A Quality Improvement Approach to External Infliximab Infusions in Pediatric Inflammatory Bowel Disease

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ABSTRACT

Objectives: We used a quality improvement (QI) approach to improve access and reduce barriers to care by increasing the number of external infliximab infusions at our pediatric inflammatory bowel disease center.

Methods: Using an iterative QI strategy, pediatric patients ≥12 years of age with inflammatory bowel disease were offered the opportunity to receive infliximab infusions at home/an external infusion center. They were required to first have >5 infusions at the hospital without any significant infusion reactions. Data were collected and tracked monthly using P-charts. Comparisons between control chart centerlines were analyzed using the Fisher exact test.

Results: Fifty-four patients received external infusions, 87% had Crohn disease, 63% boys, average age 17.6 ± 2.9 years, and 89% with private insurance. From September 2016 to January 2018, the percentage of eligible patients receiving external infusions was approximately 7%, increasing to approximately 30% by January 2018. A centerline shift, representing a statistically significant change, occurred in October 2016 and June 2017 ($P < 0.001$). No serious safety concerns have occurred.

Conclusions: Through a multidisciplinary team of stakeholders using QI strategies, we now offer external infusion service options to all appropriate patients as routine practice. Home infusions are a viable option to reduce barriers to care, and our patients did not experience any safety events.

Key Words: children, Crohn disease, home infusions, infliximab, infusion services, ulcerative colitis

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What Is Known

- Infliximab infusions are a common treatment for children and adolescents with inflammatory bowel disease.
- Receiving infliximab infusions at hospital-based infusion centers may create burdens for our patients and families (eg, travel, limited scheduling, cost, missed school/work).

What Is New

- We developed a safe alternative to hospital-based infusion services for pediatric patients receiving infliximab infusions using a quality improvement approach.
- External infusion options may improve access to infliximab infusion services and reduce the treatment and financial burden.

Antitumor necrosis factor (TNF) alpha agents, such as infliximab, are a mainstay of treatment for inflammatory bowel disease (IBD) (1–4). Studies have shown that most patients experience a response to infliximab, and a delayed need for surgery (5–9). There are, however, several practical disadvantages to this modality of treatment. Infliximab treatment is only available as an infusion, which is costly and may take several hours. Furthermore, the infusions have traditionally been provided at hospital-based infusion centers, often requiring travel and time off from work and school, and an additional cost as compared to free-standing infusion centers. As such, insurers are beginning to mandate that infusions occur outside of the hospital setting.

More than 200 patients with IBD seen at Nationwide Children's Hospital (NCH) are receiving infliximab infusions. Many patients and their families had expressed concerns regarding a lack of flexibility of infusion times leading to missed school, activities, and work. We therefore explored alternative options such as external/home infusions to improve convenience and decrease cost to the families. We found that home and external infusions could be offered at more times, including weekends, than our hospital infusion clinic, and the cost was significantly less.

As a consequence, we sought to develop a safe and reliable alternative to hospital-based infusions using an iterative quality improvement (QI) approach. We have previously used this approach to increase the utilization of enteral nutrition in pediatric

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patients with Crohn disease (10) and decrease safety event rates, preventable harm, and hospital mortality (11).

Project Aim

Our aim was to increase the percentage of patients ≥12 years of age with IBD treated with infliximab who are receiving external infusions from 5% to 15% by December 2016 and then 30% by June 2017, and maintain for 6 months.

METHODS

Setting

This project was conducted at NCH in The Center for Pediatric and Adolescent Inflammatory Bowel Disease. Our division includes 40 medical providers and treats more than 650 patients with IBD. The IBD Center is composed of 4 IBD-focused physicians, who provide care for the majority of patients with IBD at NCH. Approximately 50% of our IBD population is treated with anti-TNF therapy, the majority receiving infliximab. Before September 2016 when this project began, patients rarely received external infusions unless there was an extenuating circumstance (eg, mandated by insurance provider).

We assembled a multidisciplinary team of stakeholders, which included: IBD physicians, a nurse practitioner, a social worker, nurses, a parent (of a child already receiving home infusions), NCH homecare, an external home care company representative, QI services, our QI data analyst, a pediatric resident, a pharmacist, and an administrative assistant.

This was a QI project and did not require Institutional Review Board approval.

Inclusion Criteria

Patients receiving infliximab were eligible for participation if they were 12 years or older and had received at least 6 infusions (3 induction and 3 maintenance). We selected age 12 as the minimum age due to our impression that freestanding infusion clinics and adult-focused home health agencies might be less comfortable/competent in caring for younger children. The initial project design included non-NCH options; however, these options were rarely used; thus, the strict age criterion was eventually lifted. We selected 6 completed infusions as inclusion criteria because our patients were changed to a rapid infusion protocol after the fifth dose, and we wanted to assure that the rapid infusion was tolerated before the transition to an external infusion.

Key Drivers and Interventions

Through a series of in-person meetings and telephone calls, we developed an Aim and Key Driver Diagram and process map (Fig. 1 and Appendix A, Supplemental Digital Content, *http://links.lww.com/MPG/B669*, respectively). Key drivers included external infusion centers and home infusion availability;

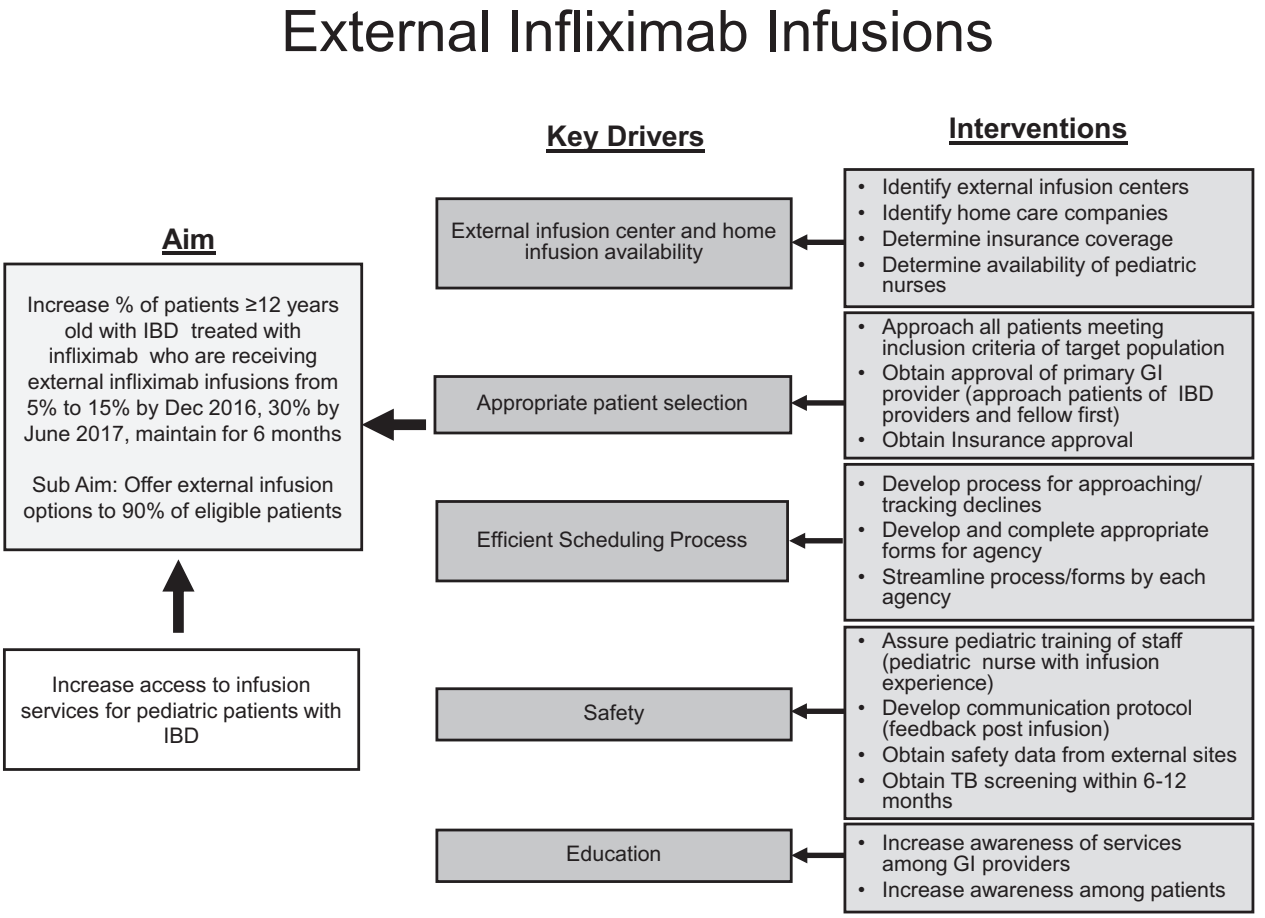


FIGURE 1. Key driver diagram. GI = gastrointestinal; IBD = inflammatory bowel disease; TB = tuberculosis.

appropriate patient selection; efficient scheduling process, safety; and education. Using the model for improvement, we used an iterative approach of Plan-Do-Study-Act cycles to identify key drivers and implement interventions.

1. External infusion centers and home infusion availability and selection. Our social worker worked with insurance companies and families to identify possible external infusion centers and home care companies that could provide services for our patients. We arranged follow-up calls, assisted with the prior authorization process as needed, and developed standard infusion order forms across infusion sites. Two homecare companies were chosen based on their affiliation with the hospital and coverage by a majority of insurance companies. NCH home care services were used first given our familiarity with the services and ease to immediately implement processes. Several meetings were held with these companies to ensure that the services requested would be executed per our requirements (eg, they would provide pediatric trained nurses, use our standard order forms, place a call to our office notifying us of the infusion and any concerns, etc). We then expanded services to include other infusion and home care companies meeting our standards.
2. Appropriate patient recruitment. We initially only offered external infusions to IBD team physicians for patients residing in counties serviced by NCH home care. As we became more experienced, we expanded it to include eligible patients from all providers and all counties.
3. Our initial approach was to send each provider a list of their eligible patients and ask that they contact their patients to offer external infusions. Due to provider time limitations, this was unsuccessful. We then tested discussing home/external infusions at clinic visits. In addition, our IBD nurse practitioner would offer external infusions to eligible patients being seen in our health maintenance IBD clinic (multidisciplinary visits led by our IBD nurse practitioner and include assessments by the social worker, psychologist, and dietitian), with prior approval from their primary gastroenterologist. If the family agreed or wanted additional information, our social worker discussed the external infusion options and what to expect during the process. If families were interested, an external infusion agency was identified and the physician completed the home/external infusion orders. The home care company/agency worked with the family to schedule the first infusion.
4. Efficient scheduling process. We designed specific pediatric infusion order sets for both NCH Homecare and one of the main external infusion companies. The standardized order sets streamlined the ordering process and assured that appropriate forms were completed for the agencies. The social worker helped develop a process for approaching eligible patients and guiding patients and families through initiating external infusions as noted above. Orders would then be placed by the primary provider, supplies were delivered to the infusion location, and the patient would receive their first external infusion.
5. Safety evaluation. We wanted to assure high-quality home infusion services on par with those given in our infusion clinic, including pediatric nurses who are Pediatric Advanced Life Support certified. Upon completion of every infusion, the infusion nurse called the IBD nurse with an evaluation of the infusion. This evaluation includes whether or not the infusion was completed and if the patient suffered any adverse events, the patient's weight, dose received, and when the next infusion was scheduled. The IBD nurse documented this information in our electronic health record. We declined to use any company that would not provide this communication service. The social worker called the family after the first infusion to discuss their personal experiences with the infusion and to obtain feedback. If any concerns were identified, the issues were discussed and resolved immediately with the agency.
6. Education. We increased external infusion awareness among the gastrointestinal (GI) providers by providing email communications and QI updates at our business meetings.

Eligible patients are offered an external infusion option during our health maintenance IBD visits and routine clinic visits. We also introduce this as a future option when starting infliximab. The only change was that they would be receiving their infusions at an external site or at home. Typically, patients are seen in clinic the same day as their hospital-based infusion. Patients receiving external infusions are usually seen every 3 to 4 months (after the first external infusion, the average length of time to subsequent clinic visit was 90 days). Switching to external infusions did not add any extra appointments and was favored well by families, although satisfaction was not formally evaluated. Early in the process, we recognized that obtaining labs with infusions was challenging. To improve the ease of ordering and obtaining labs (eg, specimens that require special handling such as quantiferon gold), and assuring samples were collected and arriving to the laboratory on time, we elected to obtain labs during routine clinic visits, although a few patients chose to continue to obtain labs with infusions. Therapeutic drug monitoring has not been significantly affected either, as postinduction levels are drawn while patients are still receiving infusions at our infusion clinic. When additional drug levels are indicated, we discuss this with the family and they obtain trough levels before their infusion.

