PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Design and Development of the Pediatric Urology Recovery After Surgery Endeavor (PURSUE) Multi-Center Pilot and Exploratory Study
AUTHORS	Rove, Kyle; Strine, Andrew; Wilcox, Duncan; Vricella, Gino; Welch, Timothy; VanderBrink, Brian; Chu, David; Chaudhry, Rajeev; Zee, Rebecca; Group, PURSUE Study; Brockel, Megan

VERSION 1 – REVIEW

REVIEWER	Bernhard Haid Department of Pediatric Urology, Ordensklinikum Linz, Hospital of the Sisters of Charity, Linz, Austria
REVIEW RETURNED	10-Apr-2020

GENERAL COMMENTS	The time for ERAS in pediatric surgery and pediatric urology definitively has come, however, in order to reproduce the benefits seen in adult patients, robust evidence on pediatric ERAS protocols is needed. The PURSUE trial will be able to deliver this information and therefore this study is of highest priority and importance to the field of pediatric urology. The study protocol clearly outlines the rationale, the design, the statistical implications as well as potential limitations to this study. In regard to (1) the frequency of these interventions which is low even in high-volume centers and (2) the heterogeneity of the patients to be included (neurogenic / on neurogenic / bowel...) clear inclusion criteria are well defined in this protocol. In the ERAS items (Table 1 Comprehensive list) regional anesthesia is mentioned only under "intra operative" - it is to be assumed there is a reason for that, otherwise an epidural catheter might provide optimal postoperative regional anaesthesia in line with the ERAS philosophy (promoting bowel activity via symphaticomimetic effects, avoiding opioid use). Also, chewing gum use is part of many ERAS protocols with good evidence in the adult population - and enthusiastic acceptance in the pediatric population (at least here in Europe). The outcome measures are clearly defined as well - from a european perspective the non-opioid pain medication use could be an interesting factor (we rarely prescribe opioids postoperatively, with very few exceptions e.g. if an epidural catheter is not possible - this could theoretically be another - positive - component of ERAS - use of NSAIDs - as opioids are not promoting bowel movements). However, in view of the setting of this trial this is a logical decision. As there are no validated patient reported outcome measure for such a setting it seems appropriate to use open-ended surveys.

	Epidural (also postoperative) analgesia might influence some of the endpoints - this could be used as stratum for the propensity matched analysis. This is a perfectly set-up study protocol, the authors are to be commended for publishing it. The results of the PURSUE trial will help significantly shaping the way how we all care for our patients.

REVIEWER	Ewan M Brownlee Department of Paediatric Urology Southampton Children's Hospital University Hospitals Southampton United Kingdom
REVIEW RETURNED	30-Jun-2020

GENERAL COMMENTS	This is an excellent idea! Congratulations on a very thoroughly planned protocol for this pilot and exploratory study. Your planned use of historic cases as a control group seems to be the pragmatic approach given the small numbers of these cases any centre performs and the potential confounding factors of other study options as described well in the study design section. I have adopted several of the measures you plan to study for lower urinary tract reconstruction and feel subjectively that these are helpful, so am very excited to see the results of your trial and will be very interested to see if ERAS is proven for these patients!

REVIEWER	Eric Jelin Johns Hopkins University
REVIEW RETURNED	15-Sep-2020

GENERAL COMMENTS	I think this is a well thought out way to prospectively study ERAS. The methodology is well presented and will be a model for other fields trying to study pediatric ERAS. I am confused why no oral preoperative antibiotics will be used. There is clearly data that supports this element in general surgery. I would expect this to be quite important in cases that involve violation of the GI tract. The data on mechanical bowel prep with antibiotics is also compelling. I think this should be directly addressed.

VERSION 1 – AUTHOR RESPONSE

The time for ERAS in pediatric surgery and pediatric urology definitively has come, however, in order to reproduce the benefits seen in adult patients, robust evidence on pediatric ERAS protocols is needed. The PURSUE trial will be able to deliver this information and therefore this study is of highest priority and importance to the field of pediatric urology.

The study protocol clearly outlines the rationale, the design, the statistical implications as well as potential limitations to this study. In regard to (1) the frequency of these interventions which is low even in high-volume centers and (2) the heterogeneity of the patients to be included (neurogenic / on neurogenic / bowel...) clear inclusion criteria are well defined in this protocol.

Response: We appreciate the feedback. We aimed to create a study protocol that would be generalizable to other pediatric urologists and surgeons who perform similar operations on a heterogenous group of patients.

In the ERAS items (Table 1 Comprehensive list) regional anesthesia is mentioned only under "intra operative" - it is to be assumed there is a reason for that, otherwise an epidural catheter might provide optimal postoperative regional anaesthesia in line with the ERAS philosophy (promoting bowel activity via symphaticomimetic effects, avoiding opioid use). Also, chewing gum use is part of many ERAS protocols with good evidence in the adult population - and enthusiastic acceptance in the pediatric population (at least here in Europe).

Response: The reviewer is correct that although we have listed regional analgesia under intraoperative, this was only to denote when it is started. The ERAS protocol recommends that providers continue the catheter-based regional analgesia into the post-operative period up to postoperative day 5. This is explained in the Supplemental Table 1. Regarding the use of chewing gum, this was debated in the initial design of the clinical protocol. The study group felt that ordering a diet (clears postoperative day 0 and regular postoperative day 1) would provide adequate stimulation of the gastrointestinal tract and that gum chewing would not necessarily add benefit. Additionally, gum is not made readily available to patients at some the participating centers.

The outcome measures are clearly defined as well - from a european perspective the non-opioid pain medication use could be an interesting factor (we rarely prescribe opioids postoperatively, with very few exceptions e.g. if an epidural catheter is not possible - this could theoretically be another - positive - component of ERAS - use of NSAIDs - as opioids are not promoting bowel movements). However, in view of the setting of this trial this is a logical decision. As there are no validated patient reported outcome measure for such a setting it seems appropriate to use open-ended surveys.

Response: We had hoped to stick to validated questionnaires but, as you correctly point out, there are few that address the area of recovery in children and young adults. There are some more recently developed questionnaires within PROMIS that may be suitable but do not provide a broad picture of recovery and are more focused in scope (pain interference, mobility, etc).

Epidural (also postoperative) analgesia might influence some of the endpoints - this could be used as stratum for the propensity matched analysis.

Response: We plan to perform secondary stratified analyses on certain covariates of interest, including regional analgesia.

This is a perfectly set-up study protocol, the authors are to be commended for publishing it. The results of the PURSUE trial will help significantly shaping the way how we all care for our patients.

Response: We appreciate the feedback.

Reviewer #2:

This is an excellent idea! Congratulations on a very thoroughly planned protocol for this pilot and exploratory study.

Response: Much appreciated

Your planned use of historic cases as a control group seems to be the pragmatic approach given the small numbers of these cases any centre performs and the potential confounding factors of other study options as described well in the study design section.

Response: We agree this should provide a pragmatic approach. While retrospective abstraction is not without its pitfalls, we have found the outcomes of interest are reliably documented as part of standard of care and thus missing data should be very minimal. Additionally, initial analysis of historical data show that outside of ERAS, the overall surgical approach has not changed dramatically, thus offering suitable comparison.

I have adopted several of the measures you plan to study for lower urinary tract reconstruction and feel subjectively that these are helpful, so am very excited to see the results of your trial and will be very interested to see if ERAS is proven for these patients!

Response: We look forward to sharing our results with our peers.

Reviewer #3:

I think this is a well thought out way to prospectively study ERAS. The methodology is well presented and will be a model for other fields trying to study pediatric ERAS. I am confused why no oral preoperative antibiotics will be used. There is clearly data that supports this element in general surgery. I would expect this to be quite important in cases that involve violation of the GI tract. The data on mechanical bowel prep with antibiotics is also compelling. I think this should be directly addressed.

Response: This is an important point and one we have discussed extensively within the study group. The data on oral antibiotic and mechanical bowel preparation have been extrapolated from adult studies on colonic (large bowel) resections. While there is excellent data to support their use in an adult population for this specific resection, the vast majority of lower urinary tract reconstruction is performed using small bowel. We are not sure the practice of oral antibiotics and mechanical bowel preparation are generalizable to these surgeries. This is not to say we are not interested in this question, as it is an important one. We believe that our historical controls at some centers may have used this practice and we hope to study this in a secondary analysis to see if there is a difference, particularly in the incidence of surgical site infections (deep or superficial). Previous study in pediatric lower urinary tract reconstruction of mechanical bowel preparation alone vs no bowel preparation did not show any differences in urinary tract infection, surgical site infection, or ventriculoperitoneal shunt infection (Gundeti 2006). The rarity of this particular population has made it very difficult to answer this question. We do still hope that our data set will be able to provide some illumination to the topic. We have added a statement under Methods and Analysis - ERAS Protocol Development to address this ongoing controversy.

VERSION 2 – REVIEW

REVIEWER	Eric Jelin Johns Hopkins University
REVIEW RETURNED	18-Oct-2020

GENERAL COMMENTS	concerns addressed.