lower urinary tract reconstructive surgery.

- Each participating free-standing pediatric center will take part in a pilot phase to understand barriers to implementation, protocol compliance, and protocol uptake and an exploratory phase to demonstrate clinical outcomes related to the ERAS care pathway as compared to propensity matched recent historical controls.

- Primary and secondary outcomes of interest are relevant to the underlying quality improvement initiative to implement a standardized care pathway (ERAS), reflect clinical outcomes, and include patient-reported outcome measures to understand the patient and family perspective.

- The comparator group will be recent historical patients who have undergone the same operations. Propensity score matching based on *a priori* identified covariates will be used to reduce confounding based on non-random assignment of perioperative care (e.g., routine care versus ERAS protocol). Time-series analysis will provide insight into any ongoing changes occurring over time with regards to either process, clinical, or balancing measures.

Introduction

Background

Lower urinary tract reconstruction represents some of the most challenging surgical operations performed by pediatric urologists. These operations can be long, complex, and often involve a bowel resection and anastomosis. Patients undergoing these operations are at high risk for postoperative complications, including nausea and vomiting, ileus, surgical site infection, urinary tract infection, and pyelonephritis.[1] To date, the optimal perioperative care for these patients has not been well-defined, with practices varying widely from institution to institution.[2,3]

Relevance

Since its initial description in the late 1990s, enhanced recovery after surgery (ERAS) has emerged as an innovative tool in the care of adult surgical patients. ERAS represents a multidisciplinary protocol with a strong implementation framework that targets all phases of care for the surgical patient.[4] ERAS has been shown in various adult surgical populations to maintain adequate pain control and facilitate earlier return to baseline function without adverse impact on complication or readmission rate through evidence-based care.[5-7] A large multicenter ERAS study of adult colorectal resection and hip fracture repairs demonstrated clinically-significant reductions in length of stay (0.4–0.9 days), postoperative major complications (rate ratio 0.28 compared to pre-ERAS controls [95% confidence interval 0.12–0.68]), and decreased opioid use (by 31–42%).[7] Data audits function as an essential part of an ERAS protocol, allowing teams to review compliance and use continuous quality improvement methodology to iterate and target areas requiring amelioration, further improving clinical outcomes.[8] Standardizing perioperative care of complex pediatric urology patients using an

approach like ERAS has potential to reduce undesirable variations in care, optimize recovery, and lead to improvements in surgical outcomes.[9]

To date, experience with ERAS in pediatric patients has been limited. Published studies have methodological limitations including retrospective nature, lack of specified inclusion and exclusion criteria, poorly defined ERAS protocol elements, small sample size, lack of audits, and/or limited follow up.[10,11] A single-center, prospective pilot trial of 13 pediatric urology patients undergoing procedures with ERAS, compared to 26 historical controls, demonstrated fewer complications and reduced length of stay from 8 to 5.7 days.[12] Another group studying a similar population retrospectively reported even greater improvements in length of stay.[13] These small experiences reflect that some pediatric operations occur with far less frequency than common adult operations, increasing variability in postoperative care and overall experience from center to center and surgeon to surgeon. The evidence base for perioperative practices are not necessarily well developed or even valid in a pediatric population. Additionally, parents, guardians and families are integral to the care of pediatric surgical patients and their involvement in a pathway should be considered.[11]

Anticipated Impact

To address these issues, a collaborative multicenter effort was initiated by the study authors with goals of defining and implementing an ERAS protocol adapted for pediatric urology patients and studying both implementation and outcomes prospectively. Centers will gain valuable experience in implementation, which requires stakeholder engagement and multidisciplinary participation, while the study group seeks to understand system, provider, and patient-level barriers to protocolized surgical care.

Furthermore, study of ERAS in a pediatric and emerging young adult population undergoing metabolically stressful operations has the potential to demonstrate the value of standardized care similar to gains seen in adult counterparts.

Objectives

Pediatric Urology Recovery After Surgery Endeavor (PURSUE) study has two primary objectives: 1, to determine if an ERAS protocol can decrease variation in care for complex pediatric patients while simultaneously improving recovery time from surgery without any change in balancing measures, and 2, to broaden exposure of the pediatric urology community to ERAS by engaging study centers in ERAS protocol implementation at geographically-diverse medical centers. In this report, we describe study design considerations, ERAS protocol definitions, and rationale for the PURSUE study.

Methods and Analysis

ERAS Protocol Development

The study group first met to discuss the proposal for a multicenter study at The Societies for Pediatric Urology Fall Congress in September 2016 in Dallas, Texas, USA. Follow up phone conferences were held several times over the following year. The participants at the initial meeting included attendings, fellows, and residents from pediatric urology and pediatric anesthesiology. Six institutions participated in the original discussions and committed to the study (represented by the authors).

Prior to this work, the study group was only aware of a single pediatric urology ERAS protocol that was adapted for use in patients predominantly with neurogenic bowel and bladder (e.g., myelomeningocele).[12] This was used as a starting point and was similar

to existing adult urology ERAS protocols for radical cystectomy.[14] Modification and addition to this protocol were arrived at by literature review and group consensus. Highlights of the original protocol include omission of formal preoperative bowel preparation, multimodal analgesia with regional blocks for all, no nasogastric tube postoperatively, early feeding (clear liquids in evening after leaving operating room, regular diet following day), and early discontinuation of intravenous fluids by postoperative day 2. **Table 1** lists all 20 ERAS protocol elements defined for the purpose of this study.

The authors identified several important components to add to the original pilot protocol, including ensuring a preoperative clear liquid complex carbohydrate load up to 2 hours prior to surgery and encouraging patients to eat a regular diet the night before surgery. Minimizing *nil per os* duration is crucial to limit metabolic stress, minimize catabolic response from surgery, reduce risk of short term atrophy of the gastrointestinal villi, and protect patients against developing insulin resistance, which has been associated with postoperative complications.[5] Specifically, the study group sought to avoid situations where patients drink only clear liquids for several days prior to the operation, nullifying the intentions of ERAS precepts. Bowel preparation remains an open debate.[3] Given the lack of supporting data for this specific patient population, the study group chose to omit formal bowel preparation in the ERAS protocol but aims to study this question secondarily.

Venous thromboembolism (VTE) prophylaxis was added with the caveat that it should apply only to those patients with certain risk factors (age ≥ 14 years, BMI ≥ 30 kg/m^2, history of VTE, history of malignancy, history of coagulation disorder). The primary

recommendation was for sequential compression devices to be placed on the patient prior to induction. No recommendation was made for pharmacologic prophylaxis on the basis that the risk/benefit profile may not make sense in children.[15,16] Since creating this clinical pathway, there have been new reports regarding clarification of pediatric risk factors for VTE.[16,17] Future revisions of the protocol will require adjustment to match newer evidence.Normothermia was also added and defined as a core body temperature between 36–38˚C from incision to close time. Any value outside this range nullifies the measure. Maintaining normal temperatures may minimize risk of wound infection in adults.[18,19] Notably, normothermia promotes normal metabolic demands on the body (including pharmacokinetics of anesthetics) and minimizes stress from hypo- or hyperthermic conditions.[20] This was a Surgical Care Improvement Project core measure (SCIP-INF-10).[21] The evidence underlying this measure is not level I, but the study group included it for its importance from a physiologic perspective and to match existing published ERAS principles.

