FINAL PROGRESS REPORT

Title of Project:
Pursuing Perfection in Pediatric Therapeutics

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Abstract

Purpose: The 2007–2012 Cincinnati Children's CERTs Research Center (RC) aimed to improve outcomes for children by optimizing the use of therapeutics. Subthemes included quality and patient safety, practice-based research and improvement networks, pharmacogenomics, and performance metrics.
Scope: The RC created a research core that supported clinicians and scientists in developing and testing innovative therapeutics and education projects. In addition, the RC created new knowledge about how to use therapeutics effectively and how to translate that knowledge more rapidly into practice, resulting in safer and more effective clinical practice and improved patient outcomes.
Methods: The RC utilized existing capabilities to develop and disseminate evidence-based research and education programs in order to improve patient outcomes. The RC linked an acknowledged leader in innovation and improvement; a research core skilled in evaluation science, improvement science, and education; and partners capable of disseminating research and education programs to the vast majority of the nation's pediatric practitioners and tertiary care settings.
Results: The RC successfully supported the initiation of multiple national multisite pediatric research and improvement networks
Key Words: Pediatrics, Improvement Networks, Pharmacogenomics, Safety, Quality Improvement Research

Purpose

Children receive less than 50% of indicated care.[i,ii] This stark fact illustrates the chasm between evidence and practice and highlights continuing deficiencies in pediatric safety and quality. Effective use of therapeutics is fundamental to improving care and outcomes for children: "What does it take to deliver the right therapeutic to the right child at the right time in the right way–every time?"[iii] Without substantial progress in answering this question, the nation's investment in basic and translational research on pediatric therapeutics will fall short. More importantly, children and their families will suffer unnecessarily.

With the receipt of an initial 4 years of funding, the Cincinnati Children's (CCHMC) CERTs Research Center (RC) aimed to improve outcomes for children by optimizing the use of therapeutics. Subthemes included quality and patient safety, practice-based research and improvement networks, performance metrics, and pharmacogenomics.

The CCHMC CERTs RC leadership was composed of faculty from the James M. Anderson Center for Health Systems Excellence (formerly the Center for Healthcare Quality) at Cincinnati Children's. The dissemination partners included the American Academy of Pediatrics (AAP; a medical specialty society), the American Board of Pediatrics (ABP; a certifying body), the National Association of Children's Hospitals and Related Institutions (NACHRI), Children's Hospital Corporation of America (CHCA), Ohio Medicaid, the University of Cincinnati, College of Pharmacy, UnitedHealth Group, and several parent organizations. The RC also included an advisory committee composed of individuals and representatives of organizations working to improve care for children.

Within this framework, the RC aimed to create new knowledge about how to use therapeutics effectively *and* how to translate that knowledge more rapidly into practice, resulting in safer and more effective clinical practice and improved patient outcomes. The specific aims were to:

1. Support clinicians and scientists in the development and testing of innovative therapeutics and education programs by creating a research core to bring together individuals with broad expertise in evaluation, health services research, quality improvement methods, analysis of large databases, quality of life, chronic illness, and medication adherence.

2. Develop and implement a range of educational approaches that result in broad improvements in the use of therapeutics in the pediatric population, building on well-established partnerships and strong working relationships with public and private organizations.

Scope

Many important differences between adults and children create unique challenges for the use of pediatric therapeutics. These child-specific issues have been characterized as 'the four D's,[iv,v,vi] (development, dependency, differential epidemiology and demographics). Children experience rapid and continuous physical, emotional, cognitive, and social *developmental* changes that have implications for the safety, dosage, and metabolism of medications. Caregivers play substantial roles in determining use of prescribed drugs, devices, and services. This *dependency* increases the need for shared decision-making tools. Although most children experience numerous mild, self-limited illnesses, 14% are children with special healthcare needs,[vii] (CSHCN), an AHRQ priority population. Finally, *demographic differences* are profound. One fifth of US children live in poverty, 63.6% of whom are minorities.[viii] These low-income, minority children are an AHRQ priority population, and research in therapeutics in children has particular implications for minimizing disparities in care.

Most drugs, biologics, and medical devices marketed to adults are investigated using randomized controlled trials, but these modalities are rarely tested in children, in large part because individual centers do not have enough children to achieve large and representative sample sizes. Furthermore, in the absence of standardized care delivery, variations in care are prevalent, reducing statistical power to make valid conclusions. Therefore, basic evidence to establish safety and efficacy of therapeutic interventions in children—let alone their effectiveness in real-world settings—is lacking.

The RC utilized existing capabilities to develop and disseminate evidence-based research and education programs in order to improve patient outcomes. The RC linked an acknowledged leader in innovation and improvement; a research core skilled in evaluation science, improvement science, and education; and partners capable of disseminating research and education programs to the vast majority of the nation's pediatric practitioners and tertiary care settings.

Practice-Based Research and Improvement Networks make significant contributions in testing different models for diffusing innovations in pediatric subspecialty care and evaluating effectiveness of elements of chronic care models. They are also useful for developing infrastructure for primary data collection to support pediatric comparative effectiveness research to improve patient-centered healthcare.

Project teams participating in networks in which the 2007–2012 CCHMC CERTs contributed to design and/or implementation include clinicians and researchers at 94 sites, 35 states, Washington, DC, London, and Toronto as well as 44 of the 55 Clinical and Translational Science Awards (CTSA) Institutions.

The following six networks were supported by the 2007–2012 CERTs RC funding:
1. Improve Care Now (ICN): ICN is an international practice-based research and improvement network that aims to improve care and outcomes for children with inflammatory bowel disease (IBD) (www.improvecarenow.org).
2. Solutions for Patient Safety (SPS): SPS is composed of eight Ohio children's hospitals. These sites are collaborating to improve outcomes in medication safety and surgical site infections.
3. Ohio Perinatal Quality Collaborative (OPQC): OPQC is a statewide consortium of perinatal clinicians, hospitals, and policymakers that aims, through the use of improvement science, to reduce preterm births and improve outcomes of preterm newborns (www.opqc.net).
4. The Joint Council on Congenital Heart Disease (JCCHD) National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC): The NPC-QIC is composed of US pediatric surgical centers for infants with complex congenital heart disease (CHD) working to reduce mortality and readmissions, optimize growth, and improve care transitions and coordination (www.jcchdqi.org).
5. Pediatric Rheumatology—Care and Outcomes Improvement Network (PR-COIN): PR-COIN is an early-stage Learning Network focused on improving outcomes of children with juvenile idiopathic arthritis (http://pr-coin.org/).
6. Studies of Pediatric Liver Transplantation (SPLIT) Research Group: SPLIT, a robust research network founded in 1995, explored the use of QI methods to develop initiatives to optimize nutrition in children pre-transplant and reduce perioperative infections. Dr. Lannon, RC PI, is leading QI design efforts.

The following three projects were also supported by the 2007–2012 CERTs RC funding:

1. Pharmacogenetics: This project attempted to assess the impact of pharmacogenetic testing on the treatment of children with risperidone. As it turned out, we were unable to recruit sufficient patients to participate in the study. We built on this experience to develop a manuscript summarizing successful recruitment practices for pharmacogenetic testing.
2. Adverse Drug Events: This project developed successful strategies to decrease harm from adverse medication events through the use of reliability science; this project was the basis for one of the initial projects through the Ohio SPS network.
3. National Performance Measures: This project utilized two practice-based networks to assess the use of performance metrics for otitis media with effusion, including the use of therapeutics.

Methods

A primary RC focus was on the development and testing of strategies to understand how practice-based research and improvement networks can most effectively prevent, treat, and improve care and outcomes of children with chronic disease.

Although these projects focused on care for children, the methods and knowledge generated extend beyond the pediatric population and have advanced the field of therapeutics by creating new knowledge about the infrastructure need to support multisite improvement and research, how to integrate high-reliability methods into care systems, and how to use quality improvement methods and collaborative learning to test and accelerate the diffusion of innovations into practice.

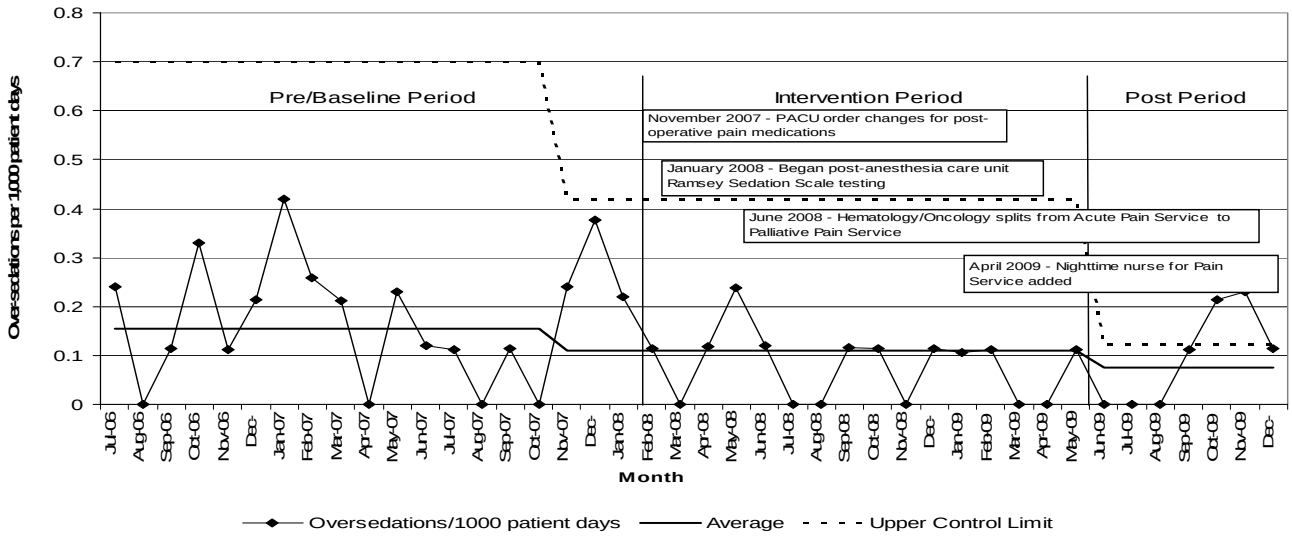
Results

Project teams participating in networks in which the 2007–2012 CCHMC CERTs contributed to design and/or implementation include clinicians and researchers at 94 sites, 35 states, Washington, DC, London, and Toronto as well as 44 of the 55 Clinical and Translational Science Awards (CTSA) Institutions. The networks varied in stage of development, but many were able to demonstrate improvements in the delivery of and outcomes of care for children. Below is a summary of networks key accomplishments:

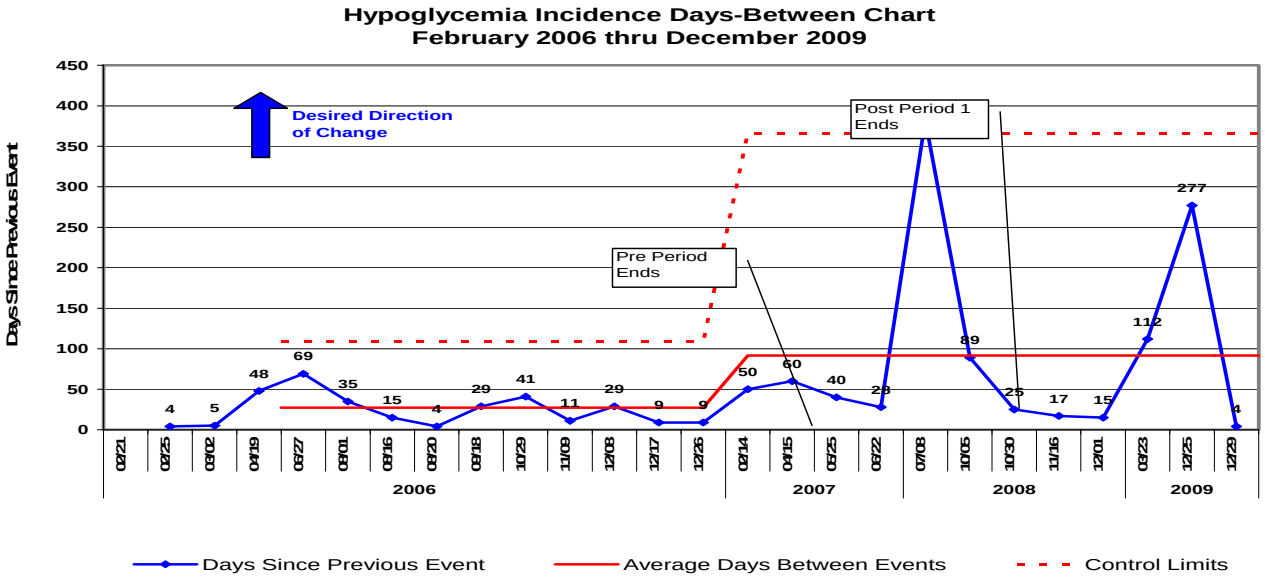
Solutions for Patient Safety (SPS)

Initial work at CCHMC funded by CERTs addressed whether automated trigger detection and implementation of high-reliability strategies can decrease frequency of Adverse Drug Events (ADEs). An article that describes this model and shows how trigger tools can be used to affect safety was published. Next, we focused on three specific triggers (opiate oversedation, hypoglycemia in nondiabetic children treated with insulin in the ICU, and IV infiltrates) and achieved reductions in ADEs (please refer to the following three run charts for status of triggers as of April 30, 2009).

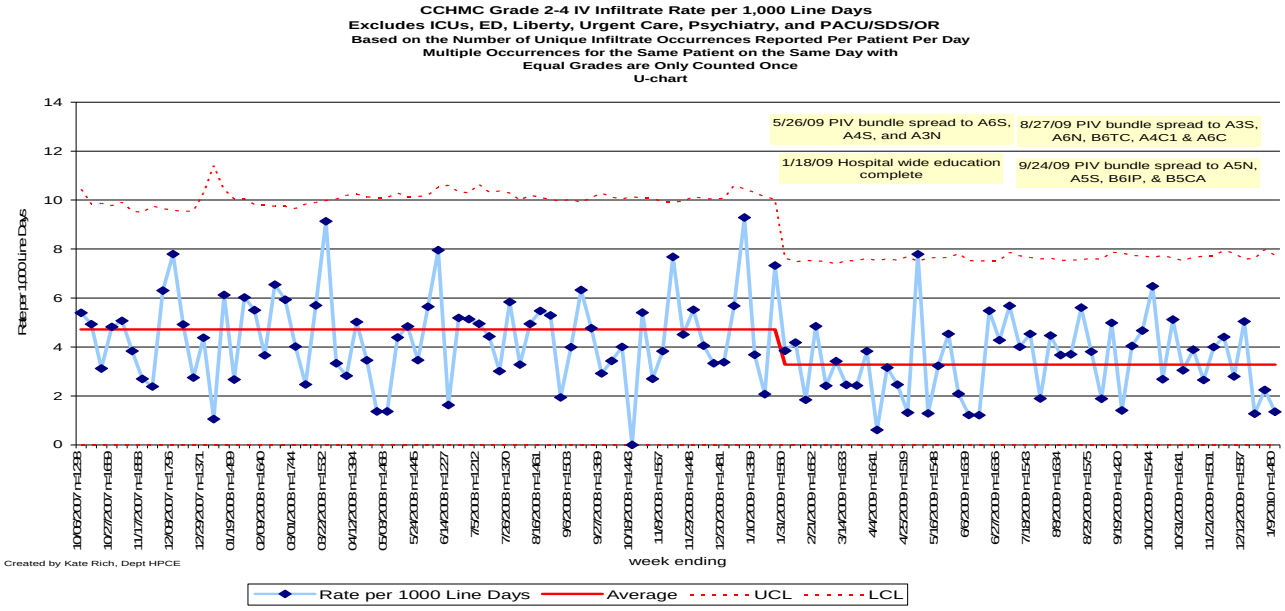
Opiate oversedation



Insulin-related hypoglycemia



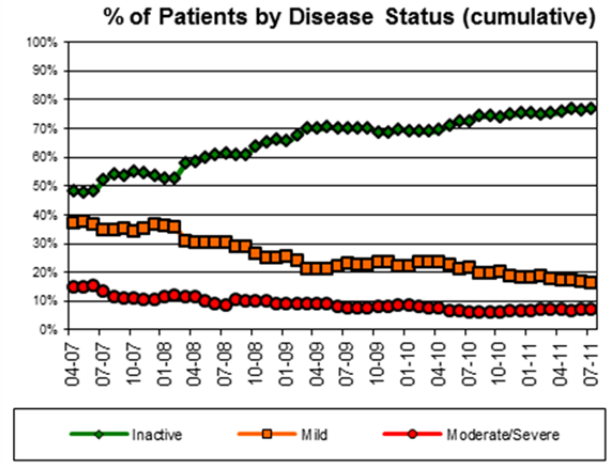
IV infiltrates



The Adverse Drug Events work supported by the CCHMC CERT has improved care and outcomes for children in one large hospital and has implications in generalizing knowledge about improving patient safety. Of note, Cincinnati Children's received a Child Health Corporation of America (CHCA) RACE for Results performance improvement award for reducing serious safety events based in part on these efforts.
Building on this CCHMC CERTs trigger tool project, all eight Ohio children's hospitals began a collaboration known as **Solutions for Patient Safety (SPS)** to improve outcomes in medication safety and surgical site infections. Between 1/2009 and 12/2010, the project resulted in a 60% reduction in surgical site infections in designated procedures and a 34.5% reduction in overall ADEs, saving an estimated 3,576 children from harm and saving over $5.2 milllion in healthcare costs. CERTs funded the Program on Organization Studies at the Boston University School of Public Health to conduct a series of interviews with quality and safety teams at each of the eight hospitals to evaluate the facilitators and barriers involved in implementing the safety initiatives. This public-private partnership continues with a focus on reducing eight types of harm by 50% in the next 24 months. In addition, based on initial results in the eight hospitals, the Ohio SPS received a CMMI grant to spread the methods and lessons learned to an additional 25 children's hospitals in 2012 with additional scale-up and spread over the next 2 years.

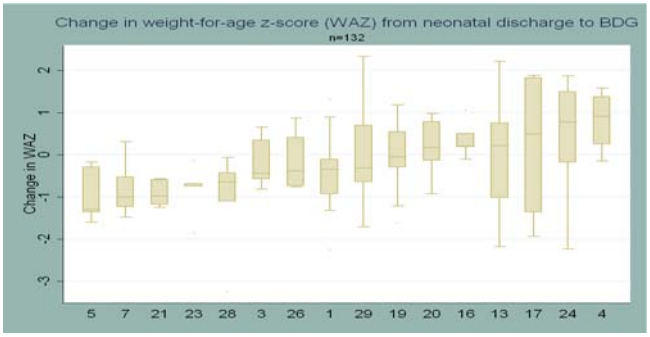
ImproveCareNow (ICN): ICN has evolved into a 29-site, international practice-based research and improvement network that aims to improve care and outcomes for children with inflammatory bowel disease (IBD). From 1/2007 to 10/2009, the remission rate in network sites increased from 49.1% to 76.6% ($p<0.001$) without the use of new medications but via increased adherence to protocols for the use of existing therapies. ICN has developed and is testing tools to implement a model care guideline for IBD, a self-management support workbook (including medication adherence), and a population management report (using data from their population registry). Dr. Margolis, RC faculty, is ICN's Scientific Director. Two important research efforts build on the ICN foundation: 1) an AHRQ Enhanced Registries grant and 2) an NIH-funded Transformative TR01 grant that is using an open-science framework to link researchers,

clinicians, and patient/family communities in the process and innovation of improving health. C3N is testing multiple innovative approaches to improve chronic illness; a description of each is provided in appendices. The lessons learned will be applicable not only to the care of children with chronic disease but also to other improvement networks, extending their impact.



A graph of the percentage of Crohn's disease and ulcerative colitis patients with inactive disease, shown to the left, demonstrates an increase from 50% to 75% from 2007 to 2011. During that time, the percentage of patients not taking prednisone also increased, and the processes of care have improved as well.

The Joint Council on Congenital Heart Disease (JCCHD) National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC): Teams from 46 pediatric cardiology centers, representing one third of all US pediatric surgical centers for infants with complex congenital heart disease (CHD), are working to reduce mortality and readmissions, optimize growth, and improve care transitions and coordination. This network is the first QI effort in pediatric cardiology (www.jcchdqi.org). CERTs funding supported network research efforts that identified significant variation among centers in growth in infants during the interstage, resulting in a nutritional algorithm, currently being evaluated in multiple cardiology centers. This work has resulted in several publications.



The figure (left) describes the variation across 16 of the largest centers in the change in weight-for-age z score during the interstage period. Patients who have a positive change in this score over the interstage have weight gain, versus those with negative scores. NPC-QIC used information from the highest-performing sites to develop a Growth Bundle (of best practices) that is currently being tested in 35 sites.

Pediatric Rheumatology—Care and Outcomes Improvement Network (PR-COIN): PR-COIN is an early-stage Learning Network focused on improving outcomes of children with juvenile idiopathic arthritis. Eleven teams participated in the networks first Learning Session in June 2011 and are now focusing on interventions around TB screening, uveitis, and joint count as well as monthly registry data collection.

Ohio Perinatal Quality Collaborative (OPQC): Initial OPQC projects, supported by a CMS Neonatal Transformation grant, resulted in 1) a 20% sustained decrease in bloodstream infections in premature infants among 24 NICUs and 2) a 40% decrease in near-term deliveries without medical indications (20 OB units). This has resulted in annual decreases of 6,000 fewer than expected Ohio births at 36-38 weeks and 150-250 fewer near-term infants admitted to the NICU. Together, the reductions in infections and NICU admissions created estimated savings of at least $11 million annually. CERTs funding supported the collection of pilot data among the 20 obstetric hospitals to better understand why only 80% of eligible pregnant women receive antenatal corticosteroids. These data have helped develop a current OPQC project in the maternity hospitals.

Studies of Pediatric Liver Transplantation (SPLIT) Research Group: SPLIT, a research network founded in 1995, evaluated whether their data registry could be utilized to develop initiatives to optimize nutrition in children pre-transplant and reduce perioperative infections. Through a pilot effort, it was determined that the retrospective registry data lacked the detail needed to provide specific enough baseline information to inform a QI project.

Importantly, the network-based projects described above contributed to an understanding of the infrastructure and programmatic components necessary for initiating, developing, and sustaining successful network initiatives. This has spawned useful knowledge, facilitated new collaborations, and helped to establish a strong foundation that will enable us to accelerate and support effective new efforts.

Below is a summary of the results of the additional projects that the 2007–2012 CERTs RC supported:

National Performance Measures:
The center, in conjunction with the American Academy of Pediatrics (AAP) and with the collaboration with the American Medical Association, summarized the results of the project to assess the reliability and accuracy of performance measures developed to evaluate the care of Otitis Media with Effusion by the AMA Physician Consortium for Performance Improvement. One of the measures is being considered for inclusion in the core set of measures for the Child Health Insurance Program Reauthorization Amendment. This resulted in a publication in Pediatrics.

This project has implications for 1) emphasizing the importance of testing measures prior to adoption and 2) understanding how quality measures developed for accountability can be utilized to support improvements in care that will lead to effective use of pediatric therapeutics.

Pharmacogenetics:
An objective of our initial project on pharmacogenetics was to develop methods that will be required to study the application of pharmacogenetic testing to various conditions. Unfortunately, despite multiple adjustments in recruiting strategies, the initial project (The Impact of Pharmacogenetics on Outcomes and Safety of Children and Adolescents on Risperadone) could not recruit sufficient numbers of patients to conduct the analysis. As a result, the project leads developed a manuscript summarizing successful recruiting practices among several CCHMC projects focusing on pharamcogenetics. In addition, we supported two projects that evaluated the use of pharmacogentic testing in specific clinical settings: 1)

attention deficit hyperactivity disorder and 2) renal transplant. These projects resulted in publications.

List of Publications and Products

Select publications and products from the 2007–2012 CERTs RC are listed below:

Kugler JD, Beekman III RH, Rosenthal GL, et al. Development of a pediatric cardiology quality improvement collaborative: from inception to implementation. From the Joint Council on Congenital Heart Disease Quality Improvement Task Force. *Congenit Heart Dis*. 2009 Sep-Oct;4(5):318-28.

Margolis P, Halfon N. Innovation networks: a strategy to transform primary health care. *JAMA.* 2009 Oct 7;302(13):1461-2.

Muething SE, Conway PH, Kloppenborg E, et al. Identifying causes of adverse events detected by an automated trigger tool through in-depth analysis. *Qual Saf Health Care.* 2010 Oct;19(5):435-9.

Simpson LA, Peterson L, Lannon CM, et al. Special challenges in comparative effectiveness research on children's and adolescents' health. *Health Aff* (Millwood). 2010 Oct;29(10):1849-56.

Crandall W, Kappelman MD, Colletti RB, et al. ImproveCareNow: The development of a pediatric inflammatory bowel disease improvement network. *Inflamm Bowel Dis*. 2011 Jan;17(1):450-7.

Kappelman MD, Crandall WV, Colletti RB, et al. Short pediatric Crohn's disease activity index for quality improvement and observational research. Inflamm Bowel Dis. 2011 Jan;17(1):112-7

Baker-Smith CM, Neish SR, Klitzner TS, et al. Variation in postoperative care following stage I palliation for single-ventricle patients: a report from the Joint Council on Congenital Heart Disease National Quality Improvement Collaborative. *Congenit Heart Dis*. 2011 Mar-Apr;6(2):116-27.

Brown DW, Connor JA, Pigula FA, et al. Variation in preoperative and intraoperative care for first-stage palliation of single-ventricle heart disease: a report from the Joint Council on Congenital Heart Disease National Quality Improvement Collaborative. *Congenit Heart Dis*. 2011 Mar-Apr;6(2):108-15.

Pasquali SK, Sun JL, d'Almada P, et al. Center variation in hospital costs for patients undergoing congenital heart surgery. Circ Cardiovasc Qual Outcomes. 2011 May;4(3):306-12.

Tundia NL, Heaton PC, Kelton CM. The national burden of E-code-identified adverse drug events among hospitalized children using a national discharge database. *Pharmacoepidemiol Drug Saf*. 2011 Aug;20(8):866-78.

Crandall WV, Boyle BM, Colletti RB, et al. Development of process and outcome measures for improvement: lessons learned in a quality improvement collaborative for pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2011 Oct;17(10):2184-91.

Vermaire D, Caruso MC, Lesko A, Kloppenborg E, et al. Quality improvement project to reduce perioperative opioid oversedation events in a paediatric hospital. *BMJ Qual Saf*. 2011 Oct;20(10):895-902.

Froehlich TE, Epstein JN, Nick TG, et al. Pharmacogenetic predictors of methylphenidate dose-response in attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2011 Nov;50(11):1129-1139.e2.

Saldaña SN, Hooper DK, Froehlich TE, et al. Characteristics of successful recruitment in prospective pediatric pharmacogenetic studies. Clin Ther. 2011 Dec;33(12):2072-81.
"Anderson JB, Iyer SB, Schidlow DN, et al. Variation in Growth of Infants with a Single Ventricle. *J Pediatr*. 2012 Feb 14."

Heaton PC, Tundia NL, Schmidt N, et al. National burden of pediatric hospitalizations for inflammatory bowel disease: results from the 2006 Kids' Inpatient Database. *J Pediatr Gastroenterol Nutr*. 2012 Apr;54(4):477-85.

ImproveCareNow website:
www.improvecarenow.org

Link to video:
http://www.improvecarenow.org/joinus

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