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ORIGINAL ARTICLE

# Medication stewardship using computerized clinical decision support: A case study on intravenous immunoglobulins

Demetra Tsapepas[1,2] | Caroline Der-Nigoghossian[1] | Khilna Patel[1] | Karen Berger[1] | David K Vawdrey[1,2] | Hojjat Salmasian[1,2,3]

[1]NewYork-Presbyterian Hospital, New York, NY, USA

[2]Columbia University, New York, NY, USA

[3]Brigham and Women's Hospital, Boston, MA, USA

**Correspondence**
Demetra Tsapepas, NewYork-Presbyterian Hospital, 622 West 168th Street, PH12-1281, New York, NY 10032, USA.
Email: det9021@nyp.org

## Abstract

**Background:** Healthcare delivery organizations face increasing pressure to manage the use of medications in terms of safety, waste reduction, and cost containment.

**Objective:** To describe a computerized provider order entry (CPOE) system intervention to optimize use of a commonly ordered, high-cost therapeutic: intravenous immune globulin (IVIG).

**Design:** Description of IVIG order configuration, medication use patterns, and subsequent order set configuration development in a CPOE system.

**Measurements:** IVIG orders were extracted from the CPOE system before and after the implementation of a specialty orderset to determine the indications for use, dosing, and duration of therapy. Orders were compared to a theoretical dosing schedule created from published evidence and data from a prior medication use evaluation.

**Results:** During 36 months before the implementation of the IVIG order set, 1965 IVIG orders were reviewed. The prescribed IVIG dose varied considerably from the expected dose (mean = −1.8, range = −4.9-1.5). In the 27 months after order set implementation, 848 IVIG orders were reviewed. The prescribed IVIG dose was closer to the expected dose (mean = −1.2, range = −3.9-2.6, $P < .0001$).

**Conclusions:** Order configuration processes are cumbersome and time-consuming, but can be streamlined to enhance a medication's usage in the healthcare system. A better understanding of institution-specific ordering patterns may facilitate more efficient and effective order configuration and optimize drug use.

KEYWORDS

clinical decision support, electronic health record, intravenous immune globulin, safety

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## 1 | INTRODUCTION

Healthcare organizations have increasingly utilized information technology (IT) to develop tools within computerized physician order entry (CPOE) platforms to transform healthcare delivery.[1-3] CPOE and computerized clinical decision support (CDS) systems embedded with care protocols have the potential to enhance efficiency, quality and safety of medication use, while promoting fiscal stewardship of medication therapy management.[4-8] Order configuration begins with basic order entry capabilities for admission/ transfer/ discharge, nursing orders, laboratory and radiologic studies, procedures, and medication orders.[9] Preconfigured orders such as in the case of an "order set"—that is, a collection of related orders grouped for a clinical purpose—may facilitate standardized treatment of a particular condition, embody a specific care pathway, or standardize medication use particularly for expensive medications.[7,9] Order set development within a CPOE system can be time-consuming and expensive. New ordersets may change provider workflow by increasing the time spent on order input, as a valid order must be constructed from a list of choices that are pertinent to the patient being cared for.[9,10] Despite the aforementioned potential barriers, carefully implemented order sets may encourage evidence-based or institution-specific care through the influence on provider behavior.[8,9,11,12] While it is evident that order sets are effective tools embedded in a CPOE system, literature describing their development is scarce.[7] Several reports have identified that the lack of information sharing and exchange of generalizable knowledge about the types and development of healthcare information technology (HIT) and implementation processes contribute to the slow progress that has been made in this arena.[13]

The objective of our study was to design a CDS solution to provide medication stewardship, using input from the providers and an iterative approach. We picked intravenous immunoglobulin (IVIG) as the first target drug for our approach. IVIG has potent immunomodulatory, immunoregulatory, and anti-inflammatory properties and is used across a wide spectrum of therapeutic areas including neurology, transplantation, infectious diseases, hematology-oncology, dermatology, and autoimmune diseases.[14-16] IVIG is a costly medication and its broad applicability often translates into extremely high expenditure for healthcare organizations.[15] Stewardship practices described for IVIG to date have been manually intensive and required formalized pharmacist involvement to approve each order placed.[17]

The order set was developed in a data-driven manner; we used historical ordering patterns in the CPOE system, and also collected direct input from the providers during the various stages of order set development. The ultimate goal of this order set was to improve IVIG stewardship, therefore we conducted a pre-post comparison to quantify its impact on IVIG utilization and reduction of inappropriate use of this expensive and widely used medication. Herein, we present our CDS design and multi-modal bundled approach as well as the results of this pre-post evaluation.