Minimizing surgical drains is another ERAS goal. To adapt this to lower urinary tract reconstruction, it was defined as avoiding placement of intraperitoneal or subcutaneous drains. This measure does not include urinary drains, as the group felt these to be important to protect and maximize drainage of the urinary tract postoperatively as a matter of urologic principle. To account for those patients in whom a clinical decision has been made to leave an intraperitoneal or subcutaneous drain, a postoperative measure was added that any such drains should be removed on or by postoperative day four. This day was proposed on the basis of pilot data showing that many patients are ready to go home and that these drains are rarely helpful.

The remainder of the measures from the pilot study were adopted and definitions updated to be internally consistent and account for most foreseeable scenarios. Refer to **Supplementary Table 1** for complete definitions of all 20 ERAS protocol measures. Importantly, the ERAS protocol as defined was to be adopted by all participating centers as standard of care for treatment of patients undergoing urologic reconstructive surgery.

Study Design

Several study designs were debated and discussed, including randomized controlled trials (RCT) of various permutations as well as prospective observational studies. Important characteristics discussed included ensuring both implementation and study design were feasible with minimal overhead, robust data collection through the use of a shared REDCap database, *a priori* defined ERAS protocol definitions and outcomes, inclusion of both pediatric (ages 4–17 years) and emerging young adult (18–25) patients undergoing lower urinary tract reconstruction, and identification of an adequate control group to demonstrate clinically meaningful differences.

Several centers (Children's Hospital Colorado, St. Louis Children's Hospital, and Cincinnati Children's Hospital Medical Center) already had ERAS protocols in place (or started them concurrently during study startup) and randomization by patient was felt to lack equipoise on the basis of pilot data showing substantial patient benefit. Randomization by protocol item was deemed too complex and not feasible. Randomization by surgeon was also felt to lack equipoise, although this is debatable from the standpoint that opposing views on ERAS implementation details may represent unknowable qualities of the intervention. Randomization by center would suffer similar pitfalls identified above. Blinding and allocation concealment are staples of RCTs, but

are not possible in the setting of implementation of a complex protocol involving tens of interventions that touch nearly every aspect of the diffuse perioperative space. Furthermore, ERAS relies on standardization of perioperative care, and having patients on either an ERAS protocol or ad hoc care would necessarily create an unwelcome opportunity for cross contamination issues. A stepped wedge cluster randomized trial design was also considered and is being planned for a separate large multicenter effort in pediatric bowel resection for inflammatory bowel disease.[22] Because two centers in this study group already had existing ERAS protocols, this was not compatible with this option.

The notion that RCT may not be appropriate in all circumstances, particularly within the realm of surgical procedures, is not new and has been discussed previously.[23] There is an applicable framework for advancing surgical care through research and creation of evidence-based practices called the Idea, Development, Exploration, Assessment, and Long-term study (IDEAL) framework.[24] In this classification, surgical innovation passes through several different stages. ERAS in pediatric urology is in the beginning stages and falls under stages 2 (Development) or stage 3 (Exploration), given the ground work shown in two small early studies.[12,13] The IDEAL framework defines goals and methods that are best suited to each stage. At stage 3, prospective study is carried out in either an uncontrolled manner or in smaller size than a full-blown controlled trial. Because of the limitations posed by ERAS, equipoise, and surgeon experience, the study group determined the best study would be a case-control study, with ERAS patients making up a prospective observational arm and propensity-matched controls coming from recent patients not exposed to the ERAS protocol.

After discussion, the study group defined two study phases. First, a pilot phase will assess study recruitment across sites, ERAS implementation, protocol adherence, and study procedures. Second, an exploration phase will prospectively compare all patients on the ERAS protocol to recent historical controls matched on propensity to undergo surgery with utilization of an ERAS protocol, should they have been treated presently, using clinically-important covariates deemed most likely to affect recovery. Data from the pilot study will be fed forward into the exploratory study. The decision for a built-in pilot study allows each center to build comfort level with study procedures along with maturation of the ERAS protocol. From a methodological standpoint, a pilot study is setup like a smaller version of the larger study without the need to define sample size or demonstrate clinically important outcomes but rather examine outcomes related to the setup of the study itself.[25] A built-in pilot component at each center (first five patients) will allow ascertainment of treatment team perceptions of ERAS and barriers to protocol implementation. While five is a small number, high-volume centers only perform 10–15 of these cases per year.[26]

Center Eligibility and Patient Selection

Centers will be allowed to enroll patients in the study if the center performed a minimum of five lower urinary tract reconstructive operations in the year prior to center enrollment. This constitutes a baseline measure of quality and familiarity with the care of these complex patients perioperatively.

Surgeons and research assistants at each respective center will be responsible for subject identification and recruitment through existing clinical relationships. Patients aged of 4–25 years old undergoing the following lower urinary tract reconstructive

operations may be enrolled after providing informed consent (and assent, when applicable, see **Supplementary Files – Consent and Assent** for examples): augmentation enterocystoplasty, creation of continent urinary channel (appendicovesicostomy, ileovesicostomy, or colovesicostomy), creation of an antegrade continence enema channel, and incontinent urinary diversions (ileal conduit with or without cystectomy or ileovesicostomy). Because some of these operations may be done with or without a bowel anastomosis—which is a major risk factor for surgical stress, increased operative time, and risk of ileus—bowel anastomosis will be tracked and used for matching cases to controls as it is a strong effect modifier. Some providers noted patients with neurogenic bowel not on a bowel management program (retrograde enemas, oral stool softeners, or rectal suppositories) may be at increased risk prolonged return of bowel function, ileus, bowel obstruction, or anastomotic bowel leak. For this reason, clinically constipated patients defined as Bristol 1 or 2 stools more than once per week, bowel movement interval greater than every other day, or palpable stool in > 50% of colon on physical preoperative exam will be excluded from the study. Patients with these findings become eligible if their stooling pattern is addressed at least 4 weeks in advance of surgery with implementation of a bowel management program continued up to the night before surgery.

