Original Article

# Outcome Evaluation of a Subcutaneous Immunoglobulin Clinical Management Program

*Julia Zhu[1], Gretchen Ayer[2], Heather S. Kirkham[1], Chi-Chang Chen[3], Rolin L. Wade[3], Swapna U. Karkare[4], Chester H. Robson[5], Jordan S. Orange[6,7]*

[1]Health Analytics, Research and Reporting, Walgreen Co., Deerfield, IL, USA

[2]Business Development, Option Care Inc., Bannockburn, IL, USA

[3]Health Economics and Outcomes Research, IQVIA, Plymouth Meeting, PA, USA

[4]Health Economics and Outcomes Research, IQVIA, Deerfield, IL, USA

[5]Office of Clinical Integrity, Walgreen Co., Deerfield, IL, USA

[6]Baylor College of Medicine, Houston, TX, USA

[7]Texas Children's Hospital, Houston, TX, USA

**Received:** April 2018.
**Accepted:** January 2019.

ABSTRACT

**Objective:** The aim of this study is to compare clinical and cost outcomes of patients undergoing subcutaneous immunoglobulin (SCIG) therapy who were managed by a clinical management program to the matched controls in the United States. **Methods:** This was a retrospective cohort study using administrative claims data from the PharMetrics Plus™ (PMTX+) database. The patients from a high-touch SCIG clinical management program were matched to nonprogram patients in PMTX+ database using 1:4 propensity score matching without replacement. All patients were followed for 1 year during the study from September 1, 2011, to June 30, 2014, and both clinical and cost outcomes were compared between the two cohorts using the generalized estimating equation model. **Findings:** The clinical outcomes were measured by infection- and infusion-related adverse events (AEs). Most of them were not significantly different ($P > 0.05$) between the intervention group and matched controls. Although the proportion of patients who had a mild less common AE was higher (4.4% vs. 0.0%; $P = 0.04$), it could be due to increased reporting among the intervention group. The annual adjusted mean total health-care costs of patients in the program ($n = 45$) were \$20,868 lower compared to matched controls ($n = 180$), representing a 24% lower costs (\$66,450 vs. \$87,318; $P = 0.009$). **Conclusion:** This study may demonstrate that clinical management programs for SCIG may be associated with lower health-care costs and comparable infection and severe AE rates. The limitations of this study included a small sample size and a reliance on administrative claim data.

**Keywords:** *Clinical outcomes, cost outcomes, home infusion, specialty pharmacy, subcutaneous Immunoglobulin*

## Introduction

Therapeutic immunoglobulin (IG) is a purified preparation of normal human polyclonal IG derived from pooled donor plasma. It is used for treating immunodeficiency and autoimmune diseases.[1,2] In many of these conditions, long-term administration of IG is needed. Primarily because of the laborious processes required for purification of IG from plasma, treatment is costly, particularly for chronic conditions. Depending on the dose, infusion time, the length of treatment, and site of care, the estimated annual cost of IG therapy can ranges from \$30,000 to \$90,000 per patient.[2,3]

The main administration routes for IG therapy are intravenous (IVIG) and subcutaneous IG (SCIG).[4] IVIG therapy has been available for decades and its use is well established in multiple disease states. SCIG has been approved for the use in the United States since 2006 and provides an alternative for patients with difficult vascular access and intolerable side effects when using IVIG or for patients desiring more independence

*Address for correspondence:*
Dr. Heather S. Kirkham, E-mail: heather.kirkham@walgreens.com



Access this article online

Quick Response Code:

Website: www.jrpp.net

DOI: 10.4103/jrpp.JRPP_18_36

How to cite this article: Zhu J, Ayer G, Kirkham HS, Chen CC, Wade RL, Karkare SU, *et al.* Outcome evaluation of a subcutaneous immunoglobulin clinical management program. J Res Pharm Pract 2019;8:52-63.

and convenience in their therapy.[5] SCIG is usually given every 1–2 weeks,[6] and can be self-administered by patients after initial training by health-care professionals.[1]

Serious bacterial infections (SBIs) and overall infections have been the primary and secondary phase III clinical study end-points of SCIG therapy, respectively.[7,8] Adverse events (AEs) associated with IG administration are recorded in clinical trials and broader clinical experience (often as text notes in physician records or clinical program data) and include local and systemic reactions. Local infusion site-related AEs, such as swelling, erythema, bruising, and pain, are more common among patients receiving SCIG as opposed to IVIG.[9,10]

SCIG provides increased yet consistent serum IgG levels throughout an infusion cycle and is equally efficacious to IVIG therapy in IgG replacement therapy for primary immunodeficiency (PID).[8] In a multicenter, open-label, crossover randomization study, 40 patients with PID were randomly assigned to either SCIG or IVIG replacement therapy for 1 year and then switched to the alternative treatment groups in the year 2 to serve as their own controls. No significant difference in the number of infections, the severity of infections, or adverse reaction rates was noted between IVIG and SCIG therapies when receiving equivalent doses.[8]

Despite the efficacy of IG therapy, patients receiving treatment can still experience disease-related complications. One of the major PID disorders treated with IG is a common variable immune deficiency (CVID). CVID patients experience several disease-related complications such as infections, primarily pneumonia, sinusitis, and otitis, although such complications should be reduced by IG treatment.[11] However, other conditions such as chronic lung disease, autoimmunity, non-Hodgkin's lymphoma, and other cancers may or may not be modified by IG therapy. Immunodeficiency patients, in particular, may paradoxically develop autoimmunity, due to their dysregulated immune system. In one of the original CVID cohort studies, 22% of patients developed at least one autoimmune condition, such as idiopathic thrombocytopenic purpura or rheumatoid arthritis.[12]

Several studies have examined the cost outcomes of SCIG therapy.[13-17] In a 2016 study conducted by Perraudin *et al*. in Switzerland,[16] the annual mean total health-care costs of home-based SCIG ranged from $30,929 to $ $36,095. A 1-year Italian study conducted by Lazzaro *et al*. in 2013 found medication cost accounted for 94% of the overall $76,778 in costs for SCIG therapy.[15] Similarly, the medication was found to be the main cost driver in an Iranian study by Sadeghi *et al*. in 2015 and a German study by Hogy *et al*. in 2005.[14,17] Few studies were conducted in the United States, and none was found to evaluate both costs and clinical outcomes.