## 2 | MATERIALS AND METHODS

A multi-disciplinary team comprised of clinical pharmacists, physicians, nurses, informaticians, and IT specialists undertook a comprehensive project to improve and standardize IVIG utilization throughout the institution Figure 1. The team was convened as a workgroup from the Formulary and Therapeutics committee which serves as the governing body for medication use and safety at the organization. Several key elements for intervention were identified and a four-step approach was implemented to improve IVIG usage: (a) automated dose rounding to commercial vial strength to facilitate optimized dispensing practice; (b) generation of a complete list of indications for IVIG, from internal data capture; (c) development and implementation of an order set with coded indications and dosing including dose adjustment for indication and patient's weight; and (d) evaluation and ongoing tool optimization.

### 2.1 | STEP 1: Automated dose rounding and dispensing practice change [3-month process]

A workflow analysis identified that the prescribing practices and pharmacy preparation process was contributing to drug waste. The previous practice consisted of pooling IVIG from individual vials into a large glass bottle to provide the precise number of grams that a patient was prescribed. If a patient had an order placed for a 32-g dose of IVIG, the pharmacist would mix one 20-g vial, one 10-g vial, and one-third of a 5-g vial into a large glass bottle. This pooled preparation often resulted in the partial use of a vial and subsequent drug waste (unless it was immediately used for a second dose in a concurrent patient, which was extremely uncommon). In addition, pooled preparations only had a 24-hour expiration time, so if there was a delay in therapy or the patient being treated developed a reaction during the infusion, the entire, or the large majority of a dose had the potential to be wasted. The current commercially available IVIG preparations are available in a variety of vial sizes, primarily in 5 g increments. Dose rounding to the commercially available increments (such as rounding a 32 g dose to 30 g) allowed for dispensation of the entire product vial, which enabled the dispensing practice to change from pooling to commercial bottle dispensing (Figure 2A); the latter prevented the waste of unused vials which had expiration dates much longer than 24 hours if stored appropriately. In addition, this practice resulted in reduced pharmacy preparation times.

Our CPOE system was configured with medical logic modules (MLM) written using Arden Syntax to integrate a process of dose rounding (Figure 2A). When prescribers entered a desired dose, the dose was automatically rounded up or down to the nearest 5-g increment. If IVIG administration was delayed, discontinued, or a patient had a reaction the remaining unused vials, so long as they were stored properly, could be returned to the pharmacy department to use for a subsequent patient.