The use of historical controls has long been felt to be controversial, secondary to the retrospective nature of their identification and data collection and potential biases. Using quality improvement methodology, in which historical controls are often used to compare outcomes to an intervention cohort, run diagrams and interrupted time-series analysis can provide insight into changes occurring over time with regards to either

process, clinical outcome, or balancing measures.[27] This has the benefit of ensuring that the prospectively enrolled patient outcomes are attributed to the intervention (ERAS) and not to changes in patient care that were already underway prior to implementation. While use of prospective controls from non-ERAS institutions might serve as a better comparison (reduced bias, prospective data collection, parallel comparison of modern surgical patients undergoing similar operations), the study group felt that observational bias (Hawthorne effect) might influence malleable outcomes such as length of stay.

Outcome Measures

The pilot phase outcomes of interest include enrolling a minimum of two patients per center in first six months, and completing at least 90 days follow up on the first five enrolled patients (**Figure 1**). A goal of ≥ 70% protocol item adherence (out of 20) at ≥ 75% of study centers was set. Finally, barriers to implementation will be identified and may determine if there is a need to optimize the protocol for wider application.

The primary outcome of the exploratory phase is adherence to the ERAS protocol with number of items achieved (out of 20). Secondary outcomes include length of stay, 30-day readmissions, 90-day reoperations, 90-day returns to the emergency room, 90-day complications by Clavien-Dindo classification (see **Table 2** for full list of defined complications), number of long-term complications within 1 year (**Table 3**), minimum, median, maximum daily pain score during first 7 days after surgery, and mean daily IV morphine equivalents (mg/kg) usage during first 3 days after surgery.[28] It is important to clarify that because this is an observational trial and the ERAS protocol is

implemented as standard of care at each center, the collection of complications here is a clinical outcome measure rather than one seen as a result of study intervention.

In addition to the objective clinical outcomes listed, patient- and family-reported outcome measures will be administered to assess the impact of surgery on work and school (e.g., missed days of each) and adjustment time at home needed to return to "normal" (i.e., daily routines not impacted heavily by having had surgery). These instruments include open-ended, non-validated parent and child surveys to be given pre- and postoperatively, and a Quality of Recovery 9 questionnaire to assess overall return of function (given before and after surgery, and again at clinic follow up).[29] **Figure 2** demonstrates which outcome measures will be tracked over time with respect to the index surgery. Patients will be followed for one year, specifically to ensure that patients with a ventriculoperitoneal (VP) shunt do not experience increased rates of externalization, infection, or revision which has long been a concern of the community.[30]

Data Collection

A shared REDCap database has been designed, tested, and implemented for use for this study. Data use agreements have been executed between centers and data sharing language was incorporated into patient consent to allow sharing of de-identified data sets maintaining patient confidentiality. The majority of perioperative process, outcome, and balancing measures are charted within the medical record as part of standard of care. Where possible, these will be automatically abstracted electronically as five out of the six study centers use the Epic electronic health record system. In cases where data is not normative or where it requires clincal interpretation or cannot be abstracted

electroncially, manual chart review by research assistants trained by the study team will be done. Continuous data quality checks will be completed quarterly, including analysis of missing required data and any discrepancies. The study commenced enrollment in 2017 and aims to conclude in 2021.

After primary accrual is completed, the study committee plans to transition the shared database into a shared clinical registry for ongoing data collection to continue to study ERAS and further refinements to the care pathway.

Statistical Analysis

A total of 64 ERAS patients will be needed to detect a decrease in mean overall LOS by 2 days, with type I error of 5% (false positive) and type II error of 20% (false negative) based on data from the pilot study showing mean LOS of 8.0 days (SD 7.3) for historical patients versus 5.7 days (SD 5.1) for patients who were treated under the ERAS protocol. Patients will be propensity score-matched on likelihood to have been treated under an ERAS protocol 1:2 to recent historical controls from 5 years prior to the initiation of the ERAS protocol. Propensity matching controls for measured baseline covariates before analysis of the outcomes to reduce confounding. Based on pilot data (mean 2.1 complications/patient [SD 1.9] historically and versus 1.3 complications/patient [SD 1.2] under ERAS), this study will also be powered to detect a decrease in any grade complications per patient by 50%. Patients will be divided into two strata: those who underwent and did not undergo a bowel anastomosis as part of the index operation. Propensity score-matching within the two strata using nearest-neighbor algorithm (also referred to as greedy matching) will occur on the following variables: age, sex, chronic kidney disease, presence of VP shunt, planned bladder

augmentation, history of prior abdominal surgery (other than VP shunt), diagnosis of myelomeningocele, ambulatory status, and center. Bowel anastomosis was determined by the study group to be a strong effect modifier and thus patients will be exactly matched on that variable (creating two strata) and propensity matched on remaining covariates to avoid overfitting.

Because of the nature of propensity-matched data, care must be taken for comparison of historical controls and ERAS cases. Differences in baseline characteristics between matched groups will be assessed using methods that are not influenced by sample size and that do not refer to a hypothetical population (i.e., standardized differences).[31] The Mantel-Haenszel test will be used to compare proportions, and generalized linear modelling with generalized estimating equations to adjust for the matching design will be used to assess association of outcomes and predictors.[32] Two-tailed p-values < 0.05 will be considered significant. No interim analyses are planned.

Study Committee

Given the importantance of a strong implementation serving as a foundation for success, the study group has created several committees, including an organizing committee and audit committee. The organizing committee is charged with overseeing data collecion, arranging study conference calls and meetings and adjudicating authorship for subsequent papers laid out through a set of bylaws. The organizing committee serves as a backstop to proper trial conduct under the purview of study (KOR) and site primary investigators (ACS, GJV, RC, DIC, RSZ). The audit committee arguably serves a more important role, overseeing regular clinical audits of ERAS protocol compliance. The committee is charged with meeting after each center's pilot

phase (5 patients) and ad hoc thereafter, and they will review overall compliance and serve as an external study group as part of plan/do/study/act (PDSA) quality improvement methodology to identify challenging areas and suggest solutions that may be novel for that center. This highlights the point that the ERAS clinical pathway sets high-level goals, but leaves implementation details and specifics to each center. This creates heterogeneity that mirrors real-world quality improvement projects, improving the generalizability of the project, but can lead to maladaptive internal center processes. The audit committee's goal is to help each center identify issues early in the implementation and find creative solutions.

Stengths and Limitations of the Study Design

Strengths of this study design include its multicenter nature, which the authors aim to use to demonstrate feasibility of ERAS implementation in a variety of geographically-diverse pediatric-focused settings. Prospective data collection, *a priori* definitions of protocol elements, and an exhaustive list of potential short and long-term complications also lend strengths to its design. The SPIRIT checklist was used when preparing this report.[33] Potential limitations of this study include variation in protocol implementation, unsuccessful attempts at protocol implementation, unobserved patient characteristics or other biases affecting outcome measures, and use of historical, retrospective controls. The study group notes that there is very little level I evidence for protocol items in pediatric patients. Some are extrapolated from adult evidence and may not hold true. Additionally, patient-reported outcomes in this population are lacking. Pain interference and validated general function measures are available but were not designed nor tested expressly to measure recovery after surgery. When examining clinical outcomes,

propensity matching on clinically-relevant patient characteristics will allow meaningful comparison, and run charts of patient care variables over time will shed light on any changes in care patterns or outcomes that may have already been underway.