Based on evidence from other disease states with high health-care costs and the potential for AEs, the patient management programs have been shown to improve the patient outcomes.[18] Over the past few years, a home infusion specialty pharmacy provider in the United States implemented a "high-touch" SCIG clinical management program, which includes patient training provided in the home by an IG-specialized registered nurse (RN), ongoing clinical management of infusions, AEs, and dosing, as well as disease-specific patient education. Clinical management components and disease-specific patient-reported outcomes are provided in a patient level report for the treating physician. The care team regularly communicated with the physicians about the issues identified in the clinical management process and provided timely interventions with the goals of improving clinical and cost outcomes for the patients.

This study may be the first in the United States to examine the effectiveness of a high-touch IG clinical management program on the cost and clinical outcomes of SCIG patients. Our research objective was to assess AEs, infection rates, and health-care costs for patients in this IG clinical management model compared to the matched controls.

## Methods

This retrospective cohort study compared clinical and cost outcomes of SCIG patients who were managed by an IG clinical management program to those who were not in the program using an administrative claim database in the United States from September 1, 2011, to June 30, 2014.

The IG clinical management model is standard of care for all IG patients at a national home infusion specialty pharmacy, and includes: (1) Pre-infusion clinical evaluation by a pharmacist, including evaluation for comorbidities affecting the risk of adverse drug reaction (ADR), coordination with prescribing clinician for individualized infusion plan to avoid ADR, and educating the patient to proactively address concerns; (2) Self-infusion instruction by an RN in the patient's home until the patient is determined to be independent by RN; and (3) Pharmacist regular clinical follow-up with the patient that is communicated to the prescribing clinician, including patient adherence, AE reporting and management, dose recommendations, and

disease-specific patient-reported outcome measures. Clinical follow-up is performed over the phone by the pharmacist, that occurred every 30–60 days and on an as-needed basis to address any AEs, and also depends on patient availability. This program also facilitated patient insurance authorization and provided financial consultation.

This study was conducted using data from the PharMetrics Plus™ database (PMTX+) to derive dependent outcomes and covariates for both intervention and control cohorts. As previously described by Akinbosoye *et al*.,[19] this large longitudinal database is comprised of adjudicated medical and pharmacy claims for ≥150 million unique, commercially-insured members across the United States since 2006.

For both intervention and control cohorts, the inclusion criteria were patients who received at least one claim (prescription or administration procedure) for SCIG therapy between September 1, 2011, and June 30, 2013, had continuous eligibility in the PMTX + database for a minimum 6 months before and 12 months after the index date (i.e., the date a patient received the first SCIG therapy in the study period), had at least four SCIG claims in the 12-month post-index period and one claim of SCIG on or after month 6. Similarly, both intervention and control cohorts excluded patients who were administered IVIG during the follow-up period (including the index date), had incomplete or invalid data, were prescribed products that can be administered through both SC and IV (i.e., Gammagard Liquid™; Gamunex-C™; and Gammaked™), or had a IVIG Current Procedural Terminology (CPT) or J code or a non-specific J code (J1561, J 1569) within 7 days of the National Drug Code (NDC) claim date [Appendix 1].

Data from the national home infusion specialty pharmacy were linked to the PMTX + databases to identify the intervention group, which was made up of the patients in the high-touch IG clinical management program. The program was administered across multiple locations in the United States. We used a census of all 158 patients at the national home infusion specialty pharmacy who received the services from the high-touch IG clinical management program, met the inclusion criteria, had the data in the PMTX + database were eligible for the control group [Appendix 1].

Patients in the cohorts were stratified by their autoimmune disease status, and then propensity matched on six demographic, clinical, and cost characteristics. Autoimmune disease status was categorized as: (a) IVIG-treatable autoimmune disease, (b) non-IVIG-treatable autoimmune diseases, or (c) non-autoimmune disease, using a set of the International Classification of Diseases (ICD)-9 codes [Appendix 2]. Within each autoimmune disease status category, the control group was selected from patients who were not in the program and matched 1:4 using greedy propensity score match without replacement in the PMTX + database.[20] The propensity scores were obtained by regressing the following covariates into a logistic model: age at index date, gender, patient's proximity to 102 IG treatment centers (the list of treatment centers is not included due to space limitation), four geographic regions, Charlson Comorbidity Index score,[21] and 6-month pre-index total health-care costs [Table 1]. The covariates were selected based on the interests of outcome variables through literation review and clinical judgment of our internal and external clinical experts. Propensity matching was selected because some of our outcomes were rare (SBI and serious AEs).

Infection- and infusion-related AE rates [Appendix 2] were evaluated as both the proportion of patients experiencing events of interest as well as numbers of events per patient per year as a primary clinical outcomes. All patients were followed for a 1-year postindex date to identify infections or AEs. Infections were considered in three categories: SBIs, other infections, and all infections (including both SBIs and other infections).[7,8,22] Infusion-related AEs were categorized as serious AEs and mild less common AEs. These categories were created based on the severity and frequency of the AEs [Appendix 3].

The primary cost outcome was direct medical costs per person over the 12-month post-index period, which was defined as the amount the health plan allowed for a particular service and includes the plan paid amount plus any member liability (e.g., co-payment, deductible, and co-insurance). For calculations, the denominator included all patients in the cohort whether they experienced utilization in a service category or not. Total health-care costs were reported along with inpatient, emergency care center (EC), and outpatient costs. These costs were adjusted to 2014 prices using the Medical Care component of the US Consumer Price Index for All Urban Consumers for inflation. The following categories of direct medical costs were included: total allowable costs (calculated based on NDC, Healthcare Common Procedure Coding System (HCPCS) or CPT codes; both total IG-related and non-IG-related allowable costs were considered), total inpatient cost, total EC costs, and total outpatient costs (IG drug/administration costs which were based on HCPCS/CPT codes and nonIG-related costs), and total pharmacy costs (IG drug/administration costs were calculated based on NDC codes). Annual

**Table 1: Baseline Characteristics of Study Population before and after Propensity Score Matching**

| Characteristics | Subcategory | Before Propensity Score Matching | | | | *P* | After Propensity Score Matching | | | | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Intervention (*n*=73) | | Control (*n*=831) | | | Intervention (*n*=45) | | Control (*n*=180) | | |
| Age, Mean (95%CI†) | | 42.3 | (37.8-46.7) | 38.9 | (37.5-40.4) | 0.178 | 38.4 | (32.5-44.3) | 40.7 | (37.8-43.6) | 0.493 |
| Age Group, *n* (%) | 0-18 years | 12 | 16.4% | 191 | 25.1% | 0.242 | 11 | 24.4% | 37 | 20.6% | 0.947 |
| | 19-30 years | 8 | 11.0% | 63 | 8.3% | | 4 | 8.9% | 18 | 10.0% | |
| | 31-54 years | 27 | 37.0% | 296 | 39.0% | | 18 | 40.0% | 73 | 40.6% | |
| | 55+years | 26 | 35.6% | 210 | 27.6% | | 12 | 26.7% | 52 | 28.9% | |
| Male, *n* (%) | | 26 | 35.6% | 276 | 36.3% | 0.906 | 18 | 40.0% | 57 | 31.7% | 0.289 |
| Census Region, *n* (%) | Northeast | 33 | 45.2% | 136 | 17.9% | <.0001 | 11 | 24.4% | 34 | 18.9% | 0.745 |
| | Midwest | 11 | 15.1% | 286 | 37.6% | | 11 | 24.4% | 44 | 24.4% | |
| | South | 27 | 37.0% | 295 | 38.8% | | 21 | 46.7% | 97 | 53.9% | |
| | West | 2 | 2.7% | 43 | 5.7% | | 2 | 4.4% | 5 | 2.8% | |
| Proximity to Center, *n* (%) | | 50 | 68.5% | 408 | 53.7% | 0.015 | 27 | 60.0% | 109 | 61.0% | 0.946 |
| Autoimmune disease, *n* (%) | IVIG treatable autoimmune | 26 | 35.6% | 236 | 31.9% | 0.718 | 16 | 35.6% | 64 | 35.6% | 1.000 |
| | Non-IVIG treatable autoimmune | 4 | 5.5% | 55 | 7.4% | | 3 | 6.7% | 12 | 6.7% | |
| | Non-autoimmune immunodeficiency†† | 43 | 58.9% | 448 | 60.6% | | 26 | 57.8% | 104 | 57.8% | |
| CCI†††scores, *n* (%) | 0 | 18 | 24.7% | 269 | 35.4% | 0.166 | 14 | 31.1% | 52 | 28.9% | 0.494 |
| | 1-2 | 38 | 52.1% | 372 | 49.0% | | 24 | 53.3% | 90 | 50.0% | |
| | 3-4 | 13 | 17.8% | 84 | 11.1% | | 7 | 15.6% | 29 | 16.1% | |
| | 5+ | 4 | 5.5% | 35 | 4.6% | | 0 | 0.0% | 9 | 5.0% | |
| Six-month, pre-index total costs, Mean$ (95% CI†) | | $30,559 | ($22,867-$38,251) | $31,752 | ($29,539-$33,964) | 0.756 | $25,422 | ($20,197-$30,647) | $34,854 | ($29,489-$40,218) | 0.093 |
| Categorical costs, *n* (%) | <=$15,000 | 23 | 31.5% | 229 | 30.1% | 0.995 | 16 | 35.6% | 44 | 24.4% | 0.351 |
| | >$15,000, <=$30,000 | 21 | 28.8% | 228 | 30.0% | | 13 | 28.9% | 61 | 33.9% | |
| | >$30,000, <=$60,000 | 21 | 28.8% | 219 | 28.8% | | 13 | 28.9% | 51 | 28.3% | |
| | >$60,000 | 8 | 11.0% | 84 | 11.1% | | 3 | 6.7% | 24 | 13.3% | |

†CI=Confidence Interval; ††Including common variable immune deficiency; †††CCI=Charlson Comorbidity Index

in-patient and out-patient costs for patients were considered to be outliers if they were at or above five times the standard deviation and were capped at five times the standard deviation, based on the distribution.

Chi-square or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables were used to compare differences in baseline characteristics between groups. For categorical measures, frequency and percentage of total patients observed in each category were reported. For continuous variables, the mean and confidence interval were presented.

Because some national home infusion specialty pharmacy sites modified the program during the 3-year-study period, we adjusted both clinical and cost outcomes for these site-specific differences for intervention group when possible. These sites were not dropped from the analysis to prevent further reduction in the study sample. The AE and infection rates used general estimating equation (GEE) models with a log link, negative binomial distribution to adjust for site differences. GEE models were selected to account for the within-subject correlation of the matched cases and controls. Chi-square or Fisher's exact test was used to compare the proportion of AEs and infections between groups. Unadjusted results are presented, if the GEE model did not converge.

The mean costs after adjusting for site differences were reported and compared between intervention and control groups using GEE models with a log link and gamma distribution.

$P < 0.05$ was considered statistically significant. *P* value was reported as NA if the model did not converge. All data analyses were performed at a patient level using SAS 9.2 (SAS Institute INC., Cary, NC, USA).

## Results

Baseline characteristics and clinical and cost outcomes were analyzed and compared between patients in the high-touch SCIG clinical management model and their propensity-matched controls.

After applying the inclusion and exclusion criteria, there were 73 eligible patients in our intervention group and 760 in the control group [Appendix 1]. While no significant differences were observed for age and gender between the two groups, the differences in their accessibility to an expert treatment center, geographic distribution, and autoimmune disease status were significant [Table 1]. After propensity score matching, there were 45 and 180 patients remaining in the intervention and control group, respectively, and their baseline characteristics were well balanced [Table 1].

The majority of the AEs and infection outcomes were not significantly different between the study and control groups [$P > 0.05$; Table 2]. Interestingly, the proportion of patients who had a mild less common AE was significantly higher among patients in this IG clinical management program (4.4% vs. 0.0%; $P = 0.04$), suggesting greater recognition or capture of these events.

Significantly lower costs were observed for patients who received care as a part of IG clinical management program [Table 3] compared to matched controls. The annual mean total allowable cost of patients in the program was $20,868 lower (24% lower) compared to matched controls ($P = 0.009$). Costs were also significantly lower for total inpatient and outpatient services: $7,949 ($P = 0.03$) and $21,317 ($P = 0.003$) lower among patients with IG clinical management program, respectively. Although not statistically significant, total EC and pharmacy costs were also lower by $122 ($P = 0.435$) and $7,810 ($P = 0.398$). Total IG-related costs were $10,586 lower in the IG Clinical Management Program group; IG-related outpatient costs were $23,409 lower. While total pharmacy cost was lower in the intervention group, the IG-related pharmacy cost was higher; however, this difference was not statistically significant ($P = 0.522$).

## Discussion

In this study, we evaluated the clinical and cost outcomes for patients managed by a high-touch clinical management program compared with a propensity-matched control group within a national health-care claim database. Our results showed comparable clinical outcomes between the patients managed by the home setting care model and the control patients, which could be from other potential care models, such as hospital inpatient, hospital outpatient infusion center, or physician office. Therefore, this study confirms others that demonstrated the safety of the administration of SCIG in the home setting.[22,23] The high-touch IG clinical management model relies upon strong physician–pharmacist–nurse collaborations with coordinated clinical services that include pre-infusion clinical evaluations to proactively identify risks for ADR, individualize infusion plans, identify disease-specific patient-reported outcomes measures, and education on self-infusions by RN until the patient is independent. The high-touch model aspires to provide a residual network for data reporting and communication that encourages, identifies, and rapidly responds to patient concerns.

Our results show that patients in the high-touch clinical managed group had significantly lower health-care costs across all health-care settings. The greatest cost difference

**Table 2: Infection rate and adverse event rate of comparison groups**

| Clinical Outcomes | Mean Rate (events/patient/year, 95%CI††) | | *P* | Proportion of Patients (% of patients) | | *P* |
|---|---|---|---|---|---|---|
| | Intervention (*n*=45) | Control (*n*=180) | | Intervention (*n*=45) | Control (*n*=180) | |
| Infections | | | | | | |
| All Infections | 3.13 †(1.73,4.54) | 3.28 † (2.16,4.40) | 0.5 | 30 (66.7%) | 126 (70.0%) | 0.67 |
| Serious Bacterial Infections | 0.02 (-0.02,0.07) | 0.15 (-0.03,0.33) | NA | 1 (2.2%) | 7 (3.9%) | 1.00 |
| Other Infections | 3.11† (1.70,4.52) | 3.16 †(2.05,4.26) | 0.5 | 30 (66.7%) | 125 (69.4%) | 0.72 |
| Adverse Events (AE) | | | | | | |
| Serious AE | 0.11 (-0.02,0.24) | 1.31 (-0.10,2.71) | NA | 3 (6.7%) | 22 (12.2%) | 0.29 |
| Mild Less Common AE | 0.09 (-0.04,0.21) | 0 (NA) | NA | 2 (4.4%) | 0 (0.0%) | 0.04 |

†The means after adjustment of site differences by regression model are also available for "All Infections" and "Other Infections" rates. For "All Infections," the regression-adjusted rates are 3.46 and 4.40, respectively, for the intervention and control groups. For "Other Infections," the regression-adjusted rates are 3.41 and 4.25, respectively, for the intervention and control groups; ††CI=confidence internal

**Table 3: Regression-adjusted total allowable cost of comparison groups**

| Total Allowable costs† | Intervention (*n*=45) [A] Mean (95%CI††)$ | | Control (*n*=180) [B] Mean (95%CI††)$ | | *P* | Mean difference, $[A]-[B] |
|---|---|---|---|---|---|---|
| Total Costs | 66,450 | (55,353, 79,772) | 87,318 | (71,121, 107,205) | 0.009 | 20,868 |
| IG-related | 48,248 | (40,026, 58,157) | 58,834 | (46,741, 74,056) | 0.168 | 10,586 |
| Total Inpatient Costs | 3,398 | (1,462, 7,898) | 11,347 | (4,212, 30,566) | 0.03 | 7,949 |
| Total EC Costs††† | 222 | (90, 545) | 344 | (122, 974) | 0.435 | 122 |
| Total Outpatient Costs | 28,008 | (22,164, 35,394) | 49,325 | (37,341, 65,154) | <0.001 | 21,317 |
| IG-related | 16,650 | (11,809, 23,475) | 40,059 | (26,281, 61,060) | 0.001 | 23,409 |
| Total Pharmacy Costs | 26,543 | (17,623, 39,979) | 34,353 | (20,794, 56,753) | 0.398 | 7,810 |
| IG-related | 27,887 | (18,036, 43,121) | 23,507 | (13,732, 40,241) | 0.522 | -4,380 |

†Mean costs per patient per year are means after adjustment of site differences by regression model; ††CI=confidence interval; †††EC=emergence center

was in IG-related outpatient services ($23,409), which may indicate reduced physician office visits in the intervention group.

Many of our cost results are consistent with the published literature.[15,17,24,25] For example, our study noted IG-related costs, including drug and administration costs, were the main cost driver. Similarly, several other previously published cost studies also noted that the main cost driver was IG preparation. However, most were conducted in countries outside of the US (Canada, France, Italy, and Germany) with diverse health system models, and may not have included administration costs.[15,17,24,25] In addition, another study noted that inpatient infusion was less economical, compared to alternative sites of care, in part due to benefit design.[26] Benefit design may have played a significant role in our study, depending on whether the costs were charged to the medical or pharmacy benefit. Nevertheless, our findings added new information to the existing literature by showing the value of a clinical management program. A larger scale study is needed to explore further the potential reasons for these lower costs in the intervention group.

The majority of clinical outcomes studied in this analysis (i.e., infection- and infusion-related AE rates) were similar between intervention and matched controls, although the mild less common AEs were significantly higher in the high-touch group. The observed increased rate of mild less common AE may be a reporting byproduct also due to the high-touch, ongoing clinical management of the patient. This regular communication with the patient, patient education about AE monitoring, and regular communication between the home infusion and specialty pharmacy's pharmacists or RN with the treating physician would theoretically result in more comprehensive reporting of mild AEs. We perceive this as a benefit. Ideally, the early recognition of warning signs would be of value in matching them with appropriate clinical management and preventing their further development or progression into more severe consequences. This might partially explain the significantly lower out-patient and in-patient costs in the intervention group. While this remains a hypothesis at this point, additional research would be able to demonstrate the benefits of increased reporting, communication, and "high touch," through a prospectively designed and powered study.

The current study provided important insights into the effectiveness and efficiency of a high-touch clinical management program using propensity score matching and regression adjustment to control for confounding; however, there are several limitations in our study that

must be considered. Some of these limitations are usual to most retrospective, observational studies using claims and administrative databases because administrative data sets are not designed to conduct the research. Such limitations include missing data, coding biases, and channeling bias. The populations of patients selected for one particular treatment over the other may have different characteristics leading to channeling bias. Some of these differences can be measured (age, gender) and therefore, can be controlled in this study, but others are unknown or not measurable. Furthermore, there might be the difference in the number of SGIC treatment received in the follow-up period between cases and controls. Due to the inclusion and exclusion criteria and propensity score matching process, there were only 45 patients in the intervention group. While the sample size is similar to many other SCIG studies,[8,23,27-30] this limits its power to detect a rare AE and generalizability of the study results. This study did not include new-to-therapy patients; hence, we could not extrapolate our findings to new SCIG users. The control group could be composed of patients who could receive care from a variety of clinical programs/models other than the one described in this study. Finally, from administrative data, we could not determine whether any patients in the matched control group received any services similar to the clinical management provided to the intervention group in this study.

A high-touch IG clinical management program was shown to be associated with lower health-care cost and comparable infection or AE rates. Our findings show that the provision of a high-touch IG care model can be employed in the United States without compromising cost or outcomes. With the US health-care system under increasing pressure to reduce health-care expenditure and improve clinical outcomes, these findings could provide support for the potential role that a high-touch SCIG clinical management program might provide. Further research would be needed to identify the type of patients that may benefit the most from high-touch models and compare results to other models.

## Authors' Contribution

Julia Zhu and Heather Kirkham participated in concept design, literature review, data acquisition and analysis, study design, manuscript preparation, and supervision. Gretchen Ayer participated in concept design, obtaining funding, data acquisition and interpretation, statistical analysis, and manuscript preparation. Ron Wade and Chi-Chang Chen participated in concept design, data acquisition, statistical analyses, and supervision. Swapna Karkare participated in concept design, statistical analysis, and manuscript revision. Chester Robson participated in concept design, data interpretation, and manuscript preparation. Jordan Orange participated in concept design, data interpretation, and manuscript preparation. All authors read and approved the final manuscript.

### Acknowledgments

We gratefully acknowledge Dr. Harry Leider for his support and constructive advice. We also would like to express our sincere thanks to Jingsong Lu for providing data analysis and statistical advice. Furthermore, we appreciate the clinical advice and assistance of Nancy Kupka.

### Financial support and sponsorship

This research was funded by Walgreen Co., and Option Care Inc.

### Conflicts of interest

Julia Zhu, Heather S. Kirkham, and Chester H. Robson were a full-time employee of the study sponsor, Walgreen Co. during the conduct of the study. Gretchen Ayer is a salaried employee of the study sponsor, Option Care Enterprises. Chi-Chang Chen, Rolin L. Wade, and Swapna Karkare reported grants from Walgreens during the conduct of the study. Dr. Jordan S. Orange reports personal fees from Walgreen Co./Option Care Inc., during the conduct of the study; grants and personal fees from CSL Behring, personal fees from Baxalta, from Grifols, personal fees from ASD Healthcare, personal fees from ADMA Biologics, non-financial support from BPL, and personal fees from Atlantic Research Group, outside the submitted work.

## References

1. Haddad É, Barnes D, Kafal A. Home therapy with subcutaneous immunoglobulins for patients with primary immunodeficiency diseases. Transfus Apher Sci 2012;46:315-21.
2. Tonkovic B, Rutishauser LK. Descriptive review and analysis of immunoglobulin utilization management from 2,548 prior authorization requests. J Manag Care Spec Pharm 2014;20:357-67.
3. Modell V, Gee B, Lewis DB, Orange JS, Roifman CM, Routes JM, *et al*. Global study of primary immunodeficiency diseases (PI)-diagnosis, treatment, and economic impact: An updated report from the jeffrey modell foundation. Immunol Res 2011;51:61-70.
4. Bonilla FA. Pharmacokinetics of immunoglobulin administered via intravenous or subcutaneous routes. Immunol Allergy Clin North Am 2008;28:803-19, ix.
5. Haddad E, Berger M, Wang EC, Jones CA, Bexon M, Baggish JS, *et al*. Higher doses of subcutaneous IgG reduce resource utilization in patients with primary immunodeficiency. J Clin Immunol 2012;32:281-9.
6. Espanol T, Prevot J, Drabwell J, Sondhi S, Olding L. Improving current immunoglobulin therapy for patients with primary immunodeficiency: Quality of life and views on treatment.

Patient Prefer Adherence 2014;8:621-9.
7. Orange JS, Belohradsky BH, Berger M, Borte M, Hagan J, Jolles S, *et al*. Evaluation of correlation between dose and clinical outcomes in subcutaneous immunoglobulin replacement therapy. Clin Exp Immunol 2012;169:172-81.
8. Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J, *et al*. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. J Clin Immunol 2000;20:94-100.
9. Jolles S, Sewell WA, Misbah SA. Clinical uses of intravenous immunoglobulin. Clin Exp Immunol 2005;142:1-11.
10. Stiehm ER. Adverse effects of human immunoglobulin therapy. Transfus Med Rev 2013;27:171-8.
11. Orange JS, Grossman WJ, Navickis RJ, Wilkes MM. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies. Clin Immunol 2010;137:21-30.
12. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: Clinical and immunological features of 248 patients. Clin Immunol 1999;92:34-48.
13. Daoud Y, Amin KG, Mohan K, Ahmed AR. Cost of intravenous immunoglobulin therapy versus conventional immunosuppressive therapy in patients with mucous membrane pemphigoid: A preliminary study. Ann Pharmacother 2005;39:2003-8.
14. Sadeghi B, Abolhassani H, Naseri A, Rezaei N, Aghamohammadi A. Economic burden of common variable immunodeficiency: Annual cost of disease. Expert Rev Clin Immunol 2015;11:681-8.
15. Lazzaro C, Lopiano L, Cocito D. Subcutaneous vs. intravenous administration of immunoglobulin in chronic inflammatory demyelinating polyneuropathy: An Italian cost-minimization analysis. Neurol Sci 2014;35:1023-34.
16. Perraudin C, Bourdin A, Spertini F, Berger J, Bugnon O. Switching patients to home-based subcutaneous immunoglobulin: An economic evaluation of an interprofessional drug therapy management program. J Clin Immunol 2016;36:502-10.
17. Högy B, Keinecke HO, Borte M. Pharmacoeconomic evaluation of immunoglobulin treatment in patients with antibody deficiencies from the perspective of the German statutory health insurance. Eur J Health Econ 2005;6:24-9.
18. Hamine S, Gerth-Guyette E, Faulx D, Green BB, Ginsburg AS. Impact of mHealth chronic disease management on treatment adherence and patient outcomes: A systematic review. J Med Internet Res 2015;17:e52.
19. Akinbosoye OE, Taitel MS, Grana J, Hill J, Wade RL. Improving medication adherence and health care outcomes in a commercial population through a community pharmacy. Popul Health Manag 2016;19:454-61.
20. Zhu J, Kirkham HS, Ayer G, Chen CC, Wade RL, Karkare SU, *et al*. Clinical and economic outcomes of a "high-touch" clinical management program for intravenous immunoglobulin therapy. Clinicoecon Outcomes Res 2018;10:1-2.
21. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613-9.
22. Hagan JB, Fasano MB, Spector S, Wasserman RL, Melamed I, Rojavin MA, *et al*. Efficacy and safety of a new 20% immunoglobulin preparation for subcutaneous administration, IgPro20, in patients with primary immunodeficiency. J Clin Immunol 2010;30:734-45.
23. Stein MR, Koterba A, Rodden L, Berger M. Safety and efficacy of home-based subcutaneous immunoglobulin G in elderly patients with primary immunodeficiency diseases. Postgrad Med 2011;123:186-93.
24. Membe SK, Ho C, Cimon K, Morrison A, Kanani A, Roifman CM, *et al*. Economic assessment of different modalities of immunoglobulin replacement therapy. Immunol Allergy Clin North Am 2008;28:861-74, x.
25. Beauté J, Levy P, Millet V, Debré M, Dudoit Y, Le Mignot L, *et al*. Economic evaluation of immunoglobulin replacement in patients with primary antibody deficiencies. Clin Exp Immunol 2010;160:240-5.
26. Stern D, Reissman D. Specialty pharmacy cost management strategies of private health care payers. J Manag Care Pharm 2006;12:736-44.
27. Vultaggio A, Azzari C, Milito C, Finocchi A, Toppino C, Spadaro G, *et al*. Subcutaneous immunoglobulin replacement therapy in patients with primary immunodeficiency in routine clinical practice: The VISPO prospective multicenter study. Clin Drug Investig 2015;35:179-85.
28. Maroto Hernando M, Soler Palacín P, Martin Nalda N, Oliveras Arenas M, Español Boren T, Figueras Nadal C, *et al*. Subcutaneous gammaglobulin in common variable immunodeficiency. First experience in spain. An Pediatr (Barc) 2009;70:111-9.
29. Song J, Zhang L, Li Y, Quan S, Liang Y, Zeng L, *et al*. 20% subcutaneous immunoglobulin for patients with primary immunodeficiency diseases: A systematic review. Int Immunopharmacol 2015;25:457-64.
30. Hadden RD, Marreno F. Switch from intravenous to subcutaneous immunoglobulin in CIDP and MMN: Improved tolerability and patient satisfaction. Ther Adv Neurol Disord 2015;8:14-9.

**Appendix 1: Study population attrition table**

| Criterion | Intervention, *n* (%) | Control, *n* (%) |
|---|---|---|
| Patients received SCIG during the 6 months preindex period (September 1, 2011,-June 30, 2013) | 158 (100.00) | 1819 (100.00) |
| AND met continuous enrollment in the PMTX+ database for a minimum of 6 months before the index date | 109 (69.00) | 1420 (78.10) |
| AND met continuous enrollment criteria in the PMTX+ database for a minimum of 12 months after the index date | 87 (55.10) | 1011 (55.60) |
| AND with at least four claims of index IG in the 12 month postindex period | 84 (53.20) | 916 (50.40) |
| AND with one claim of index IG on or after month six (i.e., after day 150 from index) | 80 (50.60) | 851 (46.80) |
| AND without IMIG administration (exclusion criteria) | 80 (50.60) | 851 (46.80) |
| AND not receiving both SCIG and IVIG during the 12 months postindex period | 73 (46.20) | 763 (42.00) |
| AND with complete data and valid data | 73 (46.20) | 760 (41.80) |
| Patients postpropensity score 1-4 matching | 45 (28.50) | 180 (9.90) |

IG=Immunoglobulin, SCIG=Subcutaneous IG, PMTX+=PharMetrics Plus database, IMIG=Intramuscular IG, IVIG=Intravenous IG

**Appendix 2: The classification of autoimmune disease covariate**

| Disease | ICD-9-CM | IVIG-treatable auto-immune disease | Non-IVIG-treatable auto-immune disease | Nonautoimmune disease |
|---|---|---|---|---|
| CVID | 279.0X | | | Yes |
| Immunodeficiency diseases | 279.1X, 279.2, 279.3 | | | Yes |
| Behçet's syndrome | 136.1 | Yes | | |
| Postpolio syndrome | 138 | Yes | | |
| Autoimmune cytopenia | 238.7 | Yes | | |
| Hashimoto's thyroiditis and thyroiditis with hyperthyroidism | 245.2 | Yes | | |
| Autoimmune diabetes mellitus | 250.01, 250.03 | Yes | | |
| Autoimmune disease, not elsewhere classified | 279.4X (Not 279.41) | Yes | | |
| Graft-versus-host disease | 279.5 | Yes | | |
| Hemolytic anemia, autoimmune | 283 | Yes | | |
| Autoimmune hemophilia | 286.52 | Yes | | |
| Henoch-Schönlein purpura | 287 | Yes | | |
| Idiopathic thrombocytopenic purpura | 287.31 | Yes | | |
| Posttransfusion purpura | 287.41 | Yes | | |
| Autoimmune neutropenia | 288.09 | Yes | | |
| Macrophage activation syndrome | 288.4 | Yes | | |
| Acute disseminated encephalomyelitis, autoimmune encelopathy, limbic encephalitis, Rasmussen's syndrome, demyelinative brainstem encephalitis | 323.81 | Yes | | |

*Contd...*

**Appendix 2: Contd...**

| Disease | ICD-9-CM | IVIG-treatable auto-immune disease | Non-IVIG-treatable auto-immune disease | Nonautoimmune disease |
|---|---|---|---|---|
| Alzheimer's disease | 331 | Yes | | |
| Stiff man syndrome | 333.91 | Yes | | |
| Cerebellar ataxia, opsoclonus-myoclonus syndrome, postinfectious, paraneoplastic cerebellar degeneration | 334.2, 334.3 | Yes | | |
| Paraproteinemic neuropathy | 337.00, 337.09, 356.8 | Yes | | |
| IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathy | 337.1 | Yes | | |
| Multiple sclerosis, relapsing-remitting | 340 | Yes | | |
| Epilepsy, intractable childhood | 345.61 | Yes | | |
| Narcolepsy with cataplexy | 347.01 | Yes | | |
| Lumbosacral or brachial plexitis | 353.0, 353.1 | Yes | | |
| Chronic demyelinating polyneuropathy | 356.4 | Yes | | |
| Guillain-Barre' Syndrome | 357 | Yes | | |
| Multifocal motor neuropathy | 357.89 | Yes | | |
| Myasthenia gravis | 358 | Yes | | |
| Lambert-Eaton myasthenic syndrome | 358.3 | Yes | | |
| Necrotizing autoimmune myopathy | 359.81 | Yes | | |
| Uveitis, autoimmune | 360.19 | Yes | | |
| Grave's ophthalmopathy (thyrotoxic exophthalmos) | 376.21 | Yes | | |
| Autoimmune optic neuropathy | 377.49, 377.30 | Yes | | |
| Brown-Vialetto-Van Laere Syndrome | 389.1 | Yes | | |
| Cerebral infarctions with anti-phospholipid antibodies | 434.01, 434.11, 434.91 | Yes | | |
| Polyarteritis nodosa | 446 | Yes | | |
| Kawasaki disease | 446.1 | Yes | | |
| Thrombotic thrombocytopenic purpura | 446.6 | Yes | | |
| Anti-neutrophil antibody syndrome | 447.6 | Yes | | |
| Inflammatory bowel disease | 555.0, 555.1, 555.2, 555.9 | Yes | | |
| Autoimmune chronic active hepatitis | 571.42 | Yes | | |
| Antiphospholipid antibody syndrome in pregnancy | 649.3 | Yes | | |
| Pemphigus foliaceus, pemphigus vulgaris, pemphigus, and paraneoplastic | 694.4 | Yes | | |
| Bullous pemphigoid | 694.5 | Yes | | |
| Cicatricial pemphigoid | 694.6 | Yes | | |
| Scleromyxedema | 701.8 | Yes | | |
| Chronic urticaria | 708.1, 708.8 | Yes | | |
| Systemic lupus | 710 | Yes | | |
| Systemic sclerosis (scleroderma) | 710.1 | Yes | | |
| Sjögren's syndrome (sicca syndrome) | 710.2 | Yes | | |
| Dermatomyositis | 710.3 | Yes | | |
| Polymyositis | 710.4 | Yes | | |
| Mixed connective tissue disease | 710.8 | Yes | | |
| Unspecified diffuse connective tissue disease | 710.9 | Yes | | |
| Rheumatoid arthritis, severe | 714 | Yes | | |
| Felty syndrome | 714.1 | Yes | | |
| Juvenile idiopathic arthritis | 714.3 | Yes | | |
| Juvenile idiopathic arthritis | 714.31 | Yes | | |

*Contd...*

**Appendix 2: Contd...**

| Disease | ICD-9-CM | IVIG-treatable auto-immune disease | Non-IVIG-treatable auto-immune disease | Nonautoimmune disease |
|---|---|---|---|---|
| HTLV-1-associated myelopathy | 721.1, 721.4, 721.91 | Yes | | |
| Acute idiopathic dysautonomia | 742.8 | Yes | | |
| Chronic bullous disease of childhood, epidermolysis bullosa acquisita | 757.39 | Yes | | |
| Fetomaternal alloimmune thrombocytopenia | 776.1 | Yes | | |
| Sarcoidosis | 135 | | Yes | |
| Grave's disease | 242 | | Yes | |
| Addison's disease, autoimmune | 255.41 | | Yes | |
| Autoimmune polyglandular syndrome, type I | 258.01 | | Yes | |
| Autoimmune polyglandular syndrome, type II | 258.02, 258.03 | | Yes | |
| Pernicious anemia | 281 | | Yes | |
| Encephalomyelitis | 323.9 | | Yes | |
| Retinopathy | 362.1 | | Yes | |
| Thromboangiitis obliterans | 443.1 | | Yes | |
| Churg-Strauss disease, Wegener's granulomatosis | 446.4 | | Yes | |
| Temporal arteritis | 446.5 | | Yes | |
| Takayasu's arteritis | 446.7 | | Yes | |
| Autoimmune chronic active hepatitis | 571.49 | | Yes | |
| Primary biliary sclerosis | 571.6 | | Yes | |
| Sclerosing cholangitis | 576.1 | | Yes | |
| Gluten-sensitive enteropathy | 579 | | Yes | |
| Infertility, immune mediated | 628.8 | | Yes | |
| Pemphigoid gestationis | 646.8 | | Yes | |
| Dermatitis herpetiformis | 694.2 | | Yes | |
| Linear IgA disease | 694.8 | | Yes | |
| Erythema nodosum | 695.2 | | Yes | |
| Psoriasis | 696.1 | | Yes | |
| Alopecia, autoimmune | 704 | | Yes | |
| Vitiligo | 709.01 | | Yes | |
| Other rheumatoid arthritis with visceral or systemic involvement | 714.2 | | | |
| Rheumatoid lung | 714.81 | | | |
| Other specified inflammatory polyarthropathies | 714.89 | | | |
| Unspecified inflammatory polyarthropathy | 714.9 | | | |
| Ankylosing spondylitis | 720 | | | |

IG=Immunoglobulin, ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification, IVIG=Intravenous IG, CVID=Common variable immune deficiency, HTLV=Human T-cell leukemia-lymphoma virus

**Appendix 3: Clinical Outcomes: Infections and adverse events**

| Description | Diagnosis | ICD-9-CM |
|---|---|---|
| SBIs | Bacterial pneumonia | 482.XX |
| | Visceral abscess | 324.X, 478.24. 513.0, 567.22, 567.38, 572.0, 590.2 |
| | Septicemia | 995.91, 995.92, 038.XX, 790.7, 785.52 |
| | Bacterial meningitis | 320.X, 321.X, 322.X, 047.X, 003.21, 036.0 |
| | Osteomyelitis/septic arthritis | 711.0X, 730.0X |
| Other infections | Conjunctivitis | 372.00, 372.05, 372.3, 372.03 |
| | Acute bronchitis | 466 |
| | Acute otitis | 382.0, 382.0X, 382.4, 382.9 |
| | Pyoderma/cellulitis/subcutaneous abscess | 686.XX, 682.XX |
| | Mastoiditis | 383.XX |
| | Sinusitis | 461.X, 473.X |
| | Upper respiratory infection | 465.8, 465.9 |
| Mild less common AE | Fibrosis, cutaneous or subcutaneous | 709.2 |
| | Lipodystrophy | 272.6 |
| Serious AE | Anaphylaxis/anaphylactoid reaction/ Anaphylactic shock | 995.0, 999.41, 999.49 |
| | Pulmonary edema | 518.4 |
| | Embolism | 444.X, 415.19, 445.X |
| | Seizure | 345.0X, 345.1X, 345.2X, 345.3X, 345.4X, 345.5X, 345.8X, 345.9X, 780.39 |
| | Aseptic meningitis | 322.9 |
| | Transfusion-related acute lung injury | 518.7 |
| | "Serum sickness" | 999.51, 999.59 |
| | Acute renal failure/anuria/renal tubular necrosis/blood creatinine increased/blood urea increase | 584.XX |
| | Thrombotic complications | 453.9 |
| | Dermatitis bullous/dermatitis exfoliative/epidermal | 694 |
| | Hepatitis/acute hepatitis (noninfectious)/hepatic dysfunction/ hepatic failure/hepatocellular damage/jaundice | 573.3, 070.XX |
| | Neurodegeneration | 294.1 |
| | Neurological illness | 357.9 and 348.9 |

ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification, AE=Adverse event, SBIs=Serious bacterial infections