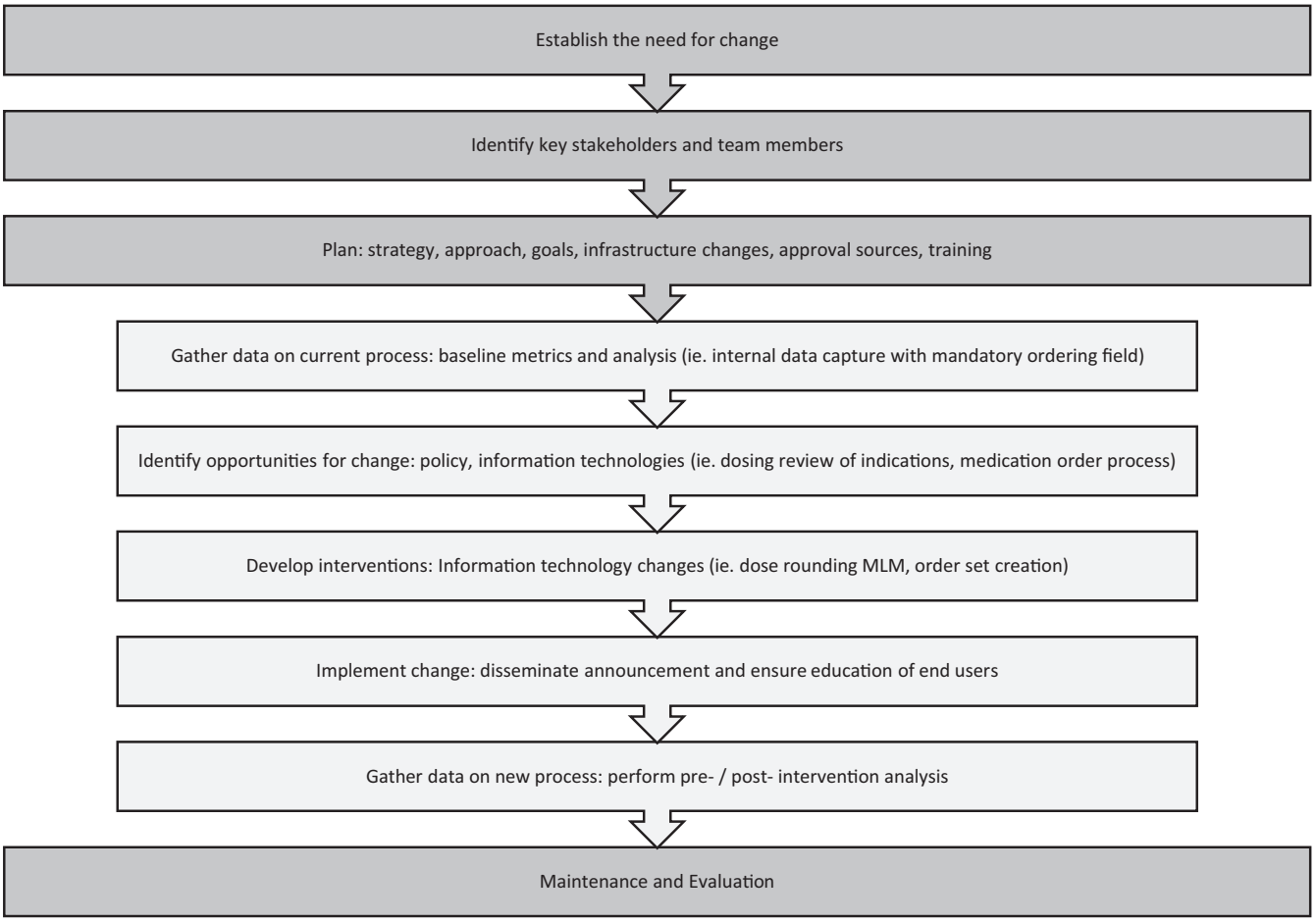


**FIGURE 1** Implementation process

## 2.2 | STEP 2: Identifying indications through passive observation [24-month process]

There is an abundance of literature describing the use and benefits of IVIG therapy for a variety of disease states, both FDA-approved and off-label. Several review articles have characterized the level of evidence that supports or refutes the use of IVIG therapy for a multitude of disease states.[14,16] Public and commercial medication-indication knowledge-bases may also be used to determine a list of indications for IVIG. However, these sources are often discordant

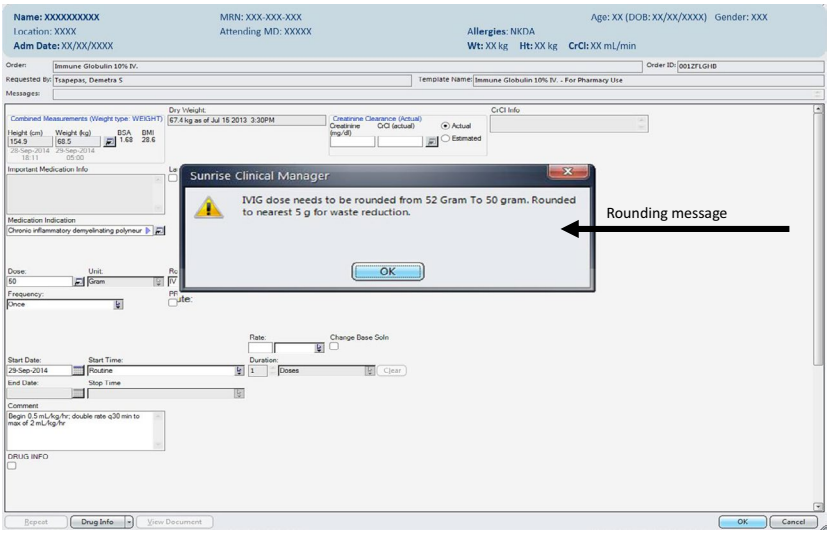


**FIGURE 2A** Dose rounding

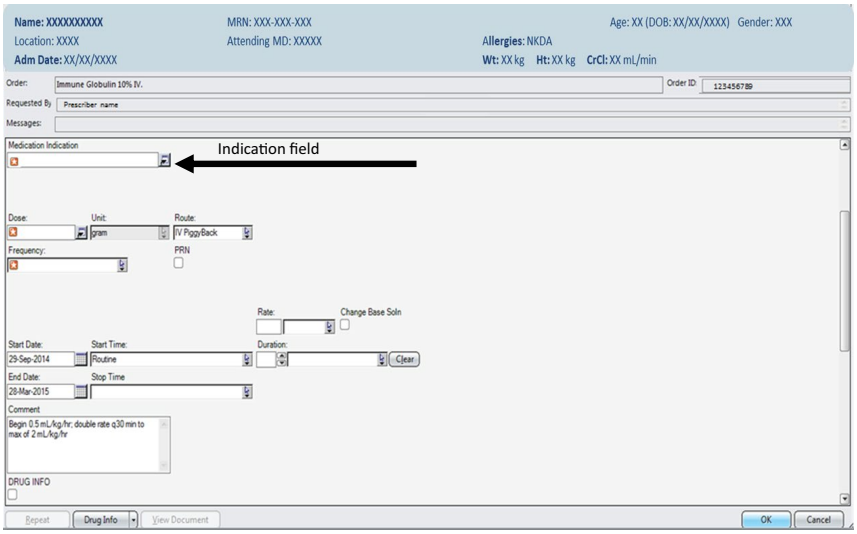


**FIGURE 2B** Free-text indication field for data collection

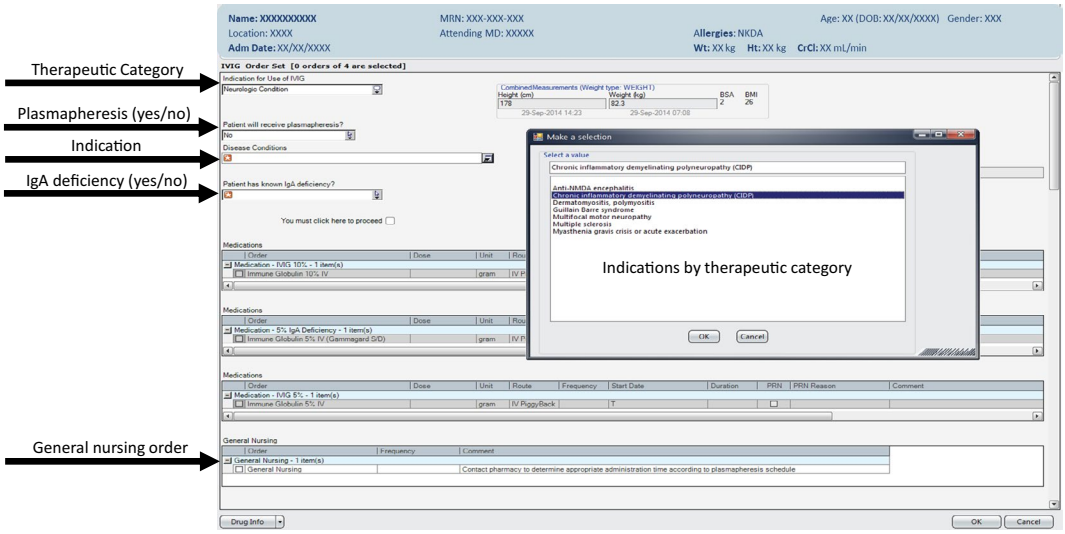


**FIGURE 2C** Order set

with one another, and usually do not include common off-label uses of a medication.[18] Therefore, it was essential to design the indication list for the IVIG order set based on the actual use cases at our study site, while conforming to evidence-based practices.

To ascertain IVIG usage patterns at our study site, a prospective, observational method was implemented to collect information as medication orders were placed in the CPOE system. First, an IVIG order entry item was created, which included a free-text field for prescribers to input the indication for which they were prescribing IVIG therapy (Figure 2BB). The field was mandatory, but not validated, and providers could enter any information; this choice was deliberately made to ensure that providers who did not choose to elaborate their decision could still easily continue with order entry. Though there were the inherent limitations, this approach enabled us to gather data and gain valuable insight on prescriber practices at our study site.