Ethics and Dissemination

This study was approved by each free-standing tiertiary care children's hospital respective institutional review board (St. Louis Children's Hospital 201703081, Children's Hospital of Pittsburgh 17070089, Children's Hospital Colorado 17-0746, Cincinnati Children's Hospital Medical Center 2017-3322, Ann & Robert H. Lurie Children's Hospital 2019-2566, and Children's Hospital of Richmond at VCU HM20015891). Prospectively enrolled patients who meet inclusion criteria will be approached for inclusion by either a urologist or research assistant prior to the day of surgery. Study protocol does not allow for patients to be approached in the preoperative area to avoid patient or family coersion. No study activites will occur prior to obtaining consent. Patients under 18 years age (and over specific ages that vary by center) will assent to enrollment. Participants retain the right to withdraw at any point for any reason. Importantly, non-adherence to the ERAS protocol or ERAS protocol deviation is not grounds for removal from the study. Not every patient will meet clinical standards for every protocol item. Rather, the goal of the ERAS protocol is to maximize evidence-based strategies to return the patient to normal function. ERAS protocol changes will only be made after completing primary accural and analysis of results in conjuction with a thorough literature review by the study committee.

Patient and Public Involvement

ERAS, in many respects, is a patient-focused quality improvement project. While no patients or families were directly involved in the design of this study or recruitment of potential subjects, families expressed interest in being notified of the study results and this will occur. Patient and families will be engaged in future revisions of the underlying ERAS clinical pathway that result from evidence gathered through this study.

In conclusion, Pediatric Urology Recovery After Surgery Endeavor (PURSUE, ClinicalTrials.gov NCT03245242) is a multicenter, prospective propensity-matched case-control cohort study that will examine outcomes in pediatric and emerging young adult patients undergoing lower urinary tract reconstruction who receive care under an ERAS pathway.[34] Results will be published in peer-reviewed journals by study group members. This protocol marks the first phase of a collaborative quality improvement effort within the pediatric urology community to improve and standardize care of patients undergoing urologic reconstructive surgery.

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collection, analysis or interpretation of data, in the writing of the manuscript, or in the decision to submit this manuscript for publication.

Conflict of Interest

None

Author Statement

KOR, BTC, and DTW organized the initial meeting to discuss study protocol concepts in Dallas, TX, USA in 2016. KOR, MAB, TPW, DIC, DTW, and GJV developed and refined the 20-protocol ERAS pathway used in the study based on literature searches, screening and review. KOR led protocol development and created patient recruitment tools. KOR, MAB and ACS chair the PURSUE organizing committee that oversees study activities. KOR is the study primary investigator. KOR, ACS, RSZ, RC, DIC, GJV serve as site primary investigators. KOR performed the power analysis and statistical analysis plans with additional input, oversight and revision by DIC. KOR, ACS, DTW, GJV, TPW, BV, DIC, RC, RSZ, PURSUE Study Group and MAB were involved in the study conception, design, protocol manuscript drafting and critical revision. All authors approve the final version.

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Figure Legends

Figure 1. Overview of study conception, implementation, center eligibility, patient inclusion and exclusion criteria, and design methodology arrived at through group consensus.

Figure 2. Timeline of patient enrollment, data collection including process and balancing measures, clinical outcomes, and patient-reported outcome measures during the PURSUE study.

Tables

Table 1. Comprehensive list of pre-, intra-, and post-operative ERAS protocol items targeted by the care pathway, customized for pediatric urology patients. The definitions for these items were arrived at through multidisciplinary consensus of the study group.

Pre-operative	Intra-operative	Post-operative
Counsel about ERAS	Regional anesthesia (catheter-based block)	Nausea/vomiting prevention
Clear-liquid carbohydrate load (10 mL/kg up to 350 mL)	Avoiding excess drains (intraperitoneal or subcutaneous)	Early feeding (clears POD 0, regular POD 1)
Avoid prolonged fasting (eat regular diet and avoid prolonged clears-only diet day prior to surgery)	Euvolemia (4–7 mL/kg/hr crystalloid)	Early mobilization (out of bed POD 1)
No bowel preparation (continue bowel regimen if on one)	Normothermia (36–38˚C during skin-to-skin time)	Adjunctive pain medication (acetaminophen and NSAID)
Antibiotic prophylaxis per AUA guidelines	Minimizing opioids (< 0.15 mg/kg IV morphine equivalents)	Early stoppage of intravenous fluids (either discontinue or lower rate to keep vein open [TKO] by POD 2)
DVT prophylaxis (≥ age 14 or risk factors)	Minimally-invasive assistance (at surgeon discretion)	Early removal of extra drains/catheters (non-urinary drain removal by POD 4)
	No nasogastric tube on leaving OR	Minimizing opioids (< 0.30 mg/kg/day IV morphine equivalents)

Table 2. List of pre-defined postoperative short-term complications.

90-Day Short-Term Complications
Clavien Grade I
electrolyte disturbance
fever (≥ 38˚C)
IV complication (infiltration)
nausea / vomiting
neuropraxia (positioning complication)
transient elevation in Cr (acute kidney injury)
wound dehiscence
incisional seroma
other grade I
Clavien Grade II
blood transfusion
catheter manipulation, ACE
catheter manipulation, Mitrofanoff / Monti / urethral / SPT ± urinary retention
ileus requiring NG tube ± TPN + nausea / vomiting
infection / bacteremia treated with Abx ± fever
infection / pyelonephritis treated with Abx ± fever
infection / superficial wound treated with bedside drainage, Abx ± fever
infection / UTI treated with Abx ± fever
infection / GI infection with Abx ± fever ± diarrhea
venous thromboembolism
lymphocele or chylous ascites treated conservatively with diet changes
other grade II
Clavien Grade III
abdominal abscess requiring IR / OR drainage
catheter malfunction / loss requiring placement in OR
fascial dehiscence / evisceration treated in OR
hemorrhage requiring embolization or OR
small bowel obstruction treated surgically in OR
urinoma requiring IR / OR drainage
ureteral obstruction requiring PNT by IR / OR
lymphocele or chyle leak requiring IR / OR drainage or intervention
other grade III
Clavien Grade IV
respiratory failure requiring ventilation
renal failure
multiorgan failure
sepsis
other grade IV
Clavien Grade V
death

Table 3. List of pre-defined postoperative long-term complications.

