

ORIGINAL ARTICLE

A quality improvement project reduces time spent at an inflammatory bowel disease infusion center with accelerated infliximab infusion protocol

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Introduction

Infliximab is an approved treatment for both the induction and maintenance of moderate to severe inflammatory bowel disease (IBD) in children and adults.^{1–3} As a chimeric mouse–human antibody targeting human tumor necrosis factor (TNF), infusions of infliximab can lead to the formation of antibodies, which may have a role in infusion reactions.⁴ The overall incidence of infliximab-related infusion reactions was 6.1%, with mild, moderate, or severe acute reactions occurring in 3.1, 1.2, and 1.0% of

Abstract

Background and Aim: Patients with inflammatory bowel disease (IBD) requiring infliximab frequently spend hours to attend treatment. Through quality improvement (QI) methodology, we aimed to shorten the time spent in the biologics infusion center using the accelerated infusion protocol and describe patient outcomes, safety, and associated cost savings.

Methods: From September 2018 through December 2019, eligible IBD patients receiving infliximab were recruited. We implemented interventions including the accelerated infusion protocol, and modifying collection location of infliximab. Statistical process control charts were created. Patients' clinical outcome and cost savings data were analyzed using descriptive statistics and Pearson's chi-square.

Results: During the study period, a total of 60 patients with IBD receiving infliximab were recruited. A total of 315 infusions were administered—152 were under accelerated infusion protocol and 163 under standard protocol. The mean infliximab infusion time was reduced by 47%, from 2.4 h (142 ± 14 min) to 1.2 h (75 ± 10 min) (142 min vs 75 min, $P < 0.001$), with total time spent in the infusion center reduced by 52%, from 3.6 h (214 ± 25 min) to 1.7 h (102 ± 14 min) (214 vs 106 min, $P < 0.001$). Three mild infusion-related reactions ($3/152 = 1.97\%$) were recorded. Estimated cost savings over the 16-month project period was SGD \$6721.4 (nursing) and SGD \$23 560 (patients). A high level of satisfaction (4.84 out of 5) with the protocol was reported.

Conclusion: Our QI project shortened the infliximab infusion time and total time spent in the infusion center, without compromising patient safety. Estimated cost savings were substantial. The protocol helps reduce work productivity loss.

infliximab infusions, respectively.⁵ The current recommendation is for infliximab to be administered over 2 h with 1–2 h of post-infusion monitoring.⁶ IBD is associated with a heavy economic burden to society. Medication costs, in particular anti-TNF α therapy, is now the main driver of healthcare costs for IBD.^{7,8} In addition, anti-TNF therapy also indirectly contributes to work productivity loss, due to sick leave (absenteeism) of patients and their caregivers, as well as expenses related to travel to the hospital. Buisson *et al.* reported that patients with IBD usually stayed

at the IBD unit for a median period of 4.5 h for the infusion,⁹ and they often took a day of vacation or rest. Short infusion (over 30–60 min) protocols have been found safe in patients with rheumatoid arthritis and IBD.^{10–12} Furthermore, accelerated infliximab infusions have been shown to reduce significantly nursing time, healthcare resources, and increase patient satisfaction.^{13–16}

Given the safety and benefits of accelerated infliximab infusion protocol, our IBD center developed a quality improvement (QI) project to shorten the average time spent at the outpatient biologics infusion center. The primary aim of this QI project was to reduce by 40%, both the average infliximab infusion time and the total time spent at the outpatient biologics infusion center. Our secondary aims were to ensure the safety of the accelerated infliximab infusion protocol, to estimate the associated cost savings, and to evaluate patient satisfaction with the protocol.

Methods

Setting. This study was performed using Standards for Quality Improvement Reporting Excellence (SQUIRE) 2.0 guidelines.¹⁷ This was a single-center project conducted at the Singapore General Hospital (SGH) IBD Center, which treats more than 700 patients with IBD. Our center comprises three IBD-focused physicians, three colorectal surgeons, three fellows/senior residents, one advanced nurse practitioner, and four staff nurses. Approximately 30% of our IBD population are treated with biological therapy, 35% of whom are treated with infliximab. Our SGH biologics infusion center is a four-chaired unit located at the gastroenterology outpatient clinic that provided 160 slots of biologics infusion per month (before the QI initiative).

We formed a multidisciplinary team of stakeholders for the QI project, which included IBD physicians, two gastroenterology senior residents, an IBD nurse clinician, nurses, clinical pharmacists, and a QI service representative. The SGH Institutional Review Board exempted the project from human subject review.

Inclusion and exclusion criteria. Patients were included if they met the following criteria: (i) 18 years or older; (ii) were diagnosed with Crohn's disease or ulcerative colitis, (iii) received infliximab. Patients receiving infliximab for non-IBD indications, or at a dose of ≥ 10 mg/kg, were excluded.

Key drivers and intervention through plan-do-study-act cycle. The study had a pre-implementation control period from June 2018 through August 2018, and a post-implementation period from September 2018 through December 2019. Time studies were conducted, and a process map (Fig. 1) was created to identify possible delays along the clinic flow. Data from the control period suggested that our patients with IBD receiving infliximab spent an average of 3.6 h for each visit in the biologics infusion center. This consisted of an hour of wait time for the biologics medication and about 2.4 h of infliximab administration. The latter also included venepuncture, blood drawing, preparation of infusion, and post-infusion monitoring.

Our QI team created a key driver diagram (Fig. 2) to depict the project objective, root causes, key drivers, and

interventions. We determined that there were two root causes in the clinic flow that consumed a significant amount of time. The first step was infliximab administration. We followed the package insert of infliximab (Remicade), which was administered to all our patients over 2 h. The second step was collection of infliximab. After a patient registered at the biologics infusion center counter, the hospital-porter would collect infliximab from the Hematology Center Pharmacy, which is located 800 meters away from the infusion center. Taking into account the time for the pharmacists to verify the prescription and prepare the medication, and the porter's travel time, it took at least 1 h for the hospital-porter to deliver the infliximab to the infusion center.

Utilizing the "plan-do-study-act (PDSA)" cycle, a key construct of the "Model for Improvement,"¹⁸ we reported the key drivers and implemented interventions.

PDSA cycle 1. Our first intervention targeted the infliximab infusion process (Plan). We devised the accelerated infusion protocol through meeting with nurses and pharmacists and identified eligible criteria. The accelerated infusion protocol refers to infusion of infliximab over 1 h. Eligible patients were included if they (i) received at least four standard infliximab infusions over 2 h, without acute or delayed hypersensitivity reactions, and (ii) were not on pre-medication prior to infliximab (pre-medication includes corticosteroids, antihistamines, and antipyretics). One pivotal aspect of this project was education for physicians, pharmacists, patients, and nursing staff in the infusion center about the new protocol (Do). The educational materials provided to all stakeholders were to introduce and increase familiarity of the protocol. Various educational interventions were used, such as tutorials, information leaflets, and workflow map, to guide physicians on the eligibility criteria. We received feedback from both nurses and patients after the new protocol was implemented (Study). Some nurses were concerned about whom to contact if patients developed infusion reaction with the new protocol. They were reassured that there was a physician on-call-roster for them to contact if patients were unwell during infusion. Some patients were concerned about increased risk of infusion reaction under the new protocol. They were educated and reassured that the accelerated infusion protocol was safe, and there were stringent criteria for referral, and the rate could return to the original if they developed reactions (Act).

PDSA cycle 2. Our second intervention targeted the waiting time for infliximab collection (Plan). We recognized that the long wait time was contributed by the travel time of hospital-porters to collect infliximab, coupled with pharmacists' unfamiliarity with dispensing the biologics and accessories including normal saline bag and filter. A new workflow (Do) was implemented so that patients who had registered in the infusion center would collect infliximab from the pharmacy next to the infusion center. The infusion center agreed to stock normal saline and filters for infusion. We received feedback from the patients (Study), after the first week of PDSA cycle 2, who were concerned about the long waiting time to collect infliximab at the pharmacy. The workflow was further modified, such that patients were offered expedited queue for collection of infliximab for infusion (Act).

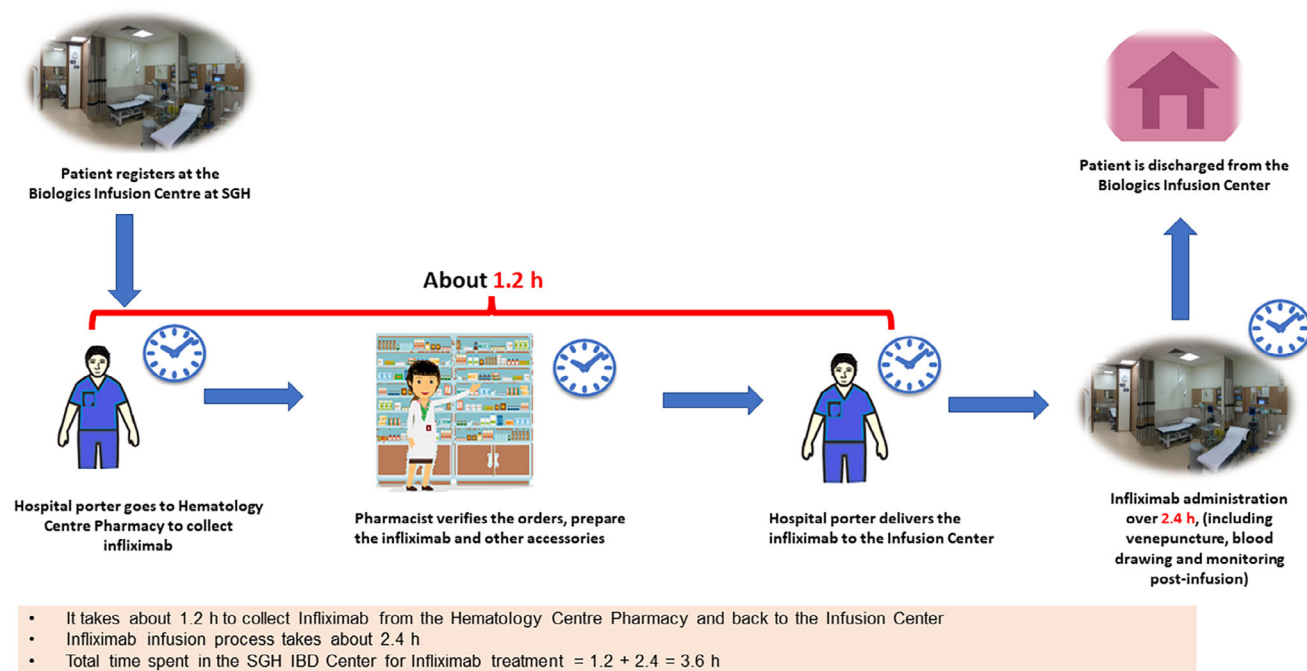


Figure 1 Basic flowchart of our biologics infusion center process. The total time spent in the infusion center is about 3.6 h. The four clocks next to the figures indicate possible areas of delays. IBD, inflammatory bowel disease; SGH, Singapore General Hospital.

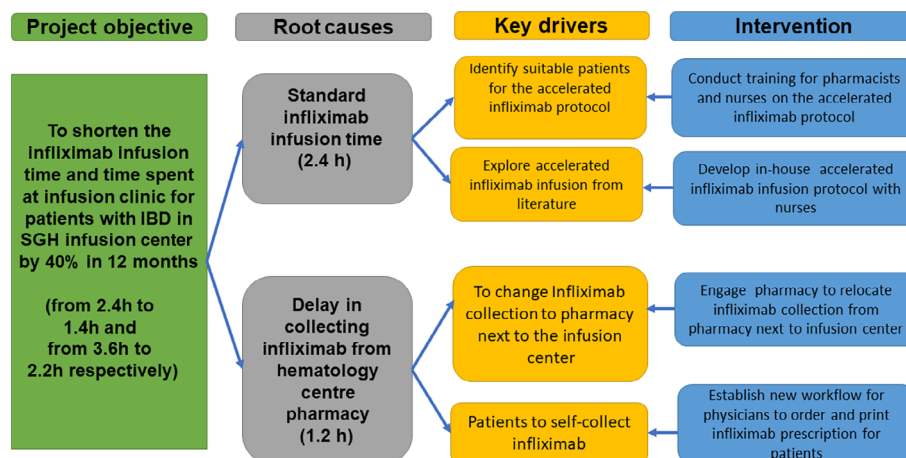


Figure 2 Key driver diagram depicting the quality improvement (QI) project objective, root causes, key drivers, and intervention necessary to achieve project success. IBD, inflammatory bowel disease; SGH, Singapore General Hospital.

Outcomes. The primary outcome for this project was the percentage of time reduced in the infliximab infusion process and the total time spent at the outpatient biologics infusion center. The total time spent was defined as the time elapsed from when a patient checked into the center until the patient left the clinic after treatment completion. The secondary outcomes were the rate of infliximab infusion-related reaction, associated cost savings, and patient satisfaction with the protocol. Infusion-related reactions include immediate and delayed hypersensitivity reactions and are classified based on the Common Terminology

Criteria for Adverse Events (CTCAE) (version 5.0) severity grading score 1 (mild) to 5 (death).¹⁹ Analysis was performed on a per-infusion basis as every infusion was at risk of an adverse event.

One potential benefit of the accelerated infusion protocol is cost savings. The cost-benefit analysis was based on two categories: (i) direct costs including direct nursing cost and cost of work productivity loss from patients; and (ii) indirect costs including time saved for the infusion center. The direct nursing cost was computed based on the QI cost saving calculator for

SGH (in Singapore dollars [SGD]). For patients in working age (18–65 years) in Singapore, the gross monthly income from full-time work (in 2019) was SGD \$4563, based on data from the Ministry of Manpower, Singapore.²⁰ Assuming 44 h of work per week, the average income per hour was SGD \$25.9.

Subjective patient satisfaction was assessed in the accelerated protocol cohort by rating satisfaction on a five-point visual analogue scale from 0 (least satisfied) to 5 (most satisfied) during the initiation phase and the accelerated phase. We performed a retrospective chart review to obtain the following: patient demographics (sex, age), disease type and characteristics, and IBD-related medications. Disease location and behavior were recorded for Chron's disease (CD) and disease location for ulcerative colitis (UC).

Statistical analyses. Categorical variables were expressed as frequencies and percentages, and continuous variables were expressed as means and SDs. Comparison of demographics, primary outcomes between the standard infusion protocol group and the accelerated infusion protocol group were made using an unpaired t-test for continuous data and the chi-square test for categorical data. Results with $P < 0.05$ in two-sided tests were considered statistically significant. Data were analyzed using Microsoft Excel for Office 365 MSO, 2020. We created a statistical process control chart to demonstrate the impact of different interventions on the infusion time and total time spent in infusion center. The chart was analyzed for evidence of common cause variation *versus* special cause variation.

Results

Patient population. Our center began to offer accelerated infliximab infusion to eligible patients in September 2018. Between 1 September 2018 and 31 December 2019, a total of 60 patients with IBD received infliximab. Twenty-two patients were eligible for the accelerated infusion protocol, while 38 patients were not (10 had non-adherence to biologics, 8 received infliximab at 10 mg/kg, 2 with existing cardiac conditions, 1 received pre-medication, 2 had hypersensitivity reaction to infliximab, 6 had switching of biologics, 3 switched back to 2-h infusion, and 6 declined accelerated infusion).

During the study period, a total of 315 infusions were administered, of which 152 were infused to the 22 eligible patients using the accelerated infusion protocol (1 h), and

163 infusions were given to the remaining 38 patients using the standard 2-h protocol. Table 1 depicts the patient demographics. The most common type of IBD was CD (77.2%), and 45.4% of patients were on immunomodulators. Among all patients who received the infliximab using the accelerated infusion protocol, the mean age was 45.0 (± 19.1) years, and 15 (68.2%) were males. There was no statistically significant difference in baseline characteristics between the groups (accelerated infusion *vs* standard infusion).