Using the indication and dose entered by providers in combination with patient demographics we conducted an evaluation on the usage and dosing ranges of IVIG. After an 18-month period, a literature search was conducted for supportive scientific evidence and recommended dosing information for the most frequently prescribed clinical indications. Clinical experts in each therapeutic area were convened over 6 months to discuss appropriateness of IVIG use and dosing for each indication. These clinicians were instrumental to delineate the approved indications with associated dosing and duration of therapy and to determine which indications were considered unapproved for the institution. Specific recommendations were aggregated into an IVIG order set using contextualization, where the orderset was adapted according to the medical condition of the patient, as the basis of the next step in our approach.

## 2.3 | STEP 3: Development and implementation of the order set with CDS [12-month process]

As opposed to the previous IVIG order entry item which was passive (only collecting data), the order set was designed to actively

**TABLE 1** Demographic and descriptive characteristics

| | Preimplementation | Postimplementation |
|---|---|---|
| Total IVIG orders | 1415 | 1398 |
| Number of unique patients | 537 | 435 |
| Number of unique admissions | 664 | 532 |
| Patient race | | |
| Black | 69 (13%) | 72 (17%) |
| White | 279 (52%) | 213 (50%) |
| Other/ Unknown | 189 (35%) | 150 (34%) |
| Patient's sex (% female) | 51.8% | 42.5% |
| Patient age (years) | 51.9 ± 16.7 | 52.0 ± 16.2 |
| Patient's adjusted weight (kg) | 69.4 ± 14.3 | 69.8 ± 14.9 |
| Patient's BMI ($kg/m^2$) | 27.1 ± 6.7 | 26.1 ± 5.9 |
| Admitting Service | | |
| Medicine | 391 (59%) | 339 (64%) |
| Neurology | 141 (21%) | 79 (15%) |
| Surgery | 104 (16%) | 102 (19%) |
| Other | 28 (4%) | 12 (2%) |

**TABLE 2** Most common prescribed indications for IVIG

| | |
|---|---|
| 1 | **Kidney Transplant antibody mediated rejection** |
| 2 | Acquired hypogammaglobinemia secondary to malignancy/ treatment |
| 3 | Lung Transplant antibody mediated rejection |
| 4 | Kidney Transplant living donor desensitization |
| 5 | Heart Transplant desensitization |
| 6 | Idiopathic thrombocytopenia purpura (ITP) |
| 7 | Myasthenia gravis crisis or acute exacerbation |
| 8 | Guillain Barre syndrome |
| 9 | Lung Transplant desensitization |
| 10 | IgG subclass deficiency with severe infection |

provide CDS to the providers at the time of order entry. This new order set consisted of four main sections (Figure 2CC). The first section contained two drop-down menu options for the therapeutic category and specific indications, and a free-text field for indications not found among the provided options (eg, off-label use). In the second section, the prescriber was prompted to answer if a patient had known IgA deficiency, which would select the correct IVIG product for dispensing. Prescribers were also prompted to answer a question as to whether the patient would undergo plasmapheresis treatment. When plasmapheresis was planned, it was important to administer IVIG after the procedure to avoid removal of the drug from plasma during this process. In these cases, a general nursing order was generated so that the nurse knew to coordinate with pharmacy for drug dispensation to occur after plasmapheresis.

An MLM was programmed with the specific details regarding the weight-based dosing for each indication as well as defaulted frequencies and durations. The MLM determined the recommended dosage based on the provider's choices in the first two parts of the order set. In the third section, the MLM was programmed to identify the latest recorded weight and height for the patient, determine whether actual weight or adjusted body weight should be used in the dosing calculation, and perform the dosing corrections as necessary. For nonobese patients, IVIG doses were calculated using actual body weight, and for obese patients (defined as those who weighed > 130% of their ideal body weight), adjusted body weight was calculated as *[Ideal body weight + 0.4 (Actual body weight − Ideal body weight)]*.

In the last section of the order set, the IVIG dose was recorded. The recommended dosage was calculated and entered, but providers could override the dosage based on their clinical judgment. Premedications (acetaminophen and diphenhydramine) to prevent or mitigate infusion related reactions and preset infusion rates (initial and titration instructions) were generated in the order and comment fields to optimize the safe administration of IVIG.

## 2.4 | STEP 4: Evaluation of the tool

We conducted a single-center, retrospective, before-after analysis of the utilization of IVIG over a 5.5-year period (October 2009-July 2016) during which the development and implementation of the order set was conducted. The final order set with CDS capabilities went into effect in December 2013, providing 2.5 years of data post implementation. This study was approved by the Institutional Review Board of Columbia University Medical Center.

All evaluated orders were electronically entered through our CPOE system. If multiple IVIG orders were placed for the same patient during the same visit, and the indication entered was different, then all orders and the patient chart were reviewed by a clinical pharmacist to identify a single, primary indication. Furthermore, we reviewed all other pertinent variables (eg, patient height and weight) for accuracy, and whenever they were inaccurate, we corrected them by consulting the patient chart (eg, in 11 cases, patient height was incorrect due to decimal point errors or issues with conversion from imperial to metric system).

Expected dosage of IVIG was calculated based on the indication, patient's actual or adjusted weight as appropriate, and the length of stay (in cases where IVIG was administered over weeks or months). This value was compared with the total amount of IVIG given to the patient, calculated using the medication administration records (MAR). To evaluate the concordance of IVIG dosage to the evidence-based recommendation, we calculated a "dosage ratio" as the natural log of the ratio of observed dosage to expected dosage, where $log(O/E) = 0$ indicates dosage met the expected value perfectly.

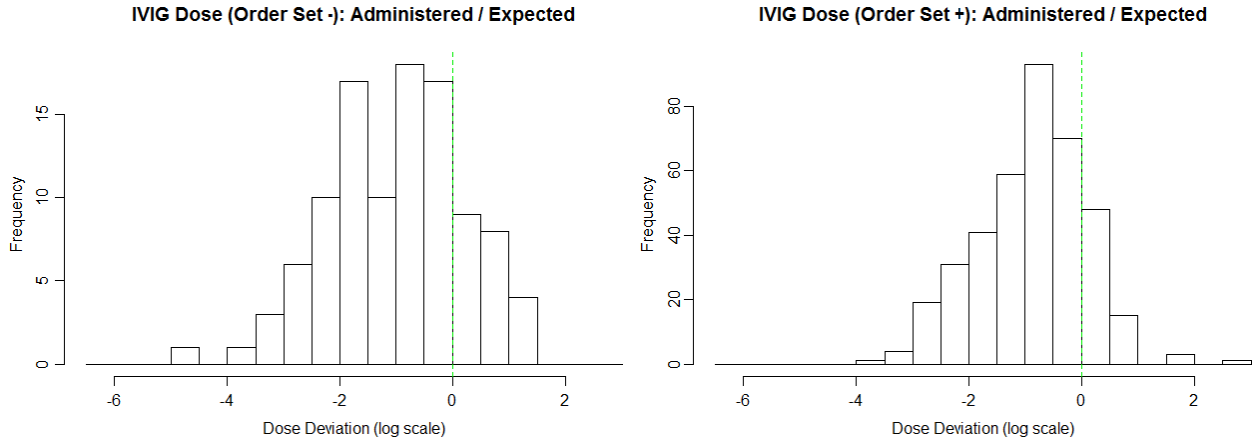


**FIGURE 3** Dosing deviations before (Order Set −) and after (Order Set +) process implementation

All analyses were performed using R version 3.3.1.[19] Rates were compared using the chi-squared test, and interval values were compared using the t-test; a cutoff of 0.05 was used for statistical significance.

## 3 | RESULTS

During the 24-month period where the passive order set was in use, IVIG therapy was prescribed for 123 unique indications. A systematic literature search of MEDLINE via PubMed for English-language articles was conducted for each indication by using key terms: intravenous immune globulin, immune globulin intravenous, ivig, and each indication to identify the best available scientific evidence for each. After analyzing the literature and consulting with the respective therapeutic committees and clinician groups, 74 unique indications were included in the final list of appropriate uses of IVIG. The appropriate dosages for each indication were programmed into the MLM that was used by the final order set with CDS capability.