1-Year Long-Term Complications
channel stenosis (any level) requiring revision
channel false passage
bowel obstruction
bladder stone formation
bladder perforation
incisional hernia
new onset metabolic acidosis
new onset chronic kidney disease
new onset renal scarring
VP shunt externalization
VP shunt infection (positive shunt tip and cerebral spinous fluid cultures)

Planning

Initial meeting at SPU Fall Congress 2016 (Dallas, TX)
Study designs debated
ERAS protocol defined
Power analysis and statistical planning

IRB

Shared REDCap database
Multicenter design with data use agreements
ERAS programs implemented as standard of care
Study is observational, no medical interventions
Prospective ERAS arm with matched historical controls
All patients / families consent prior to enrollment
Register with ClinicalTrials.gov (NCT03245242)

Pilot

Enroll 2 patients in first 6 months per center
Pilot phase ends after 5th patient at center
Outside process measure compliance audit
Goal = ≥ 70% protocol adherence
Provider surveys (before and after pilot)
Patient / Family survey pre- and post-op
Quality of Recovery 9 instrument

Exploratory

Enroll 64 ERAS patients (across all centers)
Compare to 128 propensity-matched historical controls
- matched on age, sex, diagnosis, prior surgery, center, type of operation, ambulatory status, VP shunt

1 year follow up
Primary outcome: protocol adherence
Secondary outcomes: LOS
re-admissions within 30 days
re-operations within 90 days
ED visits within 90 days
Clavien-Dindo complications
max/mean pain scores
opioid usage (mg/kg IV morphine equivalents)
patient-reported outcome measures
VP shunt infections, other surgical complications after reconstruction to 1 year

Center eligibility:

- must have performed 5 or more target operations in the last year

Inclusion criteria:

- 4 to 25 years old
- undergoing urologic reconstructive operation that includes one or more of the following:
  - bladder augmentation
  - appendicovesicostomy (Mitrofanoff)
  - ileo- or colovesicostomy (Monti)
  - ileocecostomy (Monti-MACE)
  - urinary diversion requiring a bowel anastomosis

Exclusion criteria:

- **clinically constipated** (Bristol 1 or 2 stools more than once per week, bowel movement interval > every other day, or palpable stool in > 50% of colon on pre-operative physical exam)

Figure 1. Overview of study conception, implementation, center eligibility, patient inclusion and exclusion criteria, and design methodology arrived at through group consensus.

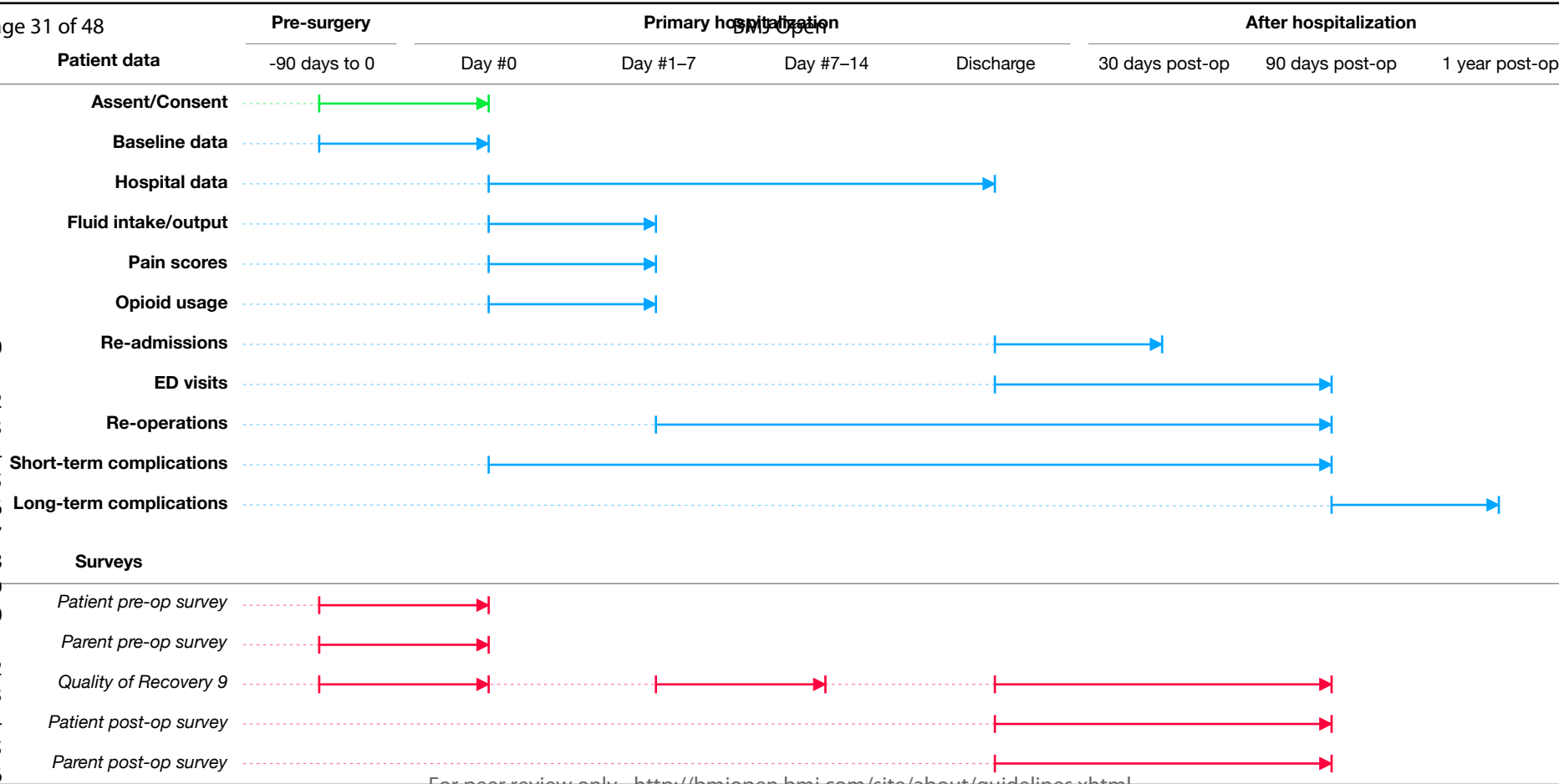

Figure 2. Timeline of patient enrollment, data collection including process and balancing measures, clinical outcomes, and patient-reported outcome measures during the PURSUE study.

Supplemental Table 1. Specific definitions of 20 ERAS process measures for pediatric lower urinary tract reconstructive operations.