Primary outcome. Before our PDSA cycle (June 2018–August 2018), the mean infliximab infusion time was 2.4 h. During our intervention period, we observed a measurable reduction in the mean infliximab infusion time from 2.4 h (142 ± 14 min) to 1.2 h (75 ± 10 min) (142 min *vs* 75 min, $P < 0.001$) (Fig. 3a), with a shift in the centerline (a run of ≥ 8 points in a row above the centerline). Similarly, the time spent in the biologics infusion center was reduced from 3.6 h (214 ± 25 min) to 2 h in September 2018 (Fig. 3b), contributed by the shortened infliximab infusion time. The total time spent in the infusion center was further reduced to 1.7 h (102 ± 14 min) from February 2019 onwards, due to shifting of infliximab collection location from the Hematology Center Pharmacy to the pharmacy near the infusion center (214 *vs* 106 min, $P < 0.001$). Overall, both the infliximab infusion time and the total time spent in the biologics infusion center were reduced by 47 and 52%, respectively, from baseline.

Secondary outcomes. With the implementation of the accelerated infliximab infusion protocol, there were three infusion-related reactions ($3/152 = 1.97\%$): one patient experienced grade 1 infusion-related reaction where he developed chest tightness. Another two patients were switched back to the 2-h infusion protocol due to headache and fever post-infusion. There were no infusion-related reactions reported in the standard infusion group.

The accelerated infliximab infusion protocol saved time and cost for nurses, patients, and hospital. The nursing time saved was 67 min ($142 - 75$ min), almost equivalent to the time taken for accelerated infusion. As our biologics infusion center offered two slots of infliximab infusion each day prior to the QI project, the time saved allowed us to operate two more slots per day for biologics infusion (from two slots to four slots per day). Using the cost savings equation specific for SGH QI

Table 1 Baseline demographics and disease characteristics

	Accelerated infusion ($n = 22$)	Normal infusion ($n = 38$)	P value
Age, mean \pm SD	45.0 \pm 19.1	43.6 \pm 16.8	0.42
Male sex, n (%)	15 (68.2%)	26 (68.4%)	0.98
Diagnosis, n (%)			0.20
Crohn's disease	17 (77.2%)	34 (89.5%)	
Ulcerative colitis	5 (22.7%)	4 (10.5%)	
Immunomodulators, n (%)			0.05
Thiopurines	5 (22.7%)	20 (52.6%)	
MTX	5 (22.7%)	7 (18.4%)	
None	12 (54.5%)	11 (28.9%)	

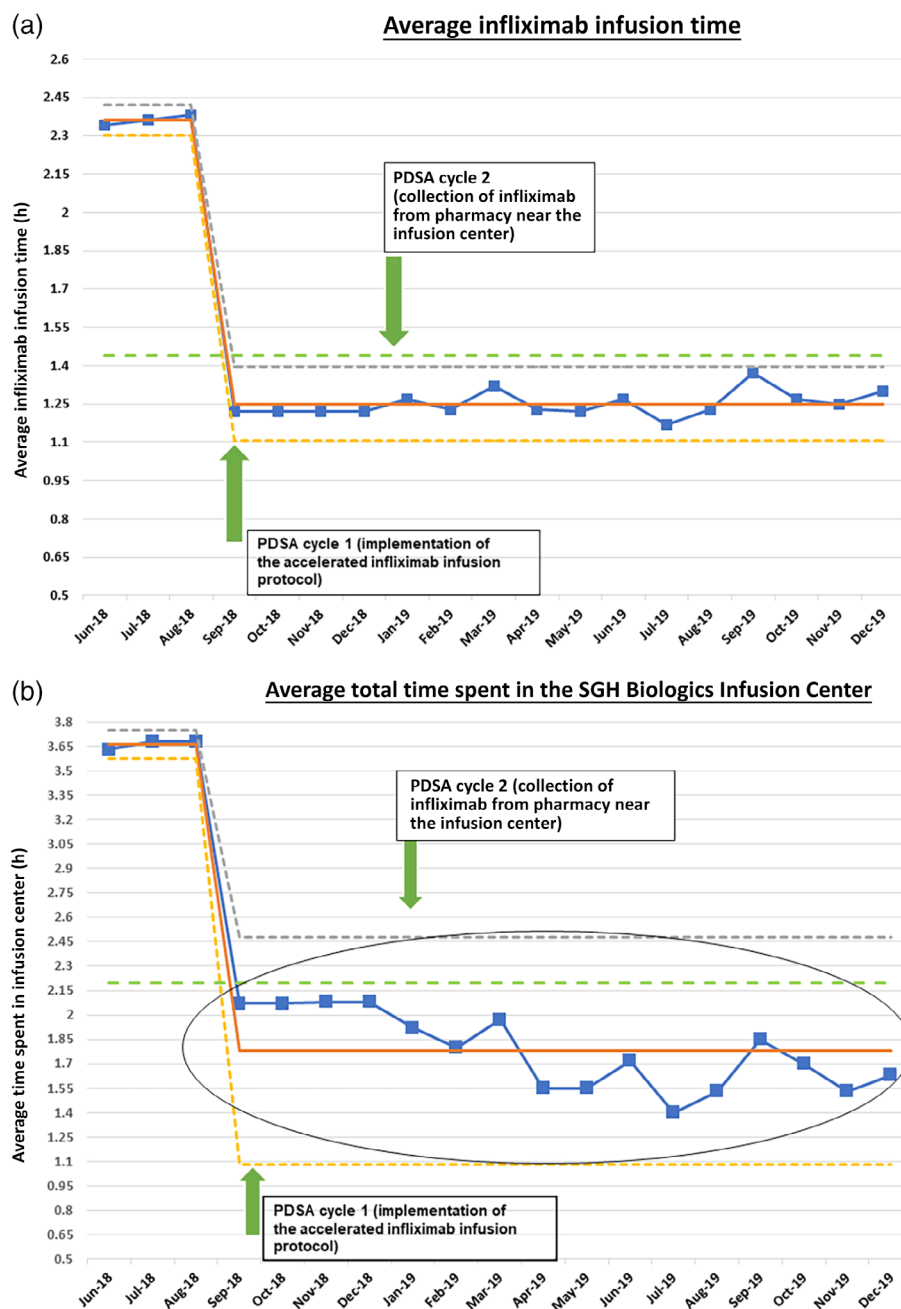


Figure 3 (a) Control chart showing the average infliximab infusion time pre- and post-intervention. The goal infusion time is 1.42 h. (b) Control chart showing the total time spent in the infusion center pre- and post-intervention. The goal is 2.16 h. (a): (—■—), Accelerated infusion; (—), control line (infusion); (---), upper control limit; (---), lower control limit; (---), goal (infusion time). (b): (—■—), Accelerated infusion; (—), control line; (---), upper control limit; (---), lower control limit; (---), goal (total time spent).

projects, the estimated cost savings for nursing care was SGD \$44.2 per infusion. Throughout the 16-month study period, 152 infliximab infusions were completed using the accelerated protocol, which translated to a total of nursing cost saving of approximately SGD\$ 6721.

Similarly, the total time saved for patients who received infliximab using the accelerated infusion protocol was 112 min (214 – 102 min). The productivity gained by patients as a result

of the time saved, and hence being able to return to work after treatment completion was therefore SGD \$155 per infusion ($\25.9×6 h), or \$23 560 (total of 152 infusions).

Patient satisfaction. Nineteen of twenty-two patients in the accelerated infliximab infusion group were interviewed.

A high level of satisfaction (4.84/5) was reported.

Discussion

Accelerated infliximab infusions of ≤ 1 -h duration are safe and could conserve healthcare resources.^{11,14,15} Our QI initiative was built on previously published work.^{14,15} In this systematic QI project, we implemented the accelerated infusion protocol and shifted the collection location of infliximab from the Hematology Center Pharmacy to the pharmacy near the biologics infusion center. Overall, both the infliximab infusion time and total time spent by patients with IBD in the infusion center were reduced, with resultant lower costs to the healthcare system and the patients. Furthermore, the accelerated infliximab infusion protocol is safe with few infusion-related reactions.

Education played a cardinal role in this QI project. Despite updated literature supporting the safety and cost-effectiveness of the accelerated infusion protocol, practice changes are still needed. Having a deeper understanding of the accelerated infusion protocol through lectures, tutorials, and education leaflets, all stakeholders (physicians, nurses, and patients) were more receptive to the new protocol. Our pharmacists and nurses in charge of the biologics infusion center reached a consensus on the new rate of infliximab infusion and monitoring frequency after multiple rounds of discussion. An action plan was devised, which stipulated that if a patient developed an infusion reaction at any stage in the protocol, the infusion rate would be reverted to a slower rate of 2 h and the IBD doctor be informed. There were also stringent criteria to enroll patients into the accelerated infusion protocol—only patients who did not develop hypersensitivity or delayed reaction after four rounds of infliximab treatment were eligible.

IBD is a chronic condition with significant impact on health-related quality of life, healthcare costs, and work productivity costs. Productivity costs are a key IBD cost burden, with absenteeism (including sick leave, early retirement, and reduced employment) and presenteeism (reduced productivity of paid work)²¹ being a substantial proportion of the total costs.²² These quality of life and societal cost considerations are important in guiding management decisions. Shortened infliximab infusions were overwhelmingly welcomed by patients in our study, as evidenced by high patient satisfaction rating on the surveys. Prior to our QI initiative, our patients used to spend half a day in the hospital, including an average of 3.6 h in the biologics infusion center, plus travel time between home and hospital, and parking. They often took a day of sick leave to attend the infliximab infusion. The work productivity loss is substantial, especially if their schedule of infliximab infusion is more frequent than 8-weekly (for example, 12 days of sick leave if the frequency of infliximab is 4-weekly). Our accelerated infusion protocol enables patients to complete their treatment and be discharged in 1.8 h. This allows them to merely take time off instead of sick leave to attend treatment and return to work the same day. In monetary terms, such reduction in work absenteeism translates into more earning for patients of SGD \$155 per infusion session (SGD \$25.9 per hour multiplied by 6 h). Moreover, the time saved from each shortened infusion session permits us to offer two more slots per day for biologics infusion (from two slots to four slots per day). The utilization of healthcare resources is more cost-effective; it also facilitates timely biologics treatment.

In planning and executing this QI project, we identified a number of limiting factors. The Hematology Center Pharmacy is

far from the biologics infusion center. It took an hospital-porter 20 min to collect the infliximab and return to the infusion center. Furthermore, the pharmacists in the Hematology Center Pharmacy were not familiar with preparing infliximab. On average, our patients waited for an hour after registration before they could commence the infliximab infusion. We engaged pharmacists from both the Hematology Center Pharmacy and the pharmacy next to the infusion center in a few rounds of discussion to improve the clinic process. We reached an agreement to allow patients to collect infliximab themselves from the pharmacy near the infusion center. As is clear from our data, the total time spent in the infusion center showed an additional drop from January 2019 after the second PDSA cycle was implemented. Further reduction in the total time spent was noticeable from April 2019, coinciding with adjustment in the workflow to allow patients expedite access to collect infliximab from the pharmacy.

Our study has some noteworthy limitations. First, our sample size of 60 patients was small and all patients were from a single center. However, we treat each infusion session as individual data point because infusion reaction could occur with each biologics administration. Second, we could not have access to financial data to evaluate cost savings. We could only approximate savings for nurses and patients using formulas for QI project provided by hospital and average income data provided by the Government, respectively. Third, we did not use formal survey assessments to assess patient satisfaction with the accelerated infusion protocol.

In summary, we successfully implemented an accelerated infliximab infusion protocol, which significantly reduced the infusion time as well as the total time spent in the infusion center without compromising patient safety. We believe that with widespread implementation, this project has the potential to dramatically increase the quality of care delivered to patients who require regular biologics treatment and allow more cost-effective utilization of healthcare resources.

Data availability statement. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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