A total of 2813 IVIG orders were placed during the study period. Demographic and descriptive characteristics are summarized in Table 1. The most common indication groups selected were transplant and neurology (Table 2). Figure 3 shows the distribution of the dosage ratio in the two study periods. Before the implementation of the final order set, IVIG dose varied notably when compared to the expected dose (mean = −1.8, range = −4.9-1.5). After the implementation of the final order set, IVIG dose variability was less, and on average, the dosage was closer to the expected dose (mean = −1.2, range = −3.9-2.6, $P < .0001$). Overall, higher-than-expected dosages of IVIG were uncommon, while lower-than-expected dosages were relatively common. Analysis of cases where the IVIG dose was notably lower than the expected dose suggested that they were all due to deviations from the order set recommendations, without a clear, documented clinical justification. These all occurred in patients with solid organ transplant undergoing treatment of rejection.

## 4 | DISCUSSION

Literature describing methodologies to assess the impact of HIT is evolving. A comprehensive understanding of the medication use process (prescriber order, pharmacist review, dispensing of the medication, and administration) is essential to implement effective and safe electronic medication optimization strategies for drug therapies. IVIG is a widely used therapeutic agent that is associated with significant cost, and many hospitals are employing stewardship programs to contain usage and cost. The work that we summarize in this manuscript demonstrates that a systematic, comprehensive, bundled approach resulted in a successful implementation for IVIG stewardship. The engagement of stakeholders, clinician experts, and end users were critical for the development and successful implementation of the tool. These groups worked to create an enterprise-level organizational medication use policy, capture data from clinical practice, and subsequently developed a clinical decision support-based order set which significantly reduced the variability in care. Though combining multiple approaches requires a significant effort, each of these approaches in isolation would only have a limited impact. Annual review of the policy from which the order set is built and continuous feedback from end users has been implemented to keep the information up to date and issues can be addressed in real time.

## 5 | DISTINCT AND COMPLEX PATIENT POPULATIONS REQUIRE EVIDENCE-BASED CLIENT CUSTOMIZATION

The potential impact of information technologies on avoidance and reduction of medication errors through safeguards in the medication use process is profound.[20,21] Maintaining, customizing, and continuously evaluating all CDS systems within a vendor supplied electronic medical record is paramount to ensure that the most applicable data are provided for patient care and safety. In our experience, the most effective CDS tools are those that integrate pertinent patient data

and best practice guidelines in real time.[22,23] In our order set, common and most frequently used dosing scenarios are automatically calculated with ease and minimizing the need for a consultation or phone call. This reserves the pharmacists time to become involved in more complex clinical scenarios and to perform other tasks important for patient care activities.

Our study is not without limitations. It was conducted as a single site for one electronic medical record system. As demonstrated in Table 1, the preimplementation and postimplementation periods do not completely match each other in terms of basic demographics; this is a known phenomenon in before-after studies, and can be addressed in future, randomized studies. However, even though some of the differences observed in the two arms are statistically significant, the actual difference is small, indicating that the statistical significance is in part due to the relatively large sample size. Due to the bundled approach for this initiative we are unable to tease out the cost savings impact of each individual component. As this was a new approach users had the ability to change the calculated IVIG dose if desired which resulted in low compliance with our guideline for some indications such as treatment for rejection among solid organ transplant recipients. Future work will evaluate outcomes associated with the various dosing strategies so that with 2 to 3 years of maturity of this data the calculations will be locked in to the order set.

In an era of the growing use of technology our program has advanced pharmacy practice through innovative activities that also translates into better care for our patients. Order configuration processes are cumbersome and time consuming, however, when these steps are implemented in a systematic manner enhancing a medications usage in the healthcare system is productive. Better understanding of ordering patterns may make order configuration and drug use more efficient since entries were configured according to prescribing patterns.

## 6 | CONCLUSION

By engaging a multi-disciplinary team, utilizing a systematic approach, we successfully developed an automated order set for IVIG stewardship, and its implementation was associated with a significant reduction in dosage variation, that is, higher concordance with evidence-based care. Implementation of this approach is generalizable to other organizations who are using the same or different electronic medical records by following the approach outlined in this manuscript.

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## CONFLICT OF INTEREST

The authors of this manuscript have nothing to disclose.

## ORCID

*Demetra Tsapepas* https://orcid.org/0000-0001-6428-5525

*Caroline Der-Nigoghossian* https://orcid.org/0000-0001-5445-9421

*Khilna Patel* https://orcid.org/0000-0002-1020-9823

*Karen Berger* https://orcid.org/0000-0003-3686-3468

*Hojjat Salmasian* https://orcid.org/0000-0002-9004-7149

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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