Phase of case	Measure	Definition
Preoperative	Counseling about ERAS	This will typically be done as part of the consent process. Patients/families should not have their sole counseling occur in the preoperative area. Patients/families will be provided a standardized handout on ERAS and what to expect from surgery throughout the process from preoperative all the way through follow up.
	Clear-liquid carbohydrate load	Patients will be provided a commercially-available complex clear liquid carbohydrate liquid preoperatively. Patients will drink 10 mL/kg up to maximum of 350 mL (1 bottle) in the 3 to 2 hours prior to surgery in concert with American Society of Anesthesiologists (ASA) guidelines. If not available, other carbohydrate-rich clear liquids are also permissible on protocol, including Gatorade, PowerAde, Pedialyte. If the patient has a G-tube, these liquids can be administered per G-tube. Water should not be used. Other liquids outside this list are not permissible as part of the protocol.
	Avoid prolonged fasting	Patients will remain adherent to ASA guidelines for pediatric patients. These include: solids up to 8 hours, non-human milk up to 6 hours, breast milk up to 4 hours, and clear liquids up to 2 hours prior to surgery. Patients should not be placed on an extended clear liquid diet prior to surgery. Patients should be encouraged to eat and drink normally up to the scheduled *nil per os* (NPO) guidelines stated above. If the patient does not eat > 24 hours prior to surgery or was placed on an extended clear liquid diet (no solid food on day before surgery) or did not receive normal G-tube feedings, if applicable, patient will not meet this criterion.
	No bowel preparation	Patients will not receive oral laxatives, suppositories, oral antibiotic agents or other bowel prep agents outside of the patient's normal regimen (if on one). Many patients undergoing urology reconstruction have concomitant neurogenic bowel and are already on bowel programs which may include daily antegrade or retrograde enemas or oral laxatives. These should be maintained up to the day prior to surgery. Patients should be evaluated adequately (clinical history) well in advance of surgery to ensure they are not constipated. Clinical judgement should be used to modify any bowel regimen program at least 4 weeks prior to scheduled OR date.
	Antibiotic prophylaxis	Perioperative antibiotics should be administered within the guidelines of the American Urological Association and best hospital practices. AUA guidelines state that prophylaxis should consist of a weight-based dose of 2nd/3rd generation cephalosporin (e.g., cefoxitin) or alternatively an aminoglycoside + metronidazole or clindamycin (e.g. gentamycin + metronidazole) to be administered within 60 minutes of procedure start time (cut time). If patients have allergies or clinical conditions that preclude these, alternatives include ampicillin/sulbactam, ticarcillin/clavulanate, piperacillin/tazobactam or a fluoroquinolone. If patient is felt to have a UTI pre-operatively or has colonization, alternative antibiotic regimens tailored to recent culture results may be used. Antibiotics in most cases should be re-dosed in the operating room according to local standard and be discontinued within 24 hours of surgery per guidelines, but may be continued at the discretion of the surgeon based on clinical circumstance.
	DVT prophylaxis	Patients with one or more risk factors should have sequential compression devices (SCDs) placed on the lower extremities prior to induction of anesthesia. This will be verified by intraoperative nursing documentation. Risk factors include obesity (BMI ≥ 30), age ≥ 14, history of malignancy, or history of venous thromboembolic event. Patients who do not have any risk factors may safely omit any prophylaxis per standard of care. SCDs should be removed at the end of the case to encourage early mobility once reaching the surgical floor.

Phase of case	Measure	Definition
Intraoperative	Regional anesthesia	Standard clinical judgement of the multidisciplinary team (urologists, anesthesia) in concert with patient/family wishes should be used to offer regional catheter-based anesthesia to all patients. Options include wound soakers, transversus abdominus plane (TAP) catheters, quadratus lumborum (QL) catheters, erector spinae plane (ESP) catheters, or epidural. If planning wound soakers, TAP/QL/ESP catheters at the end of the case, preoperative TAP blocks performed by anesthesia using 0.2 mL/kg of 0.2–0.5% Ropivacaine should be injected on each side under ultrasound guidance. Wound soakers, TAP catheters, quadratus lumborum catheters or wound catheter pain pumps should be filled with 0.2% ropivacaine and connected to an epidural infusion pump to provide a continuous rate determined by the patient's weight (0.05 mL/kg/hr, maximum 0.5 mg/kg/hr). The infusion rate can be adjusted or stopped to monitor alternative analgesics prior to catheter removal. Epidurals can be run according to standard of care at each institution, although by protocol should not include a narcotic/opioid. Initial concentrations and rates for all regional anesthetic regimens will be documented. Duration of therapy will be documented. Wound soakers, TAP/QL/ESP catheters, and epidural catheters are to be left in place up to 5 days post-operatively or at clinical discretion of treating physicians within standard of care. They can be removed on day of discharge. Those left in longer than day 5 should have documented reason. Drainage around pain catheters can occur. This is normal. Dressings should be reinforced prior to scheduled removal. The risk of infection of pain catheters is generally small, but if concern exists, clinical judgement should be used as to the disposition of the pain catheters and documented. If none of the above are deemed clinically appropriate, bilateral transversus abdominis plane (TAP) blocks, caudal blocks or paravertebral blocks can be performed by the surgical or anesthesia team either through the surgical field or ultrasound guided. These do not count, however, for this protocol item given their limited duration of effectiveness for the patient. Blocks (as opposed to catheter-based postoperative therapies) do not provide continuous post-operative anesthesia to the wound beyond 6-12 hours. Justification of the use of blocks over other continuous regional options should be documented.
	Avoiding excess drains	There is wide variability in the use of surgical drains by surgeons, according to local practice, experience and clinical scenario. Urologic reconstruction, though, typically requires drains in the form of catheters across newly-constructed catheterizable channels or catheters to drain the urinary tract to keep it under low pressure during healing. To meet this criterion, patients should not have a drain placed intraabdominally, in the space of Retzius, or subcutaneously. Acceptable catheters include: suprapubic tube, antegrade continence enema channel, appendicovesicostomy/ileovesicostomy/colovesicostomy, and/or urethral catheters. The duration of therapy will be according to surgeon preference.