Measures and Analyses

The primary measures of this project were the percentage of eligible patients that were offered external/home infusions and the percentage of eligible patients receiving external/home infusions. We tracked those that were offered external infusions as an initial process measure to assure we had an adequate process in place. Once established and the outcome measure started to improve, we no longer tracked this measure.

Statistical process control (SPC) (ie, use of control charts) employs statistical methods to monitor and control a process (12). This method is standardly used in QI initiatives and represents a statistically rigorous approach to track whether a change results in measurable improvement. We used P-charts to track performance over time, and determined centerline shifts (a statistically significant change in performance) using rules as outline by the American Society for Quality (*http://asq.org/learn-about-quality/data-collection-analysis-tools/overview/control-chart.html*). Specifically, we established a baseline using 6 months of preintervention data spanning March through August 2016, then held it constant until meeting shift rules. A centerline shift was identified based on a run of 8 in a row on the same side of the. Data were collected and tracked monthly. For those less familiar with SPC, differences in centerlines were also compared using the Fisher exact test, Minitab v. 17.1.0. A P value <0.05 was considered statistically significant.

RESULTS

Patient Population

Our center began to offer external infusions to eligible patients in October 2016. During this project period, 54 patients received external infusions (12 NCH homecare, 29 external

TABLE 1. Baseline demographics of study population

Variable	n (%)
Total number of patients	54
Number of patients with Crohn disease	47 (87)
Number of patients with ulcerative colitis	7 (13)
Age, y (avg, SD)	17.6 (2.9)
Sex	
Female	20 (37)
Male	34 (63)
Ethnicity	
White	51 (94.4)
African American	2 (3.7)
Other	1 (1.9)
Insurance coverage	
Private insurance	48 (88.9)
Crohn disease Paris classification	
L1: distal 1/2 ileum ± limited cecal	8 (17)
L2: colonic	3 (6.4)
L3: ileocolonic	34 (72.3)
L4a: upper disease proximal to the ligament of Treitz	18 (38.3)
L4b: upper disease distal to the ligament of Treitz	5 (10.6)
L4a and L4b	11 (23.4)
Disease behavior	
B1: nonstricturing, nonpenetrating	42 (89.4)
B2: stricturing	2 (4.2)
B3: penetrating	3 (6.4)
B2B3: penetrating and stricturing	0 (0)
Perianal disease	13 (27.7)
Growth	
G0: No evidence of growth delay	42 (89.4)
G1: Growth delay	5 (10.6)
Ulcerative colitis Paris classification	
Disease location	
E1: ulcerative proctitis	0 (0)
E2: left-sided UC (distal to splenic flexure)	0 (0)
E3: extensive (hepatic flexure distally)	1 (14.3)
E4: pancolitis (proximal to hepatic flexure)	6 (85.7)
Severity	
S0: never severe (PUCAI ≤65)	3 (42.9)
S1: ever severe (PUCAI ≥65)	4 (57.1)

PUCAI = Pediatric Ulcerative Colitis Activity Index; SD = standard deviation; UC = ulcerative colitis.

homecare, and 13 external infusion center). Patient demographics are outlined in Table 1. Four patients transferred to an adult GI provider or moved, and are excluded from the total number of patients currently receiving external infusions.

Outcome Measures

At baseline, providers offered external infusions to 7% of eligible patients. We noted a shift in the centerline to 22% in April 2017 ($P < 0.0001$), with the most recent month showing 48% in January 2018 being offered external/home infusions (Fig. 2). From September 2016 to January 2018, the percentage of eligible patients receiving external infusions was approximately 7%, increasing to approximately 30% by January 2018. A centerline shift, representing a statistically significant change, occurred in October 2016 (9%) and June 2017 (20%) (Fig. 3). Comparisons of the centerlines for both processes were statistically significant per Fisher exact test, $P < 0.0001$.

Of the eligible patients who were not approached, >40% were due to the provider noting they were a poor candidate (eg, prior infusion reactions, unstable home life, or significant psychosocial concerns). This category may change over time as their circumstances may change. An additional 40% of patients who were offered external infusions liked receiving their infusions at NCH infusion center and did not want to switch. Ten percent were fearful of doing infusion outside of our hospital, which may change over time as external infusions become more common. Approximately 3% were being transitioned to adult GI.

Safety Concerns

Based on the report of the infusion nurse, parent and thorough chart review, the following issues were identified: Two patients did not receive enough supplies from their homecare companies for future infusions. This was quickly identified and corrected without delaying subsequent infusions. Two patients had concerns specific to their homecare company/nurse, including poor documentation and bringing their family members with them to the patient's home. Two other patients had unusual symptoms after the infusion that were not previously experienced—1 with unexpected fatigue that spontaneously resolved and 1 with a headache that resolved after lengthening the time of the infusion. No additional safety concerns have occurred.

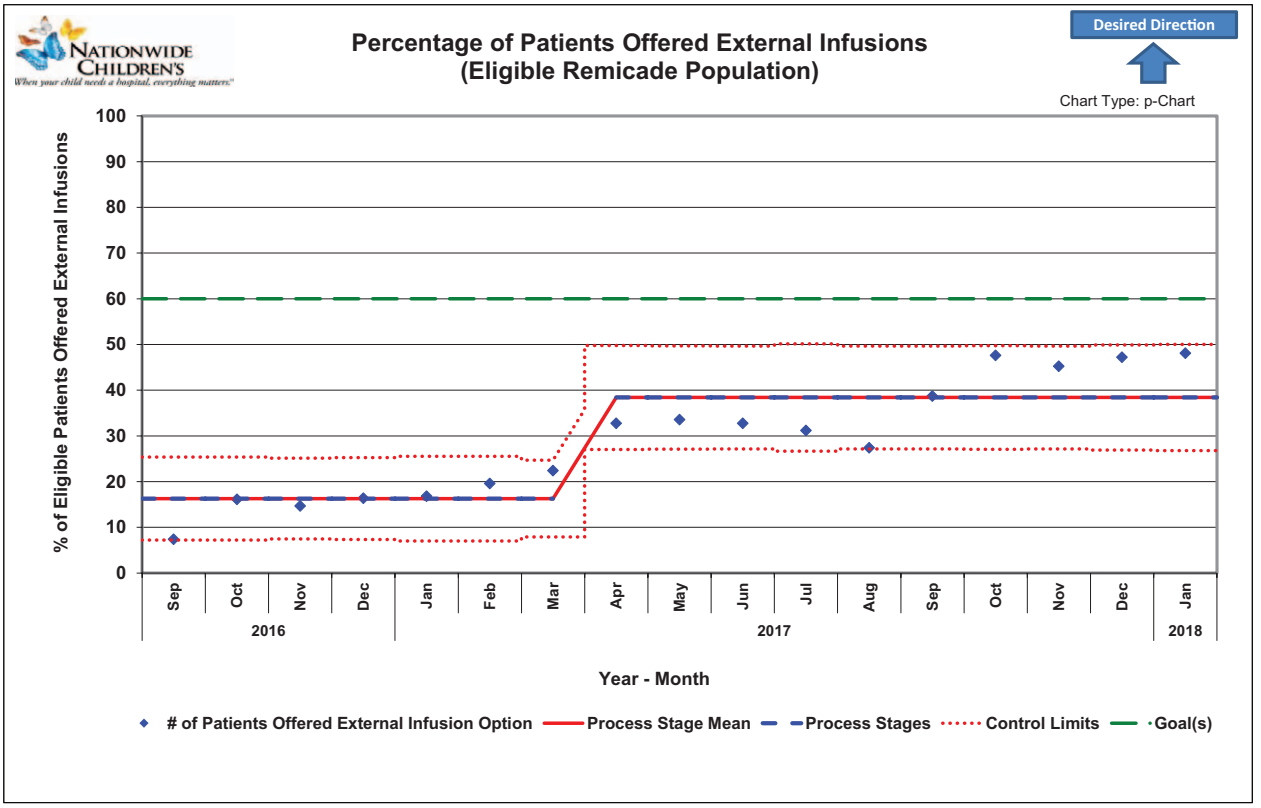
DISCUSSION

Using a systematic QI approach, we expanded infliximab infusion service options for our patients with IBD, resulting in presumed lower costs and greater flexibility. After initial steps taken by providers to approach their patients and set up infusions through a home care company, there were minimal ongoing efforts to continue external infusions. Furthermore, we were able to do so without compromising patient safety.

Infusion reactions can occur during any infusion and homecare/infusion clinic nursing must be capable of managing these events. By assuring that we only engaged infusion services that could guarantee pediatric trained nurses, that emergency medications would be available as needed, that a plan for emergency communication was in place, and that postinfusion communication would occur, we developed a system to comfortably address potential safety concerns.

The majority of the external infusions were provided by home healthcare agencies, because there were only 2 external infusion centers. Thus far, patients and their families have been satisfied with external/home infliximab infusions. Most patients and families have provided positive feedback, including less disruption with school, work, and other activities, and increased convenience. Negative feedback was infrequent and those situations led to immediate changes in the homecare company used or a change in the nurse providing the infusion.

Prior research has examined the cost of infusion services, finding it to be substantial. Afzali et al (13) reported the per patient infliximab infusion cost during years 1 and 2 were more than $30,000 and $40,000, respectively. In Belgian pediatric patients with Crohn disease, the cost per patient per year is approximately 9400 euros (or $11,000) (14). Additional research has demonstrated a cost savings associated with home infusions, with some studies also evaluating patient satisfaction. Thirteen adults with Crohn disease receiving home infusions saved >$70 per infusion and were satisfied with in-home treatment model (15). In Amsterdam, 13 adult patients with Crohn disease received home infliximab infusions (15). Patient satisfaction was rated a median of 8/10 and an average of 55 pounds was saved per infusion. A US study



Cumulative Offered	11	24	23	25	24	28	39	54	56	55	48	46	65	79	76	76	76
Eligible Patients	149	149	157	153	143	143	174	165	167	168	154	168	168	166	168	161	158

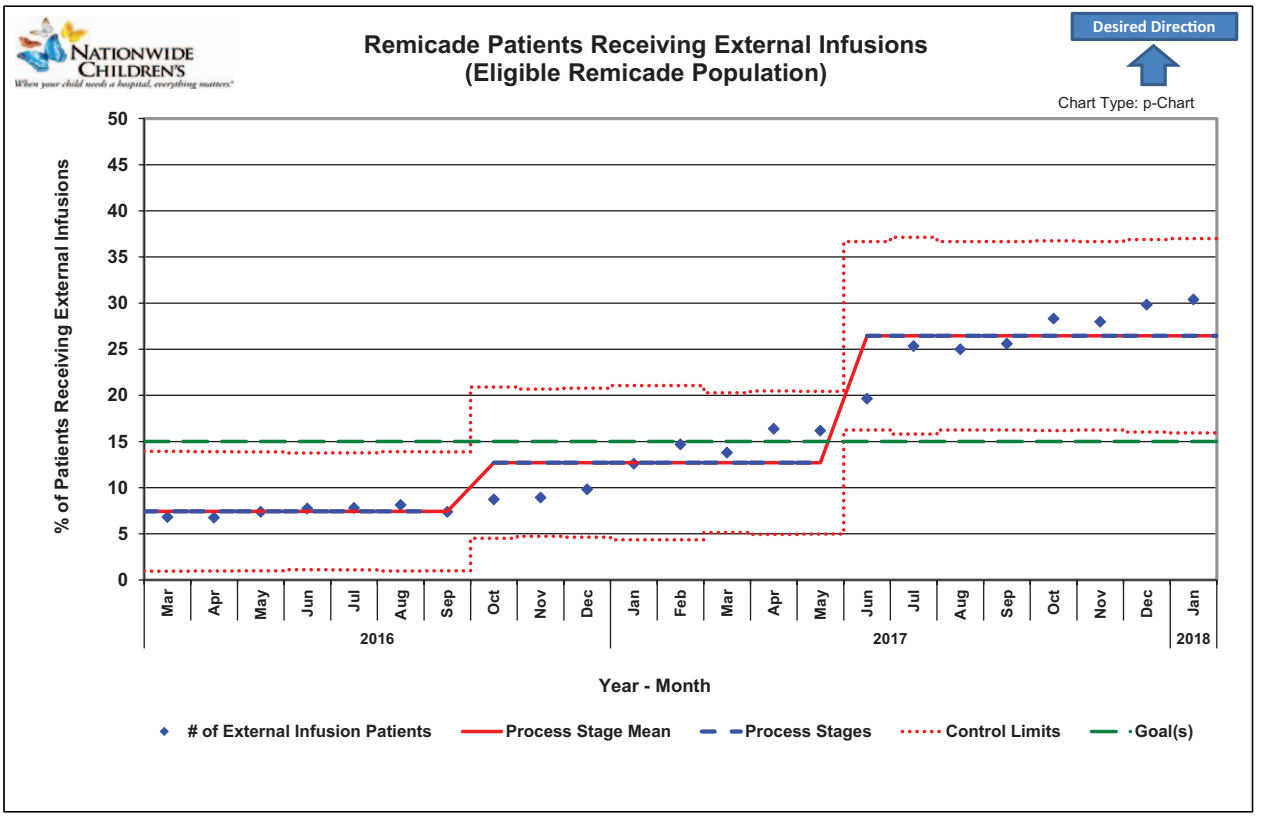
FIGURE 2. Control chart (P-chart) with control limits depicting number eligible patients who were offered external infusions. The dotted centerline represents the mean. The dashed upper and lower control limits reflect the inherent variation in the data and were calculated as ±3 sigma of the centerline. Centerline shifts, representing a statistically significant change, occurred in April 2017. Comparisons among levels on the chart were statistically significant per Fisher exact test, $P < 0.0001$.

suggests larger cost savings (16). In Colorado, 10 children received 59 home infusions offered any day of the week, thus decreasing school absenteeism (16). The average satisfaction rating was 9/10. There were no adverse events during these home infusions. Average savings per infusion was estimated to be $1335/100 mg infliximab (16). Although not formally evaluated for this project, our anecdotal experience is that our families also experienced a decrease in cost.

In planning and implementing this project, we identified a number of issues that had to be addressed to be successful. It is important determine when and how to offer this option to patients, and addressing provider comfort in offering external infusions. In addition, delays in insurance authorization, establishing and assuring expectations with providers of external infusions, and standardizing order forms across multiple homecare companies must be considered. Geographic realities, such as the limited availability of homecare options in some areas, and the inability to prescribe infliximab for some out of state students must be addressed as well. An early intervention shift occurred in October 2016. This could be attributed to early success of this project due to increased awareness of external infusion options, both at the medical provider and patient/family levels. The project's fully implemented shift occurred in June 2017. By this time, all of our processes were in place and we expanded the inclusion criteria. In March 2017, we lifted the initial requirement of NCH Homecare service counties only. In April 2017 we also changed the eligibility criteria from 5 to 6 infusions to allow patients to receive a rapid infusion before initiation of external infusions.

Two main issues needed to be resolved with the implementation of this project. Patients were at risk of missing their routine follow-up visits and laboratory monitoring. Previously, follow-up clinic visits usually occurred every 8 to 16 weeks on the same day as scheduled infusions. Thus, we developed a tracking system to assure regular follow-up visits continued to occur. We experienced several issues obtaining laboratory tests with infusions. It was a cumbersome ordering process, some labs not able to be drawn due to training and timing of specimen delivery (eg, quantiferon gold), and laboratory errors due to specimens being clotted or too old. As a group, we elected to check labs at routine office visits instead of with each home infusion. Patients and families have been receptive of this change and were willing to periodically obtain infliximab trough levels when medically indicated.

The main limitation of this study was the lack of access to financial data to evaluate cost savings. It was reasonable for patients to continue their infusions at the infusion center; however, we believe that external infusions were most cost-effective. We also did not use formal survey assessments to assess patient satisfaction. Institutions with different QI resources, expertise and experience may have more or less success in implementing a similar program. We believe that this project could be generalized to other medium to large size IBD centers with similar resources, such as an electronic



External Patients	10	10	11	12	12	12	11	13	14	15	18	21	24	27	27	33	39	42	43	47	47	48	48
Eligible Patients	147	148	149	155	154	148	149	149	157	153	143	143	174	165	167	168	154	168	168	166	168	161	158

FIGURE 3. Control chart (P-Chart) showing increased rates of eligible patients receiving external infusions. The dotted centerline represents the mean. The dashed upper and lower control limits reflect the inherent variation in the data and were calculated as ±3 sigma of the centerline. Centerline shifts, representing a statistically significant change, occurred in October 2016 and June 2017. Comparisons among levels on the chart were statistically significant per Fisher exact test, $P < 0.0001$. In March 2017, we lifted the initial requirement of Nationwide Children's Hospital Homecare service counties only. In April 2017 we also changed the eligibility criteria from 5 to 6 infusions to allow patients to receive a rapid infusion before initiation of external infusions. All key interventions were discussed and implemented at the time of project initiation. Additional process issues were addressed as they arose (eg, routine laboratory monitoring, infusion tracking within the electronic health record, etc).

health record system, nursing, social work, and partnering home care companies. Other than utilizing a spreadsheet and our internal IBD population file with a list of patient who receive infusions, there were no other tools that were used for this project.

In conclusion, initial efforts to provide external/home infliximab infusions have been successful. Overall, patients have been satisfied with the quality of services provided and the flexibility in scheduling external infusions, but no formal assessment has been completed. We have not identified any serious safety concerns to date, and have established an approach to effectively minimize such risks.

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REFERENCES

1. Hyams JS, Crandall W, Kugathasan S, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology* 2007;132:863–73.
2. Turner D, Mack D, Leleiko N, et al. Severe pediatric ulcerative colitis: a prospective multicenter study of outcome and predictors of response. *Gastroenterology* 2010;138:2282–91.
3. Hyams JS, Lerer T, Griffiths A, et al. Outcome following infliximab therapy in children with ulcerative colitis. *Am J Gastroenterol* 2010;105:1430–6.
4. Rutgeerts P, Van Assche G, Vermeire S. Review article: infliximab therapy for inflammatory bowel disease—seven years on. *Aliment Pharmacol Ther* 2006;23:451–63.
5. McGinnis JK, Murray KF. Infliximab for ulcerative colitis in children and adolescents. *J Clin Gastroenterol* 2008;42:875–9.
6. Hyam JS, Lerer T, Griffiths A, et al. *Long-term outcome of maintenance infliximab therapy in children with Crohn's disease* 2009;15:816–22.
7. Cezard JP, Nouaili N, Talbotec C, et al. A prospective study of the efficacy and tolerance of a chimeric antibody to tumor necrosis factors (remicade) in severe pediatric Crohn disease. *J Pediatric Gastroenterol and Nutrition* 2003;36:632–6.
8. Baldassano R, Braegger CP, Escher JC, et al. Infliximab (Remicade) therapy in the treatment of pediatric Crohn's disease. *Am J Gastroenterol* 2003;98:833–8.

9. Hyams JS, Markowitz J, Wyllie R. Use of infliximab in the treatment of Crohn's disease in children and adolescents. *J Pediatrics* 2000;137:192–6.
10. Shaikhkhalil AK, Boyle B, Smith J, et al. Using quality improvement to increase utilization of enteral therapy in pediatric Crohn disease: results and outcome. *J Pediatr Gastroenterol Nutr* 2018;66:909–14.
11. Brilli RJ, McClead RE Jr, Crandall WV, et al. A comprehensive patient safety program can significantly reduce preventable harm, associated costs and hospital mortality. *J Pediatr* 2013;163:1938–45.
12. Benneyan JC, Lloyd RC, Plsek PE. Statistical process control as a tool for research and healthcare improvement. *Qual Saf Health Care* 2003;12:458–64.
13. Afzali A, Ogden K, Friedman ML, et al. Costs of providing infusion therapy for patients with inflammatory bowel disease in a hospital-based infusion center setting. *J Med Econ* 2017;20:409–22.
14. De Greef E, Hoffman I, D'Haens G, et al. Safety and cost of infliximab for the treatment of Belgian pediatric patients with Crohn's disease. *Acta Gastroenterol Belg* 2012;75:425–31.
15. Kuin S, Stolte SB, Van den Brink GR, et al. Short article: remicade infusions at home: an alternative setting of infliximab therapy for patients with Crohn's disease. *Eur J Gastroenterol Hepatol* 2016;28:222–5.
16. Condino AA, Fidanza S, Hoffenberg EJ. A home infliximab infusion program. *J Pediatr Gastroenterol Nutr* 2005;40:67–9.