Phase of case	Measure	Definition
	Euvolemia	Hydration statuses of patients can vary greatly and are highly dependent on pre-operative fasting conditions, concomitant medical diagnoses like diabetes insipidus, and intraoperative fluid shifts related to insensible losses from an open abdomen, urine output and blood loss. Surgery involving the genitourinary tract can often be difficult because urine output cannot be recorded accurately throughout the case, which is often an indicator of fluid status and response to intraoperative intravenous fluid resuscitation. The goal is to maintain euvolemia and avoid bowel edema and subsequent ileus while maintaining safe cardiopulmonary function, end organ perfusion and offsetting bodily fluid and insensible losses. To meet this criterion, a goal of an average intravenous fluid volume between 3 and 7 mL/kg/hr as calculated according to the patient's preoperative weight and time from in room time to out of room time. Blood loss not requiring transfusion can be replenished in a 3:1 ratio of crystalloid to blood or 1:1 ratio of colloid to blood. Intravenous pressors should be considered to improve hemodynamics as opposed to fluid boluses. Some patients with preexisting comorbidities like diabetes insipidus may require greater than usual fluid volumes to maintain euvolemia. Such instances should be well-documented and justified.
	Normothermia	Patient's temperature should be maintained between 36°C to 38°C throughout the intraoperative period (skin-to-skin time). This can be done with a combination of warming blanket and/or alteration of the operating room environmental controls. To minimize variability, esophageal temperature monitoring should be used. Anesthesia record will be used to verify this item. Any value outside this range will not count.
	Minimizing opioids	There is no well-accepted clinical standard for minimizing intraoperative opioids. Data gathered during a pilot study were used as a basis for this definition. Patients will have met this criterion if they receive < 0.3 mg/kg IV morphine equivalents intraoperatively. This is equivalent to a total of 3.6 mcg/kg fentanyl IV. As a guideline for intraoperative opioid usage, providers may opt for no intraoperative opioids so long as the patient has some form of regional anesthesia on board starting at the beginning of the case and they show no signs of pain response. Alternatively, we recommend fentanyl may be administered in 1-2 mcg/kg doses with induction, prior to incision, and as deemed appropriate throughout the procedure by the anesthesiologist for analgesia. Opioids should only be used if clinically indicated. This total dosage equates to about 75% of mean post-operative day 0 IV morphine equivalent usage across all patients in the Phase I/II study. The last 25% of mean post-operative day 0 IV morphine equivalent is allocated toward post-operative pain control in the recovery unit or hospital ward. Patients should have their pain adequately controlled as necessary in accordance with standard of care. If pain assessments determine there is inadequate pain control, all pain pathway items should be reassessed by nursing, surgical and anesthesia teams to maximize pain control as best as possible in accordance to the ERAS pathway where possible.
	Minimally-invasive assistance	Where technically and clinically feasible, surgeons should endeavor to perform part of the surgery with either laparoscopic or robotic assistance. In many cases, the cecum, appendix and terminal ileum can be mobilized into the pelvis to allow for reconstruction through a smaller muscle-splitting Pfannenstiel incision with minimization of time the peritoneum is open. This minimizes insensible fluid losses and fluid shifts. Surgeon judgement and experience will heavily influence this part of the pathway, but should be given consideration. If laparoscopic or robotic assistance is used in any part, this criterion will be met. Of note, this item is not meant to indicate that the entire operation need be done laparoscopically or robotically. Surgeon judgement is paramount.

Phase of case	Measure	Definition
	No nasogastric tube on leaving operating room	No nasogastric (NG) tube shall be placed intraoperatively by the anesthesia team. An orogastric (OG) tube may be placed temporarily to drain stomach contents if felt necessary, but should be otherwise avoided. Placement of OG intraoperatively by definition must be removed at the end of surgery. Placement of NG tube on leaving the OR shall be documented and not qualify for this item. Patients who develop ileus and clinically require NG tube during the post-operative period still qualify for this item if no NG tube was used on leaving the OR. Such patients will require documentation of circumstances of secondary NG tube placement.
Postoperative	Nausea/vomiting prevention	Patients without clinical contraindications shall be written for weight-based antinausea prophylaxis, typically ondansetron to be given as needed on admission to the PACU or floor. Orders wills be used to verify this item. Alternatives to ondansetron such as promethazine, diphenhydramine or a scopolamine patch may be used at the discretion of the ordering physician. Regimen will be documented.
	Early feeding	Patients should receive clear liquids on the evening of surgery (counted as postoperative day 0) and regular diet starting on day after surgery (postoperative day 1). Regular diet should have no restrictions outside of clinically-indicated patient needs (e.g., soft, bland, purée, etc.). Presence of orders to this effect on the specified days will be used to verify this item.
	Early mobilization	Patients should be out of bed in some fashion on post-operative day 1. This may include transfer to a chair, ambulation with or without assistance as deemed clinically safe and feasible by the surgical team and nursing staff. Patients who do not get out of bed will not have met this criterion. Similarly, sitting on the edge of the hospital bed is not considered sufficient to meet this criterion. Activity should be encouraged and increased each subsequent hospital day. Nursing documentation of activity will be used to verify this item.
	Adjunctive pain medication	Patients should be scheduled initially (not written prn or as needed) to receive a weight-based based dose of acetaminophen and/or NSAID therapy. These may be given orally or parenterally. To meet this item, these should be scheduled after surgery for 24 hours and can then be transitioned to as needed at the discretion of the care team. If these are written as needed on leaving the operating room, patient will not receive credit for this item. In accordance with clinical standard of care, patients who have contraindications to receiving either medication (e.g. allergy, liver disease, chronic kidney disease, etc.) should not be written for them. Patients should have their pain adequately controlled as necessary in accordance with standard of care. If pain assessments determine there is inadequate pain control, all pain pathway items should be reassessed by nursing, surgical and anesthesia teams to maximize pain control as best as possible in accordance to the ERAS pathway where possible.
	Early stoppage of intravenous fluids	Patients who have tolerated oral intake (no prerequisite amount is defined) and who are clinically stable according to standard of care should have their intravenous maintenance fluids turned off (saline locked) by post-operative day 2. “To Keep Open” or TKO rates are permissible. Patients who are not well, are vomiting, have ileus or have an NG tube should not have their IV fluids removed and will not meet this criterion.
	Early removal of extra drains/catheters	If no drain was left outside the urinary tract at the time of surgery, then the patient will automatically qualify for this ERAS protocol item. If a drain was left intentionally outside the urinary tract, then it should be removed by or on post-operative day 4. If there are clinical circumstances that require the drain be continued, then the clinical team should keep it in place and document reasoning.

Phase of case	Measure	Definition
	Minimizing opioids	There is no well-accepted clinical standard for minimizing postoperative opioids. Data gathered during a pilot study were used as a basis for this definition in addition to prior study data regarding the decreased need for postoperative opioids in the setting of wound soakers. Patients will have met this criterion if they receive < 0.15 mg/kg/day IV morphine equivalents averaged over the first 3 post-operative days. This equates to less than all the postoperative IV morphine equivalent usage for 11 of 13 patients in the pilot study, where nurses were informed to use opioids only for breakthrough pain control. This is equivalent to an average of 3 weight-appropriate doses of IV morphine, IV hydromorphone or oxycodone per day. Communication with nursing staff (day and night shift nurses) and anesthesia team is key to minimizing opioid usage. Patients should have their pain adequately controlled as necessary in accordance with standard of care. If pain assessments determine there is inadequate pain control, all pain pathway items should be reassessed by nursing, surgical and anesthesia teams to maximize pain control as best as possible in accordance to the ERAS pathway where possible.

Consent and Authorization Form

17-1176 Consent
June 2019
Kyle Rove

Principal Investigator: **Kyle Rove, MD**
COMIRB No: **17-1176**
Version Date: **June 2019**

Study Title: **Multicenter Pilot and Exploration Study of Enhanced Recovery After Surgery (ERAS) in Patients Undergoing Urologic Reconstructive Surgery**

You are being asked to be in a research study. 'You' refers to the pediatric patient. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

The purpose of this research study is to evaluate procedures we have implemented to potentially speed up recovery after urologic surgery. We are interested in speed of recovery (how quickly pain improves, length of time in the hospital, and need for additional pain control).

You are being asked to be in this research study because you or your child is going to have bladder surgery requiring hospitalization. Up to 60 people will participate in the study at Children's Hospital Colorado. The study is being done at other sites around the United States. Approximately 500 people will take part in this study across all sites.

What happens if I join this study?

If you join the study, we will ask you to complete a survey about yourself before your surgery and another afterwards. We will collect health information from your medical record about your surgery and your recovery continually for 1 year after your surgery. You may skip any question which makes you uncomfortable.

What are the possible discomforts or risks?

One risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure.

To help protect your confidentiality, we will assign a study identification number to your data. We will separate information that identifies you from the rest of the study data and store all the data securely in an electronic database. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

There are no other known risks from being in this study, and you will not benefit personally. However, we hope that others may benefit in the future from what we learn as a result of this study.

Will I be paid for being in the study? Will I have to pay for anything?

You will not have any costs for being in this research study and you will not be paid.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

Who do I call if I have questions?

The researcher carrying out this study is Dr. Kyle Rove. You may ask any questions you have now. If you have questions later, you may call Dr. Kyle Rove at 720-777-6146.

You may have questions about your rights as someone in this study. You can call Dr. Kyle Rove with questions. You can also call the Multiple Institutional Review Board (IRB). You can call them at 303-724-1055.

Who will see my research information?

The University of Colorado Denver and its affiliated hospital(s) it works with have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.
The institutions involved in this study include:

- University of Colorado Denver
- Children's Hospital Colorado

Children's Hospital Colorado shares a medical record system with the Barbara Davis Center and PedsConnect; therefore, it is also possible that other healthcare professionals could view your information.

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the University of Colorado Denver and its affiliate hospitals may not be covered by this promise.

We will do everything we can to keep your records a secret. It cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Primary Investigator, at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Kyle Rove, MD
Children's Hospital Colorado
13123 East 16th Avenue B463
Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information.

- Federal offices such as the Food and Drug Administration (FDA) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB)
- The study doctor and the rest of the study team.
- Officials at the institution where the research is being conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research

The investigator (or staff acting on behalf of the investigator) will use your information for the research outlined in this consent form. They will also make *all or some* of the following health information about you collected in this study available to:

- St. Louis Children's Hospital
- Washington University in St. Louis

Your information may be used and disclosed, to do the research, to study the results, and to make sure that the research was done right.

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

Information about you that will be seen, collected, used and disclosed in this study:

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.
- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, laboratory or tissue studies, radiology studies, procedure results
- Research Visit and Research Test records

Agreement to be in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Child's Name _____Child's Date of Birth_____

Parent Signature:_____ Date:_____

Print Name:_____

Subject (age 13-18 years) Signature: _____ Date_____

Consent form explained by:_____ Date:_____

Print Name: _____

Consent and Authorization Form

17-1176 Consent
June 2019
Kyle Rove

Signature Line for witness for consent of non-reading subjects and consent using a short form, if you requested such consent procedures (see Application section L)]

_____ Date_____

Print Name: _____

Witness of Signature ☐

Witness of consent process ☐

COMIRB Assent

COMIRB #: 17-1176
Person in Charge of the Study: Kyle Rove, MD
Version Date: September 2018

Assent Form for: Multicenter Pilot and Exploration Study of Enhanced Recovery After Surgery (ERAS) in Patients Undergoing Urologic Reconstructive Surgery

What is this study about?
I am being asked if I want to be in this research study. The goal of this study is to find out more about how we can speed up recovery after your surgery.

Why are you asking me?
I am being asked to be in the study because I am going to have surgery in my abdomen.

What Do I Have to Do or What Will Happen to Me?
If I am in the study, the researchers will collect information about my surgery, recovery and pain levels for a year after my hospitalization. I will be asked to answer a short survey once before and again after surgery.
This study does not involve anything that might hurt or upset me. The questionnaire I will complete will ask about my school and about how I am doing before and after surgery.

Can I ask Questions?
I asked any questions I have now about the study. All my questions were answered.

I know that if I have a question later, I can ask and get an answer. If I want to, I can call Dr Rove at 720-777-5839.

Do I Have to Do This?
I know that I do not have to be in this study. No one will be mad at me if I say no.

I want to be in the study at this time. ☐ yes ☐ no

I will get a copy of this form to keep.

*Child's Printed Name:*_____
*Child's Signature:*_____
*Date:*_____

I have explained the research at a level that is understandable by the child and believe that the child understands what is expected during this study.

*Signature of Person Obtaining Assent:*_____ *Date:*_____

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 11, 16
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a - these are all listed on the clinicaltrials.gov website
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	16

contributorship			
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a - this is an investigator-initiated study
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	14
Objectives	#7	Specific objectives or hypotheses	9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants,			

interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	17-18
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	15-16
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a - this is an observational study
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)		14
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations		14
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size		11
Methods: Assignment of interventions (for controlled trials)				
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a - not a randomized controlled trial	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a - not a randomized controlled trial	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a - not a randomized controlled trial	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts),	n/a - not a randomized controlled trial	

		and how	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a - not a randomized controlled trial
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14-15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14-15

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15-16
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15-16
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial	17

		participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a - no additional collection of biological specimens is stipulated as part of this observational study
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a - given the observational nature of this study and implementation of ERAS as standard of care, any adverse clinical outcomes are deemed expected as part of the course of treatment and not the study itself
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
Dissemination	#31b	Authorship eligibility guidelines and any	17

policy: authorship		intended use of professional writers	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a - there are currently no plans for public sharing of the data set
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	17
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a - none are collected as part of the study

Notes:

- 2b: n/a - these are all listed on the clinicaltrials.gov website
- 5b: n/a - this is an investigator-initiated study
- 11d: n/a - this is an observational study
- 16a: n/a - not a randomized controlled trial
- 16b: n/a - not a randomized controlled trial
- 16c: n/a - not a randomized controlled trial
- 17a: n/a - not a randomized controlled trial
- 17b: n/a - not a randomized controlled trial
- 26b: n/a - no additional collection of biological specimens is stipulated as part of this observational study
- 30: n/a - given the observational nature of this study and implementation of ERAS as standard of care, any adverse clinical outcomes are deemed expected as part of the course of treatment and not the study itself
- 31c: n/a - there are currently no plans for public sharing of the data set
- 33: n/a - none are collected as part of the study This checklist was completed on 25. March 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai