Immune Globulin Screening Pilot (IGSP)

Final Report

Provincial Programs Branch, Negotiations
and Accountability Management Division

November 2017

Ontario

Acknowledgement

The Provincial Programs Branch would like to thank the following parties for their involvement in the development and implementation of the Immune Globulin Screening Pilot (IGSP). Without them, the IGSP and this report would not have been possible.

- Immune Globulin Advisory Panel
- IGSP Working Group
- Ontario Regional Blood Coordinating Network (ORBCoN)
- Exceptional Access Program (EAP), Ontario Public Drug Programs, Ministry of Health and Long-Term Care
- Ms. Na Li, Biostatistician, McMaster Centre for Transfusion Research

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Glossary: Abbreviations & Acronyms

ADEM	Acute Disseminated Encephalomyelitis
BMI	Body Mass Index
CBS	Canadian Blood Services
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
EAP	Exceptional Access Program
GBS	Guillain-Barré Syndrome
HTS	Hospital Transfusion Service
IG	Immune Globulin
IGAP	Immune Globulin Advisory Panel (formerly IVIGAP, Intravenous Immune Globulin Advisory Panel)
IGSP	Immune Globulin Screening Pilot
IGSPWG	Immune Globulin Screening Pilot Working Group
IVIG	Intravenous Immune Globulin
LEMS	Lambert-Eaton Myasthenic Syndrome
MG	Myasthenia Gravis
MMN	Multifocal Motor Neuropathy
MOHLTC	Ministry of Health and Long-Term Care
OP	Ordering Physician
OQ	Outcome Questionnaire
ORBCoN	Ontario Regional Blood Coordinating Network
PANDAS	Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections
PATB	Provincial Agencies Trillium Gift of Life Network/Blood and Specialized Programs (formerly the Blood Programs Coordinating Office-BPCO)
PHI	Patient Health Information
PPPs	Plasma Protein Products
PTs	Provinces and Territories
RE	Rasmussen's Encephalitis
SCIG	Subcutaneous Immune Globulin
TAT	Turn-Around Time after SCIG

Executive Summary

Rationale for the Immune Globulin Screening Pilot (IGSP)

Immune Globulin (IG), a plasma protein product (PPP), is used to treat conditions such as primary and secondary immune deficiencies and autoimmune disorders. IG is licensed for six indications by Health Canada. IG is increasingly prescribed for "unlabeled, potentially indicated" conditions. Except for Quebec, Canadian Blood Services provides IG to all Canadian hospitals at no cost or scrutiny of its use. Since hospitals do not pay for IG, hospital resources may not be allocated to screen orders for IG as is done for pharmaceuticals.

Ontario's IG Advisory Panel (IGAP) examined several different approaches to screening requests for IG with the intent of developing a model that could potentially impact the appropriate utilization of the product. Several reasons for this initiative are described as follows:

1. IG utilization and costs continue to grow. There are concerns about the sustainability of this growth.
2. A 2015 compliance audit funded by the Ontario Regional Blood Coordinating Network (ORBCoN) demonstrated a need for improvement in IG utilization. A gap was identified when the data entered on the Ontario Ministry of Health and Long-Term Care (MOHLTC) IG Request Form was compared to the documented information on the patient's chart.
3. There is a need for patient reassessment for those on long-term therapy to determine if the treatment and dosage continue to achieve the expected clinical response.
4. The expertise to screen requests across all specialties is not available at every hospital.
5. A provincial IG audit conducted by ORBCoN in 2012 indicated that 11.6% of Ontario's IVIG use was for unapproved conditions. This result was similar to that seen in a previous audit conducted in 2007 and prior to the implementation of the Ontario IVIG Strategy for Appropriate Utilization.

Ultimately, the IGAP chose the provincial Exceptional Access Program (EAP) as the best approach for a screening model since an infrastructure was in place and physicians were already familiar with using it for access to therapeutics. At the time it was thought the IG pilot would be able to utilize the existing EAP technology for transmitting requests and data collection.

The Immune Globulin Screening Pilot Working Group (IGSPWG), a sub group of the IGAP (Appendices A and B), was convened in December 2015 to develop and facilitate implementation of the IGSP with a limited focus on the neurology specialty only. Membership included six neurologist/ neuromuscular specialists who would provide expertise and ensure patients continued to have access to IG as appropriate treatment. Neurology was selected for the pilot as it was the largest user in grams of IG according to the 2012 provincial IG audit. There was support by the neurologists who were interested in obtaining data on ordering practices, appropriateness of requests, frequency of dosing and maintenance therapy.

Objectives

The objectives of the pilot were to determine if a more standardized and rigorous screening model would achieve the following:

- Reduce inappropriate use of IG
- Reduce wastage of IG by ensuring the minimal effective dose is being given

- Improve patient outcomes by ensuring treatment continues to be effective and that minimum effective dose is being given
- Gain a better understanding of factors contributing to increases in IG utilization
- Raise awareness of IG use and costs and influence change in how IG is ordered
- Ensure dosing was corrected for obese neurology patients (BMI equal to or greater than 30) using the dose calculator
- Develop a screening model that could be expanded to other specialties

Scope

The IGSP was implemented in all hospitals in Ontario that order and issue IG and applied to all neurology requests. It was originally designed to be a six-month pilot running from May 30, 2016 to November 30, 2016. It was later extended to January 31, 2017 to obtain more complete outcome data via Outcome Questionnaires (OQ) (Appendix D) and to collect data over the three months (November 2016-January 2017) that could be compared to the same three month timeframe for ORBCoN's database pilot (2015-2016). The intent was to use the information obtained from the database initiative as a pre-IGSP pilot baseline measure, provided the data points were valid and similar.

Structure

Unfortunately the IGSP could not be administered utilizing the EAP's IT framework and existing letter templates for a number of reasons which included;

1. Overarching regulatory requirements that could not be extended to the pilot;

2. Short implementation timeline and the pilot nature of the project; and

3. IGSP communication requirements did not align with the existing database capabilities.

As such, a manual system was developed for operationalizing the pilot that modelled the EAP process but could not utilize the complete IT infrastructure. The process was labour intensive for all parties on a number of fronts including communication, increased documentation requirements, variability in the way the data was documented and documentation errors. The errors and variability created challenges in the data analysis. A separate patient consent process was required and it was optimally to be obtained in written format. However, provisions were made when only verbal consent could be performed.

The ordering physician (OP), delegate or practitioner, was required to fax all neurology IG requests, using the IGSP Request Form (Appendix C), to the IGSP Dedicated Fax Line. The OP was also required to send a copy of the request form to the HTS to provide notice that an order for IG may be coming.

An in-house IGSP assessor (a pharmacist) screened all initial requests for approved indications with standard or reduced dose, in accordance with Ontario IVIG Utilization Management Guidelines (Ontario IVIG Guidelines). All other requests were sent for external review by a neurologist/ neuromuscular specialist, including:

- Requests for subcutaneous immune globulin (SCIG)

- All renewal requests; which required submission of an Outcome Questionnaire with the request form
- Requests for approved conditions, with dosing outside of the Ontario IVIG Guidelines
- Requests for other conditions (i.e. indications not listed in Ontario's IVIG Utilization Guidelines)

The IGSP assessor scanned the request, entered it into a spreadsheet and then screened the request. If the IGSP Request Form was incomplete, the IGSP assessor would fax an Additional Information Required (Appendix E) letter to the OP requesting the specific missing information. Additionally, if the request was for a non-neurology indication, the OP would receive a Request for Non-Neurology Use notification (Appendix F) indicating that the IGSP process is not required; the regular IG request stream (i.e. screening by the hospital transfusion service-HTS) should be utilized.

Once screening was complete, the IGSP assessor would send either a Notice of Approval (Appendix G) to both the OP and HTS, or if the request did not meet the IG guidelines, forward it on for external review by a neurology expert. If the request was approved, the IGSP assessor would send both the OP and the HTS a Notice of Approval. Once the HTS received both the Notice of Approval and an internal hospital order form, the HTS could then issue IG.

If the request was not approved, IGSP would send both the OP and the HTS a Notice of Rejection (Appendix H) and the HTS would not issue any IG.

The HTSs were not supposed to fill the hospital order without the IGSP Notice of Approval, except for urgent cases and during the early transition phase to the IGSP process. The urgent process was established to deal with critical patients who required IG within 12 hours which is not within the stated turn-around time (TAT) for the screening process.

Physician/hospital information and personal health information (PHI) were redacted on documentation going to external reviewers to address patient privacy concerns and to allow for unbiased adjudication. External reviewers were anonymous to both the hospitals and their fellow reviewers.

All renewal requests required an Outcome Questionnaire to be submitted with the IGSP Request Form. The purpose of the OQ was to confirm that IG treatment continued to be effective; to ensure that the minimum effective dose was being requested; and to collect data to develop outcome criteria.

The OPs also had an appeal process option. This was accomplished by the resubmission of the Request Form and Notice of Rejection to the EAP with the provision of additional information specifically addressing the rejection rationale. The assessor would provide the original reviewer all of the additional information. If the request was rejected a second time, the appeal was automatically sent to two other reviewers for adjudication. The majority decision (2/3) was considered the final decision.

Results

Table 1: Summary of IGSP Activity

Unique Requests Received	Requests Reviewed	Requests Approved	Requests Rejected	Number of Adjustments (dose, frequency, duration)	Number of Actual Dose Adjustments	Number of Patients
1,478	811	1,187	11	187*	38	1,167

Executive Summary

*Note: the pilot was not long enough to assess impacts due to duration adjustments

A total of 1,478 unique requests were processed during the IGSP, which represented 1,167 patients. There were 27 non-neurology requests that were redirected to the regular IG screening process. Of the remaining 1,187 requests that were **approved**, 811 were initially referred for a neurologist's review to examine the indication, dose, frequency and/or duration. Adjustments (dose, frequency and/or duration) were made on 187 reviewed requests. Eleven requests were rejected. There were 92 hospitals that participated in the IGSP and whose data are represented in these results. There were 38 dose adjustments which were mainly for dose reductions, however 10 doses were increased. The total number of grams of IG requested for approved conditions was 747,000g but only 674,152g were approved for the duration of the treatment request. Therefore 72,848 grams of IG were potentially conserved at a possible cost savings of $4.5M (2017 pricing), if hospitals abided by the reviewers' recommendations.

A compliance assessment following the pilot was carried out to determine adherence to the recommendations for dose adjustments. This indicated that only 51% of the IGSP approved dose was the actual dose administered at the hospital. Some anecdotal reasons given for noncompliance with the dose specified on the Notice of Approval form were:

- The decrease in frequency of dose was missed in error
- No approval was ever received, so the previous dosing scheme was used
- Clerical errors occurred in the data spreadsheet provided by EAP. Some doses were documented incorrectly. For example the Notice of Approval indicated a higher dose than what was documented on the spreadsheet. Therefore, the dose on the chart (the correct dose) appeared to be higher than the approved dose, when in fact it was not
- Dose was increased over the approved dose because the patient's condition worsened when given the reduced dose indicated on the Notice of Approval

If this compliance rate is applied to the 72,848g potentially saved, the cost savings is reduced but still substantial at $2.3M. The overall EAP costs (i.e. including screening by the IGSP assessor, documentation, faxing, filing and other administrative work, preliminary data analysis) were estimated at $140,000 (rounded to nearest thousand) therefore final estimated cost savings are $2.2M. This translates to a 1.5% savings in overall IG use in Ontario in 2016/17, and an estimated 3.7% savings in neurology utilization.

The Outcome Questionnaire analysis demonstrated IG's effectiveness in treating neurological conditions. The chances of improving or stabilizing with IG were 26 times greater than the condition worsening.

Conclusions

The IGSP had a successful outcome overall in that it provided:

1. A standardized approach for reviewing neurology IG requests across the province.
2. Ordering physicians and hospitals with access to an expert, external reviewer for questionable orders, which was particularly valuable for hospitals lacking neurology expertise.

[1]Estimated EAP costs: salary and wages for IGSP assessors, administrative support, IGSP project lead from EAP and remuneration costs for expert reviewers

3. A potential 72,848g reduction in the amount of IG ordered for a cost savings of over $2M, when the 51% compliance rate is applied.

4. Validation of the appropriateness of requests for IG in the specialty of neurology in that there was a very low rate of actual refusals.

The IGSP also demonstrated that the manual process in place for this pilot was labour intensive and was not sustainable for the EAP group, the OPs or the HTSs due to the many levels of manual work involved and the issues with data collection. Therefore the maintenance of the IGSP is not recommended for neurology nor should any other specialties be rolled into this present manual system. If requisite technology was developed to support such a screening process, this initiative should be revisited with consideration to the "Challenges and Lessons Learned" (page 35).

Background

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About Immune Globulin

Canadian Blood Services (CBS) procures over 40 plasma protein products (PPPs) – many are derived from blood plasma – which are in high demand and used to treat various conditions, for example, hemophilia, fluid loss in burn/trauma patients, immune deficiencies and severe infections.

Immune Globulin (IG), a PPP used to treat immune related conditions such as primary and secondary immune deficiencies and autoimmune disorders, is licensed for six indications by Health Canada; IG is increasingly prescribed for "unlabeled, potentially indicated" conditions. Average treatment can cost anywhere from $5,000 to $250,000 annually per patient depending on the dose, number of treatments and duration of the treatment.

CBS ships IG to Ontario hospitals based on hospital orders. There is no cost to the hospital nor are they required to meet any eligibility criteria to obtain IG.

Provincial/Territorial governments (PTs) fund CBS based on units shipped to hospitals in their respective jurisdictions. The current funding model creates a gap between the user (i.e. hospital/ordering physician) and payer (i.e. the ministry). Since hospitals do not pay for IG, hospital resources may not be allocated to scrutinize orders for IG as is done for pharmaceuticals.

History

In 2012, in order to mitigate the concerns about the sustainability of the increases in IVIG utilization, the Ministry of Health and Long-Term Care (MOHLTC) implemented the IG Utilization Management Strategy (IG Strategy), in partnership with the Ontario Regional Blood Coordinating Network (ORBCoN) and the Ontario IVIG Advisory Panel (IVIGAP). The IG Strategy includes the following directives:

1. Adherence to Ontario IVIG Utilization Management Guidelines (v2.0 March 2012)
2. Implementation of the MOHLTC IVIG Request Form
3. Review/Approval for Indications Not Listed on the MOHLTC IVIG Request Form
4. Dosing Through "Adjusted Body Weight" Calculation
5. Evaluating Clinical Outcomes and Need for Reassessment
6. No Outdating of Product
7. Provincial IVIG Utilization Audit in September 2012

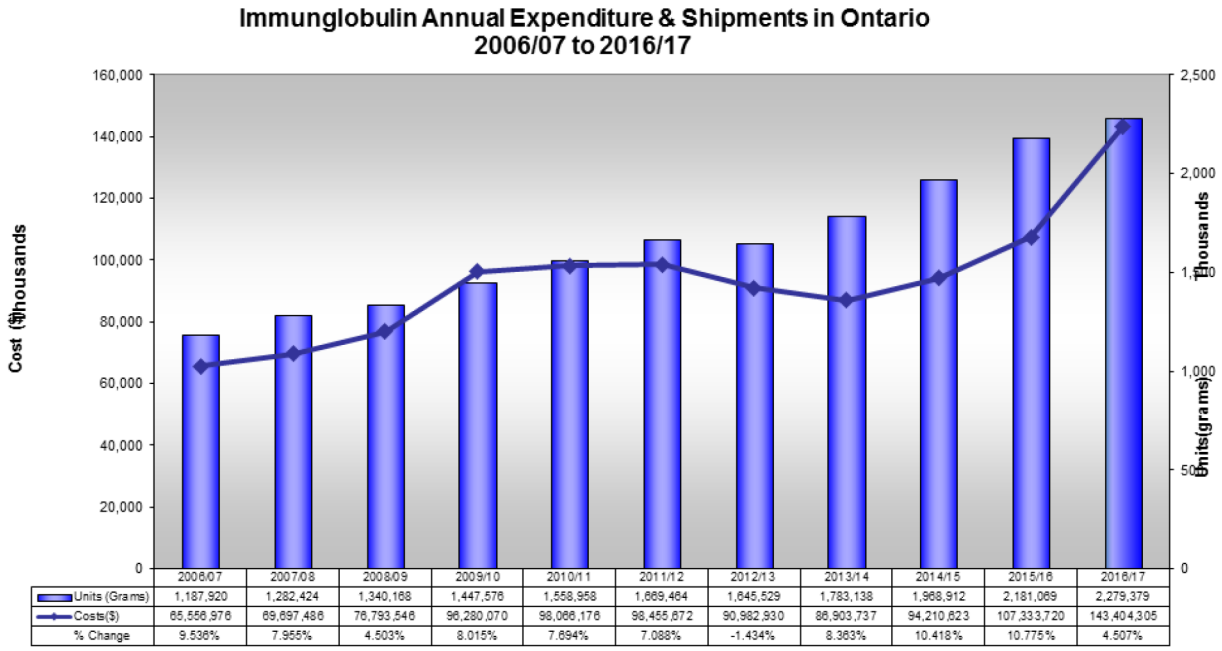
Context for Action

The IG Strategy implemented some gatekeeping mechanisms to mitigate Ontario's increasing utilization of IG. There was some initial success with the IG Strategy as shipments decreased by 1.4% in 2012/13; this decrease was transient and more aggressive strategies were felt to be needed, for the following reasons:

1. **Utilization and costs continue to grow.** IG is the largest cost for Ontario's total PPP budget, representing about 42% of total PPP expenditures ($100.0M/$236.7M) in 2015/16. Shipments have been increasing at an average annual rate of approximately 7% from 2006/07 to 2016/17. See Figure 1 for IG hospital

shipment data and the corresponding cost in Ontario. IG pricing continues to increase and the last fiscal year, $143,404,305 of IG was shipped to Ontario hospitals. Like most PPPs, IG is purchased in US dollars so is subject to an exchange rate.

Figure 1: Cost and Utilization of IG in Ontario*



	2006/07	2007/08	2008/09	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17
Units (Grams)	1,187,920	1,282,424	1,340,168	1,447,576	1,558,958	1,669,464	1,645,529	1,783,138	1,968,912	2,181,069	2,279,379
Costs($)	65,556,976	69,697,486	76,793,546	96,280,070	98,066,176	98,455,672	90,982,930	86,903,737	94,210,623	107,333,720	143,404,305
% Change	9.536%	7.955%	4.503%	8.015%	7.894%	7.088%	-1.434%	8.383%	10.418%	10.775%	4.507%

*CBS Shipment Data from May 2017

2. **Compliance Audit 2015.** A retrospective audit, led by McMaster University and conducted in four hospitals in central Ontario, compared 2015 data recorded on the MOHLTC IVIG Request Form to information in the patient's chart to:

a. Determine the case mix for new IVIG requests;

b. Authenticate information provided on the Request Form; and

c. Assess clinical effectiveness of IVIG in patients.

Out of the 179 patients assessed:

- Over half of the patients (51.7%) did not meet criteria for IVIG use for the medical condition indicated on the request form
- 84 patients (47.2%) were not dosed to ideal body weight
- 58 patients (32.6%) did not meet diagnostic criteria for the medical condition for which IVIG was used. E.g. in Guillain-Barré Syndrome (GBS), IVIG is only indicated when the disease is classified as greater than grade 2 severity or for progressive severity within two weeks of symptom onset
- 61 (34.2%) of patients had *subjective* improvement; and
- 34 (19%) had a discrepancy between indication on the form & diagnosis in the clinic record

3. **Need for Reassessment.** There are many patients on long-term IG therapy who are not reassessed to determine if treatment continues to be effective and if they are receiving the minimum effective dose,

potentially resulting in less than optimal patient outcomes and product wastage.

4. **Lack of Expertise/Authority.** Transfusion medicine medical directors, pathologists and medical laboratory technologists are currently responsible for screening requests for IG to ensure compliance with provincial guidelines. There continues to be feedback that they feel some lack the expertise to question and/or deny requests from ordering physicians who are specialists, especially for requests for IG for unapproved indications.

5. **Unapproved Use.** According to the 2012 provincial IG utilization audit, about 11.6% of IG issued was for unapproved indications; a potential savings of about $1.9M based on 2012/13 pricing; $2.2M using 2016/17 pricing, if these requests were denied.

In summary, to address concerns with variations in dosing and screening practices and to mitigate unsustainable growth, and to determine the degree, if any, of inappropriate use, the decision was made to implement a more formal, rigorous screening model.

Immune Globulin Screening Pilot

Immune Globulin Screening Pilot (IGSP)

Background

IG screening programs have been employed in other jurisdictions including British Columbia, Atlantic Canada, Australia and the United Kingdom. The experience and structure of these programs informed the Immune Globulin Screening Pilot (IGSP), along with consultations with other drug screening programs, various areas within the ministry, the Immune Globulin Advisory Panel (IGAP), and the Immune Globulin Screening Pilot Working Group (IGSPWG). See Appendix A and B for a list of IGAP and IGSPWG members.

Given the complexity of the issue, it was determined to roll out any new screening model as a pilot and focus on one specialty only. Neurology was selected because it was the largest user in grams of IG according to the 2012 provincial IG audit. Furthermore, there was support by the neurologists which was vital to the success of the pilot.

The IGSPWG, a sub group of the IGAP, was convened in December 2015 to develop and facilitate implementation of the IGSP. Membership included six neurologist/ neuromuscular specialists to ensure appropriate expertise was available and ensure patients continued to have access to IG if this was considered by the specialty to be appropriate treatment.

Objectives

The objective of the pilot was to determine if a more standardized and rigorous screening model would achieve the following:

- Reduce inappropriate use of IG
- Reduce wastage of IG by ensuring the minimal effective dose is being administered
- Improve patient outcomes by ensuring treatment continues to be effective and that minimum effective dose is being given
- Gain a better understanding of factors contributing to increases in IG utilization
- Raise awareness of IG use and costs and influence change in how IG is ordered
- Ensure dosing was corrected for obese (Body Mass Index (BMI) 30 or greater) neurology patients using the dose calculator
- Develop a screening model that could potentially be expanded to other specialties

Scope

The Immune Globulin Screening Pilot (IGSP) for Neurology:

- Applied to all hospitals in Ontario that order/issue IG;
- Screened all requests for IG, both IVIG and SCIG, for medical conditions within neurology, including initial/ renewal requests for approved/unapproved indications;
- Employed an approach where only new patients and those who were due for a renewal were enrolled in the IGSP to minimize hospital and patient impacts;
- Was rolled out as a six-month pilot effective May 30, 2016 to November 30, 2016 to test the screening model; with the intent of transitioning to an ongoing program if successful;
- NOTE: this pilot was extended to January 31, 2017 to obtain more robust outcome data using the

Outcome Questionnaires (Appendix D) and to collect data that could be compared to the same 3 month timeframe as ORBCoN's database pilot which had been conducted one year earlier (2015-2016). The intent was that the information obtained from the database initiative could also be used as a pre-IGSP pilot baseline measure, provided the data points were valid and similar.

All other requests outside of the pilot followed the existing process, i.e. screening by the HTS, known as the "regular stream."

Overview

The IGSP involved screening requests for IG for neurological medical conditions outside of the usual HTS/ pharmacy stream. The pilot was a step towards regulating the use of IG within hospitals similar to that of pharmaceuticals.

The IGSP leveraged the ministry's Exceptional Access Program (EAP) infrastructure to receive, adjudicate, document and reply to requests for IG within neurology. The IGSP was managed as a separate program with dedicated staff to ensure appropriate TATs, which were one business day for approved conditions and three business days for requests requiring external review.

This model provided standardized, external, arm's length review; familiar to ordering physicians. The IGSP was unable to utilize the full functionality of the EAP because:

- The legislation under which EAP operates was not transferrable to a product overseen by a different Division outside of the Ontario Public Drug Programs
- The pilot nature of the IGSP did not support technology upgrades required
- Evidence-based screening criteria for IG was not available to enable a more streamlined process
- The hand-written data collection process was beyond the capabilities of the EAP and, as such, a spreadsheet manual documentation process was adopted

The IGSP therefore required some work-arounds in order to make the EAP-like process functional. Unfortunately, the work arounds required much manual work: documentation, redacting of personal health information and faxing. Manual documentation was fraught with omissions and transcription errors which can confound the data analysis. Many request forms contained incomplete information which required several attempts to obtain all of the pertinent information from the ordering physician (OP). This created a large work load for the IGSP assessors. Additionally, much free text was entered by EAP in the data spreadsheet which made statistical analysis more difficult. ORBCoN enlisted the assistance of a biostatistician post pilot who worked for several months cleaning and analyzing the data to ensure as much data as possible collected during the pilot could be analyzed in a meaningful way.

There was also an additional work load for the hospital laboratory staff in this manual environment, where redacted documents had to be matched up with original requests and resulted in further information chasing. The extra hospital workload and biostatistician hours were not factors incorporated into the cost of the IGSP, although it is recognized that they were significant.

Patient consent was also required on the Request Form to disclose personal health information to the ministry via the IGSP. This consent was required since the full EAP infrastructure and the confidentiality agreement could not be employed for this pilot.

The OP, delegate or practitioner, was required to fax all requests for IG within neurology, using the IGSP Request Form, to the IGSP Dedicated Fax Line, similar to how requests are submitted to EAP for drugs. The OP

also had to send a copy of the request form to the HTS to provide notice that an order for IG may be coming. See Appendix C for the IGSP Request Form.

Initial requests for approved indications with standard or reduced dose, in accordance with Ontario IVIG Utilization Management Guidelines (Ontario IVIG Guidelines), were by an IGSP assessor at the EAP office. The assessor was a pharmacist. All other requests were sent for external review by a neurologist/ neuromuscular specialist, including:

- Requests for SCIG
- All renewal requests; which required submission of an OQ with the request form
- Requests for approved conditions, with doses outside of Ontario IVIG Guidelines
- Requests for *Other* conditions (i.e. non-approved indications)

The IGSP assessor would scan the request and enter it into a spreadsheet and then screen the request. If the IGSP Request Form was incomplete, the IGSP assessor would fax an Additional Information Required (Appendix E) letter to the OP requesting the specific missing information. Additionally, if the request was for a non-neurology indication, the OP would receive a Request for Non-Neurology Use notification (Appendix G) indicating that the IGSP process is not required; the regular IG request stream should be utilized. The MOHLTC IVIG Request Form, used for the regular stream, was revised so that neurological medical conditions were no longer listed; and in its place included a note to use the IGSP Request Form to request IG for neurological conditions.

Once screening was complete, the IGSP assessor would send either a Notice of Approval (Appendix F) to both the OP and HTS, or if the request did not meet the Ontario IVIG Utilization Guidelines, forward it for external review by a neurology expert. If the request was approved, an IGSP assessor would send both the physician and the HTS a Notice of Approval. Once the HTS received both the Notice of Approval and an internal hospital order form, the HTS could then issue IG. It should be noted that a Request Form is not a hospital order form. A Request Form is completed for a *course* of IG treatment, where a hospital order form for IG is required for each infusion.

If the indication or dosing did not meet the criteria as outlined in the Ontario IVIG Guidelines, the IG assessor communicated with an expert neurology reviewer via email for a decision. The reviewer would determine if the request was appropriate as indicated, whether a modification like a dose adjustment was required or if the request was inappropriate and should be rejected. The reviewer's decision was communicated to the assessor for dissemination to the OP and the HTS via a decision letter (approval or rejection) with rationale provided in the instances of changed doses, frequency or rejection. If the request was not approved, EAP would send both the physician and the HTS a Notice of Rejection (Appendix H) and the HTS would not issue any IG.

The HTSs were not supposed to fill the hospital order without the IGSP Approval Letter, except for urgent cases and during the early transition phase to the IGSP process. Urgent cases were to be identified by the OP to the IGSP representative and the HTS on the Request Form under section C, *Request Type*. When this option was selected, the HTS filled the order immediately upon receipt of a hospital order, although the OP was still expected to fax the Request Form to EAP and the HTS. EAP would still process the order and follow up with the physician with a decision letter. EAP also monitored the number of EAP requests by physician to ensure the process was truly treated as an urgent one. This process was established to deal with critical patients who required IG within 12 hours. The following conditions were identified as possible urgent cases by the neurology specialists on the IGSPWG:

- Guillain-Barré Syndrome (GBS)
- Myasthenia Gravis (MG)
- Acute Disseminated Encephalomyelitis (ADEM)
- Autoimmune Encephalitis e.g. NMDA
- Rasmussen's Encephalitis (RE)
- Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)

One of the challenges with the urgent process was follow up with ordering physicians who were frequently emergency physicians. They work many shifts and sometimes at several sites and thus were difficult to track down for missing information, approvals, dose adjustments or rejections.

Physician/hospital information and personal health information (PHI) was redacted on documentation going to external reviewers to address patient privacy concerns and to allow for unbiased adjudication. External reviewers did not know who was on call or who the back-up reviewers were to ensure that a reviewer submitting a request as an OP would not know who was adjudicating their request and vice versa. If an on call reviewer was submitting a request as a physician that required external review, it went to the primary back-up reviewer for screening to ensure no physician reviewed their own request.

The neurology panel members providing the review service were compensated when on rotation. A pediatric neurologist was on service at all times.

The advantages of having anonymous external reviewers were the fostering of objective analysis in the IG review and removal of bias towards ordering or reviewing physicians. The disadvantages were that the collective group of reviewers did not have an opportunity to meet and harmonize reviewing strategies and criteria, nor were the OPs permitted to consult with the reviewers as in British Columbia's model.

All renewal requests required an OQ (Appendix D) to be submitted with the IGSP Request Form. The purpose of the OQ was to confirm that IG treatment continued to be effective; that minimum effective dose was being administered; and to collect data to aid in the development of more objective outcome criteria. Use of the OQ was also required, over clinic notes for example, to standardize the process and data collection.

The OPs also had an appeal process option. This was accomplished by the resubmission of the Request Form and Notice of Rejection to the IGSP screener with the provision of additional information specifically addressing the rejection rationale. The assessor would provide the original reviewer all of the additional information. If the request was rejected a second time, the appeal was automatically sent to two other reviewers for adjudication. The majority decision (2/3) was considered the final decision.

IGSP Data Analysis

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General

The high level summary of IGSP activities was as follows:

- 1,478 unique requests received
- 811 requests were reviewed
- 1,187 requests were approved
- 11 requests were rejected
- 187 requests were adjusted (dose, frequency and duration*)
- 38 requests had dose adjustments (dose and/or frequency)
- 53 subcutaneous IG (SCIG) requests
- 1,167 patients were represented

*Note: the pilot was not long enough to assess impacts due to duration adjustments

A total of 1,478 unique requests were processed during the IGSP which represented 1,167 patients. There were 27 non-neurology requests which were redirected to the regular IG screening stream. Of the remaining 1,187 requests that were approved, 811 were initially referred for a neurologist's review to examine the indication, dose, frequency and/or duration. Adjustments were made on 187 reviewed requests. SCIG requests were minor for this patient population and accounted for 53 of the IG requests. There were 92 hospitals represented by these data. There were 38 dose adjustments which were primarily for dose reductions, however 10 doses were increased. Eleven requests were rejected and the reasons for rejection included:

- Indication was initially misidentified or misdiagnosed. E.g. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and Multifocal Motor Neuropathy (MMN) cases were actually another non-approved indication
- Requests for indications that do not appear in the Ontario guidelines. E.g. paraneoplastic limbic encephalitis, Relapsing Remitting Multiple Sclerosis (RRMS), seronegative dysautonomia
- Requests for retreatment of approved indications were denied E.g. Guillain-Barré Syndrome (GBS) retreatment not meeting criteria

There were 280 requests classified as "Other" in which approval was never obtained for reasons such as:

- The IGSP ended before approval was secured
- No response by physicians for missing/additional information
- Requests were cancelled
- Duplicate requests

The total number of grams of IG requested for approved conditions was 747,000g but only 674,152g were approved. Therefore 72,848 grams of IG were potentially conserved at a possible cost savings of $ 4.5M ($4,544,258.20) at 2017 pricing, if hospitals abided by the reviewers' recommendations. It should also be noted that some OPs may have elected to choose a more accessible alternate therapy rather than use the IGSP request system. The IGSP was more labour intensive than the previous, "regular" stream, so may have discouraged some orders. These savings, if any, could not be captured in this pilot.

A summary of the IGSP requests and TAT data is illustrated in Table 2.

Table 2: Summary of IGSP Request and Turn-Around Time (TAT) Data

	Number	TAT (days, median, IQR)
Requests	1,478	2 (1 - 6)
Unique Patient IDs*	1,167	N/A
Approved requests**	1,187	3 (1 - 6)
Rejected requests	11	12 (1.5 - 16.5)
Other requests	280	1 (0 - 3)
Direct approval (assessor)	326	0 (0-1)
Urgent requests	76	1 (0-2)
Urgent, approved	51	0 (0-3)
Urgent, not approved	25	1 (0-1)
Reviewed	811	4 (2-9)
Reviewed then approved	750	4 (2-9)
Reviewed then rejected	11	12 (1.5-16.5)
Reviewed then other	50	4 (1-14.5)
TOTAL requested dose (g)	747,000	
TOTAL approved dose (g)	674,152	
TOTAL potential savings (g)	72, 848	

*4 approved requests with missing dose information **11 requests without patient IDs

The median TAT for urgent requests was one day (range 0-2), and all urgent requests for approved conditions had a median TAT of less than a day. The HTSs were supposed to issue the product immediately upon receipt of the hospital order form for urgent requests, so the urgent TAT did not affect accessibility to IG at the hospital level.

A summary of the data for average requested and approved dose along with average potential savings is summarized in Table 3.

Table 3: Average Requested Dose, Approved Dose and Potential Savings for Approved Requests

	Number	Average (SD) request dose (g)	Average (SD) approved dose (g)	Average (SD) potential saving in CAD($)
Request	1183*	631.4 (571.3)	569.9 (533.3)	3,841.30 (13,877.5)
Patient	974	763.7 (753.5)	689.7 (675.6)	4,619.80 (15,299.4)
Hospital	92	8,119.6 (14,884.6)	7,327.7 (13,564.2)	4,939.40 (98,513.5)

*the 4 missing dose requests have been deducted (see Table 1)

The IGSP requests included 13 neurology indications plus two others: an unknown category and some non-neurology indications. These indications are displayed in Table 4.

Table 4: Summary of Requested Indications Received by EAP

Indication	Number of requests	Number of reviewed requests	Number of approved requests*	Number of rejected requests	Number of requests with other decisions^
Acute disseminated encephalomyelitis (ADEM)	4	4	4	0	0
Autoimmune Encephalitis	113	65	64	2	47
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) Immune Neuropathy	530	347	456	1	73
Diabetic Neuropathy	2	1	0	1	1
Guillain-Barré Syndrome (GBS) Immune Neuropathy	180	14	145	1	34
Hereditary Peripheral Neuropathy	1	1	1	0	0
Immune Neuropathy	246	176	214	5	27
Lambert-Eaton Myasthenic Syndrome (LEMS)	7	7	6	0	1
Myasthenia Gravis (MG)	340	168	283	0	57
Multiple Sclerosis (MS)	8	5	5	0	3
Myopathy	1	0	0	0	1
Non-neurology	37	19	5	0	32
Postpolio Syndrome	1	1	0	1	0
Stiff Person's Syndrome	2	2	2	0	0
Unknown	6	1	2	0	4
TOTAL	1,478	811	1,187	11	280

*Indicates both approval processes: either by an assessor (direct) or neurologist (reviewed)

^Examples of "other" decisions: requests for more information, incomplete requests with no further information supplied, IGSP ended, cancelled requests, duplicate requests, etc.

The most requested neurology indications were CIDP (530), MG (340) and immune neuropathy (246). The indication with the highest rejection rate was immune neuropathy (5). Fifty-three of these IGSP requests were for SCIG product and 77 were urgent requests.

The group of approved only indications was analyzed by dose. These results are found in Table 5.

Table 5: Summary of Doses for Approved Requests

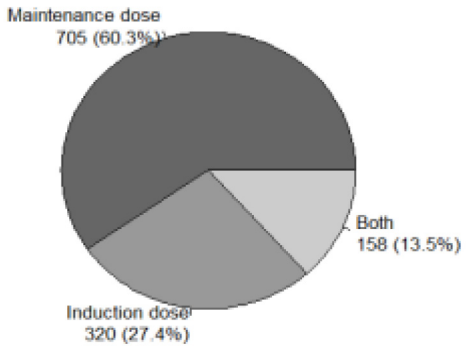
Indication	# of Pts.	# of Appr. Reqts.	Average (SD) Requ'd Dose (g)	Average (SD) App'd Dose (g)	Average Dose Change (g)	Total Requ'd Dose (g)	Total Appr'd Dose (g)	Total Dose Change (g)
Acute disseminated encephalomyelitis (ADEM)	4	4	137.8 (44)	137.8 (44)	0	551	551	0
Autoimmune Encephalitis	49	64	476.7 (626.4)	374 (402.5)	-102.7	30,508	23,935	-6573
Chronic Immune Demyelinating Polyneuropathy (CIDP) Immune Neuropathy	365	455	738.3 (522.9)	670.1 (497)	-68.2	335,913	304,894	-31,019
Guillain-Barré Syndrome Immune Neuropathy	141	145	135.7 (46.2)	134.7 (45.9)	-1	19,677	19,534	-143
Hereditary Peripheral Neuropathy	1	1	538.3	538.3	0	538.3	538.3	0
Immune Neuropathy	178	214	890.3 (669.7)	815.2 (656.7)	-75.1	190,518	174,461	-16,057
Lambert-Eaton Myasthenic Syndrome (LEMS)	4	6	1,019.7 (665.8)	891.5 (748.3)	-128.5	6,118	5,349	-769
Myasthenia Gravis (MG)	234	282	542.6 (516.3)	485.4 (479.8)	-57.2	153,022	136,891	-16,131
Multiple Sclerosis (MS)	5	5	627.4 (591.5)	490.7 (568.3)	-136.7	3,137	2,454	-683
Non Neurology	3	3	1,075 (425.4)	717.5 (750.6)	-357.5	3,225	2,152	-1,073
Stiff Person's Syndrome	2	2	1,045.8 (348.4)	846 (631.1)	-199.8	2,092	1,692	-400
Unknown	2	2	850.4 (513.2)	850.4 (513.2)	0	1,701	1,701	0
TOTAL	988*	1183	N/A	N/A	-1126.7	747,000.3	674,152.3	-72,848

*some patients were listed for multiple indications

The highest total requested and approved doses were for immune neuropathy, MG and CIDP.

Dose types were requested as an induction dose, a maintenance dose or both. The breakdown of these dose types is illustrated in Figure 2.

Figure 2: Summary of Dose Types



Maintenance doses were the most requested dose type.

A dosage summary of the 92 hospitals is seen in Table 6. The hospitals are arranged in order of the highest number of approved requests to the lowest.

Table 6: Summary of Hospital Dosing (Approved) Information – Individual Hospitals

Hospital Site	Number of approved requests	Average requested dose	Average approved dose	Total requested dose	Total approved dose
Hamilton Health Sciences-McMaster	106	819.4	774.4	86,854	82,083
University Health Network-Toronto General	96	884.4	801.9	84,902	76,983
The Ottawa Hospital-Civic	95	688.7	583.5	65,425	55,436
London Health Sciences Centre-University	64	629.9	605.2	40,312	38,731
University Health Network- Toronto Western	45	417.5	395.3	18,786	17,787
Kingston General	43	580.1	498.4	24,945	21,432

Hospital Site	Number of approved requests	Average requested dose	Average approved dose	Total requested dose	Total approved dose
Trillium Health Partners- Credit Valley	41	696.9	644.7	28,571	26,433
William Osler Health Systems- Brampton Civic	36	392.3	356.9	14,122	12,850
Hospital For Sick Children	29	260.8	145.4	7,564	4,216
Royal Victoria Regional Health Centre	26	830.1	707.2	21,583	18,387
The Ottawa Hospital- Riverside	26	446.8	427.4	11,616	11,113
Hamilton Health Sciences- Hamilton General	24	334.1	302.3	8,019	7,254
Rouge Valley Health System- Centenary Health Centre	22	662.7	561.8	14,579	12,358
Quinte Health Care- Belleville General	21	954	768.7	20,033	16,142
St. Michael's	21	570.6	503.6	11,983	10,575
Southlake Regional Health Centre	20	427.5	412.3	8,550	8,247
The Ottawa Hospital- General	20	790.6	754.4	15,811	15,089
London Health Sciences Centre- Victoria	19	659.3	540.5	12,528	10,269
St. Joseph's Healthcare Hamilton	19	523.6	481.4	9,949	9,147
Halton Healthcare Services-Oakville	18	324.2	290.6	5,836	5,231
Windsor Regional- Metropolitan	18	668.5	640	12,033	11,519

Hospital Site	Number of approved requests	Average requested dose	Average approved dose	Total requested dose	Total approved dose
Grand River	17	665.3	582.5	11,310	9,902
Joseph Brant	17	997.4	886.5	16,956	15,071
St. Joseph's Health Centre Toronto	16	470.8	372.4	7,532	5,958
Trillium Health Partners-Mississauga	16	486.6	458.8	7,786	7,341
Bluewater Health	14	397.1	332.4	5,560	4,654
Sunnybrook Health Sciences Centre	14	317.9	292.6	4,451	4,097
Thunder Bay Regional Health Centre	14	358.2	351.4	5,014	4,920
Scarborough-Birchmount	13	334.4	352.1	4,347	4,578
TEGH-Michael Garron	13	606.6	600	7,886	7,800
Sault Area	12	824.7	717.7	9,896	8,612
Health Sciences North	11	936.6	908	10,303	9,988
North York General	11	461.8	438.2	5,080	4,820
Mackenzie Health	10	374.3	360.6	3,743	3,606
University Health Network Princess Margaret	10	386.5	386.5	3,866	3,866
Children's Hospital Of Eastern Ontario	9	162.4	161.1	1,462	1,450
Humber River	9	552.9	518.9	4,976	4,670
William Osler Health Systems-Etobicoke General Hospital	9	323.9	323.9	2,915	2,915
Grey Bruce Health Services-Owen Sound	8	503.7	463.1	4,030	3,705

Hospital Site	Number of approved requests	Average requested dose	Average approved dose	Total requested dose	Total approved dose
Lakeridge Health-Oshawa	7	376.1	264.7	2,633	1,853
Markham-Stouffville	7	551	530.8	3,857	3,716
Mount Sinai	7	739.8	386.9	5,178	2,708
Guelph General	6	458.9	418.3	2,753	2510
Hawkesbury District General	6	790.7	543.3	4,744	3,260
Muskoka Algonquin Healthcare-Bracebridge	6	910.1	718.7	5,461	4,312
Queensway Carlton	6	430.1	430.1	2,580	2,580
Ross Memorial	6	1249	1249	7,497	7,497
Rouge Valley Health System-Ajax & Pickering	5	764.4	708.5	3,822	3,542
Brockville General	4	672.2	610	2,689	2,440
Hamilton Health Sciences-Juravinski	4	497.6	497.6	1,990	1,990
LWHA-Wingham	4	720.4	698.8	2,882	2,795
Niagara Health System-St. Catharines General	4	411.6	394	1,646	1,576
North Bay Regional Health Centre	4	806.7	709.2	3,227	2,837
Orillia Soldiers Memorial	4	882.8	882.8	3,531	3,531
Peterborough Regional Health Centre	4	482.5	417.5	1,930	1,670
Tillsonburg District Memorial Hospital	4	719.2	548.5	2,877	2,194

Hospital Site	Number of approved requests	Average requested dose	Average approved dose	Total requested dose	Total approved dose
Trillium Health Partners– Queensway	4	503.8	503.8	2,015	2,015
Cambridge Memorial	3	390.1	390.1	1,170	1,170
Montfort	3	589.3	593.3	1,768	1,780
Niagara Health System - Greater Niagara General	3	177	177	531	531
Perth & Smith Falls District	3	685.6	685.6	2,057	2,057
Quinte Health Care-PEC Memorial	3	1,039	1,039	3,116	3,116
Unknown*	3	1,104	1,104	3,311	3,311
Windsor Regional-Ouellette	3	141.7	123.3	425	370
Woodstock General	3	1,069	1,069	3,207	3,207
Brant Community Healthcare System	2	706.7	706.7	1,413	1,413
Cornwall Community	2	1,218	1,218	2,437	2,437
Northhumberland Hills	2	790.8	790.8	1,582	1,582
Pembroke Regional	2	1,040	1,040	2,080	2,080
Renfrew Victoria	2	382.1	382.1	764.2	764.2
Scarborough Hospital- General	2	122	122	244	244
Strathroy Middlesex General	2	462.5	462.5	925	925
Weeneebayko General	2	1,062	758.3	2123	1517
Almonte General	1	539	296.3	539	296.3
Arnprior & District Memorial	1	151.7	151.7	151.7	151.7

Hospital Site	Number of approved requests	Average requested dose	Average approved dose	Total requested dose	Total approved dose
Carleton Place & District Memorial	1	1,300	1,300	1,300	1,300
Chatham Kent Health Alliance	1	832	832	832	832
Georgian Bay General	1	1,950	1,950	1,950	1,950
Grey Bruce Health Services-Markdale	1	50	50	50	50
Haliburton Highlands Health Services	1	180	180	180	180
Kirkland District	1	3,640	3,640	3,640	3,640
Lady Dunn Health Centre	1	1,387	1,387	1387	1387
Lennox Addington County	1	303.3	303.3	303.3	303.3
Muskoka Algonquin Healthcare-Huntsville	1	165	165	165	165
Riverside Healthcare	1	100	100	100	100
SBGHC-Chesley	1	780	780	780	780
St. Thomas Elgin General	1	100	100	100	100
Stevenson Memorial	1	1,560	1,560	1,560	1,560
Stratford General	1	2,145	357.5	2145	357.5
West Parry Sound Health	1	375	375	375	375
Winchester District Memorial	1	303.3	303.3	303.3	303.3
Women's College	1	1,60	1,560	1,560	1,560
Total	1183	62,090	56,267	747,000	674,152

*Unknown = no hospital information was supplied by EAP

The largest number of requests during this pilot period was 106 resulting in 82,083g of approved product. The lowest number of requests was one. The approved dose for this group ranged from 50 – 3,640g.

Outcome Questionnaire Data

Making the product available for patients with medical conditions where there is evidence of clinical efficacy is a primary objective of the IVIG Strategy. Outcome questionnaires (OQs) are a tool that can support this objective.

OQs were required to be completed for all neurology patients within the IGSP for renewal or subcutaneous IG requests (SCIG). The purpose of the OQs was to:

1. Ensure patients were assessed every six months by a neurology specialist
2. Facilitate the review of all renewal and SCIG requests by one of the neurology reviewers
3. Verify that the IG treatment was efficacious and should continue
4. Examine opportunities to reduce dosing

Any OP request for SCIG or a neurology renewal would not be accepted without a completed OQ. Every OQ was examined by an IGSP neurologist reviewer. A total of 720 OQs were received during the pilot period. Although there were 53 SCIG requests overall, only five appeared in the data collection spreadsheet. The remaining 715 requests were presumably for renewals.

Table 7: Diagnosis and IG Treatment Summary

Diagnosis	Number (%)	Duration of Tx (y)	Dose (g/kg)	Total grams	Current G/Day
CIDP	331 (45)	5.3 [0-27]	2.1 (163)	72	3.3
GBS	13 (2)	0.3 [0-8]	1.8	132	41.3
MMN	112 (16)	7.6 [0.5-25]	1.2 (47)	83	3.5
MG	164 (22)	4.4 [0.8-20]	1.2 (89)	76	5.0
Other	80 (11)	4.4 [0.8-16]	2.8	88	7.7
Polyneuropathy	20 (3)	4.6 [0.1-20]‡	1.1	65	5.9

*total with a form of polyneuropathy: 476/720 or 66% of patients

*full dataset not available for all patients

‡outlier at 9 years; median is 0.5 years, all but one are ≤ 7.5 years

Table 8: Patient Condition Summary

Patient Status	Condition			
	CIDP	GBS	MMN	MG
Improved	68%	33%	65%	81%
Stabilized	29%	50%	32%	19%
Unchanged	0.3%	0%	0%	0%
Worse	3%	17%	3%	0%

Due to varying types of polyneuropathy and other neurological disorders within the dataset, a uniform outcome measure could not be employed. In fact, even within a single type of neuropathy, a single outcome measure cannot be standardized for use in all patients.

However, the outcomes in all patients can be broadly classed as improved, stabilized (in those who were progressively deteriorating), unchanged or worse. Using this categorization scheme, 70% improved, 27% stabilized, 0.3% were unchanged and 2% got worse. This indicates a positive benefit of IG in 97% of patients. In those with CIDP, MMN and MG, 97-100% improved or stabilized. The rate was lower in GBS at 83%. The chances of improving or stabilizing with IVIG were 26 times greater than getting worse or not changing.

The results show a strong positive therapeutic response to IG therapy in these patients with neurological disorders. Additionally, the specialty of neurology is rather unique. There are many rare indications that do not appear on the Ontario IG Guidelines solely because they are so scarce. Utilization in neurology is a complex issue for several reasons. There is a lack of alternate agents and the rarity of orphan conditions confounds the ability to obtain random clinical trial data to inform practice. Algorithms will never be possible for these conditions. For many clinicians, IG remains the treatment of choice because alternative therapies like chemotherapy have great risks for patients with dysimmune conditions and may cause sepsis and death.

Baseline Analysis

In 2015-16, ORBCoN conducted a three-month, database pilot with five hospitals to determine if the information collected on the MOHLTC IG Request Form could be collected in a database for future analysis for data points such as dosage, specialty, indication, duration, etc. Therefore, this database pilot was not originally designed to collect baseline data for the IGSP. Nonetheless, information collected in the database pilot was analyzed in an attempt to establish a baseline for neurology ordering practices pre-IGSP and to determine if a screening program affected ordering practices. JMP, a SAS package for Mac computer systems was used for the Outcome Questionnaire analysis.

Table 9 demonstrates the neurology requests by indication for the five hospitals in the database pilot.

Table 9: Summary of Database Pilot Requests by Indication (Nov 2015-Jan 2016)

Indication	Number of patients	Number of requests	Total dose (g)	Median (IQR) dose/ indication
CIDP Immune Neuropathy	39	44	18,305	352.1 (219.4 - 536.2)
GBS Immune Neuropathy	17	21	6,846	150 (118 - 185)
Immune Neuropathy	11	12	5,739	422.5 (267.5 - 617.5)
MG	10	11	4,828	325 (156.2 - 747.5)
Other	23	25	11,921	520 (130 - 676)
Total	100*	113	47,639	N/A

*NOTE: one patient had two indications listed; actual patient total is 99

Table 10 shows neurology results for the same five hospitals during the same months of the IGSP.

Table 10: Summary of IGSP Requests by Indication (Nov 2016-Jan 2017)

Indication	Number of patients	Number of requests	Total dose (g)	Median (IQR) dose/ indication
CIDP Immune Neuropathy	37	37	25,497	488.9 (373.3 - 1040)
GBS Immune Neuropathy	11	11	1,438	132 (110 - 140)
Immune Neuropathy	22	22	17,803	780 (492.3 - 1105)
MG	23	25	13,571	338.3 (160 - 780)
Other	5	5	5,637	1,040 (1022 - 1170)
Total	98	100	63,946	N/A

The number of patients with neurology requests within the two study periods is similar: 100 in 2015/16 and 98 in 2016/17. Although there are more requests in the earlier study group (113) than in the IGSP (100), the number of grams of requested IG in the IGSP period is substantially higher: 63,946 versus 47,639 in 2015/16. This difference represents 15,830g more IG in 2016/17. Therefore, it appears that the IGSP process might not have been a deterrent in any way for OPs.

Tables 11 and 12 show the request data by hospital for both time periods.

Table 11: Summary of Database Pilot Requests by Hospital (Nov 2015-Jan 2016)

Hospital	Number of patients	Number of requests	Total dose (g)	Median (IQR) dose/ hospital
A	24	27	15,028	520 (281.7 - 715)
B	16	16	4,380	150 (125.9 - 212.9)
C	5	5	638	130 (120 - 138)
D	44	51	20,607	346.7 (179.2 - 574.2)
E	10	14	6,986	172.5 (121.5 - 626.2)
Total	99	113	47,639	N/A

Table 12: Summary of IGSP Requests by Hospital (Nov 2016-Jan 2017)

Hospital	Number of patients	Number of requests	Total dose (g)	Average (SD) dose per hospital
A	38	38	27,824	529.2 (373.7 - 1105)
B	6	6	2,561	317.9 (190.4 - 418.5)
C	5	5	1,045	120 (110 - 130)
D	37	39	22,173	440 (162.5 - 942.5)
E	12	12	10,344	715 (271.9 - 1029.2)
Total	98	100	63,947	N/A

Analysis by hospital (Tables 11 and 12) reveals similar results to the indication analysis in that the both the total doses and total average doses were higher in the IGSP time frame when compared to 2015-16.

Although this is a small sample group, the baseline analysis indicates that the number of neurology patients requiring IG slightly decreased from 2015-16, but the dosage for these patients has increased at all five hospitals. Therefore the IGSP does not appear to be a barrier for IG ordering practices.

Assessment of Hospital Compliance to the IGSP Reduced Dosage 2016/17

There were 42 requests identified as having adjusted dose, frequency and/or duration in the IGSP. The hospitals that generated these requests were asked to verify that the actual dose and duration indicated by the IGSP was actually applied to the patient (In other words, did the IGSP process achieve its goal in translating the adjustment to the patient?). The response rate from the hospitals was excellent at 100%. Three requests were not traceable and two adjustments were deemed insignificant as they were only the rounding of doses. Of the remaining requests, the compliance rate was only 51%. The reasons for the dosing differences between the patient's chart and the Notice of Approval were not formally collected during this assessment, however some anecdotal reasons were provided:

- The approved dose was used as indicated, but the change in frequency was missed in error
- No approval was ever received, so the previous dosing scheme was used
- Clerical errors in the data spreadsheet that were lower doses than those indicated on the Notice of Approval
- Dose was increased over the approved dose because the patient's condition worsened under the reduced dose indicated on the Notice of Approval

If we apply this 51% compliance rate to the potential savings described in the General section of the IGSP analysis, then the potential IG savings is decreased as demonstrated in Table 13.

Table 13: Application of 51% Compliance Rate to Potential IG Savings

Potential IG and Cost Savings from IGSP			
100% Compliance Rate (Hypothetical)		**51% Compliance Rate (Actual)**	
Grams of IG	**Cost Savings**	**Grams of IG**	**Cost Savings**
72,848	$4.5 M (4,544,258.20)	37,152.48	$2.3 M ($2,317,571.70

The order reductions in this eight month pilot had the potential to save the blood system in Ontario $4.5M ($4,544,258.20). If the assumption is made that the compliance rate is similar for all hospitals, the savings are still substantial, although reduced by half. The cost of the assessor for the IGSP program was approximately $140,000 (rounded to the nearest thousand). Therefore, even at a 51% compliance rate, the realized cost savings are still $2.2 M ($2,197,571.70). This translates to a 1.5% savings in overall IG use in Ontario in 2016/17, and an estimated 3.7% savings in neurology utilization (using the 41.7% neurology rate of use established from ORBCoN's 2012 IG audit).

[2]Estimated EAP costs: salary and wages for IGSP assessors, administrative support, IGSP project lead from EAP and remuneration costs for expert reviewers

Conclusions and Recommendations

4

Key Findings

There was strong support for a screening process like IGSP based on feedback from key stakeholders including HTS, IGSP reviewers, the IGAP and the IGSPWG. Hospitals felt this process would have particular value for the smaller sites, as the IGSP provided standard, expert review of neurology requests.

As the neurologists fulfilled their reviewing duties, they felt that a high proportion of the requests fell within the acceptable guidelines. Therefore, moving forward, some recommended that only requests for high doses, unapproved conditions and renewals be submitted for external review. For renewals, the reviewers felt it was important for the OP to demonstrate clinical progress and that some tapering of IG dose had occurred and if tapering was not employed, some rationale should be provided as to why the dose could not be reduced. Interestingly, in contrast to the reviewers' opinion, the pilot actually demonstrated that the largest savings of IG occurred in the review process where the dose was adjusted, and not the rejected portion of requests. For example, the review process potentially reduced dosing by 72,848g for a cost savings of $4,544,258.20, where the rejections accounted for a reduction of 8,372g for a cost savings of $522,245.36. Once the IGSP costs were accounted for and the compliance rate applied, the cost savings were reduced, but still substantial: $2.2 M. This translates to a 1.5% savings in overall IG use in Ontario in 2016/17, and an estimated 3.7% savings in neurology utilization.

Finally, the IGSP did meet some of its objectives despite some of the barriers. Reviewers did reduce inappropriate IG use and ensured the minimal effective doses were recommended. The IGSP did raise awareness to neurology specialists and hospital administrators about the use and cost of IG. The IGSP assessors and reviewers ensured the dose calculator was applied to obese patients where applicable. This screening model could potentially be applied to other specialties, but not without the supporting technology to lessen the manual workload. Since there was no access to patient demographic and physician information, further analysis like patient age and IG use and physician ordering practices could not be performed.

The Outcome Questionnaire analysis demonstrated IG's effectiveness in treating neurological conditions. The chances of improving or stabilizing with IG were 26 times greater than the condition worsening.

Challenges & Lessons Learned

The ministry approval for the IGSP was obtained very quickly and the implementation for a province wide initiative was relatively short. It was remarkable that a pilot could be implemented so rapidly, but the short time frame did create some challenges. Some were anticipated and had processes developed to smooth the transition to the pilot. Others were either not anticipated or they were anticipated, but there was not sufficient time to develop a tool or process to deal with the issue. A summary of lessons learned includes:

1. Engage biostatisticians early on in the process to establish a functional data collection template. This will ensure data outliers will be minimized and that pertinent data is being captured correctly for data analysis.

2. Ensure the appropriate MOHLTC teams are engaged early in the planning phase, particularly the legal area.

3. Conduct robust assessment before implementing the pilot. Analyze appropriate resource and staffing requirements and a health technology assessment using a validated provider to ensure critical decisions are supported by the best available evidence. This will boost the confidence in the program and enable a robust evaluation of the intervention.

4. Ensure goals are clear and are translated correctly to obtain the appropriate data. There were challenges

translating the data and variables requested by the IGSP working group and the IGAP into a consistent data collection vehicle. There was a great deal of free texting which required several months' of work by a biostatistician to clean the data and permit an adequate analysis.

5. The IGSP ensured we had buy-in from key stakeholders (the neurologists) and implemented their feedback to ensure the pilot had traction to ensure its success.

6. Establish a process to contact all specialists in the targeted field as there were communication break downs in the pilot. The IGSP had requested that hospitals communicate with the OPs about the IGSP. However, not all specialists were notified by the hospitals when the pilot began, nor were all informed at its conclusion. For example, IGSP still received neurology requests in June and July of 2017, even though the pilot concluded January 31, 2017. Engagement of the professional bodies may have enhanced communications with all neurological users.

7. Dialogue between the HTSs and staff of the medical day clinics is crucial as they were and remain key players in the IGSP process.

8. It was difficult to get timely feedback from the experts. Consistent participation/ attendance at meetings was challenging for busy clinicians. In the future, consideration should be made to consider doubling the number of experts to account for regrets.

9. Be mindful of the time required for hospitals to implement new forms and allow ample time to transition to a new process.

10. A pre-pilot exercise proved helpful in identifying process improvement adjustments and communication improvements.

11. Several training sessions were held for hospitals via GOTO meeting to explain the rationale for the pilot and various processes involved. The subsequent discussion after these sessions resulted in several process improvements.

12. Although the final outcome of the IGSP realized a savings in IG through more appropriate dosing, the process was extremely manual in nature and was labour intensive for all of the parties involved. Therefore, while the concept of having experts monitor dosing at a provincial level is a good one; it needs to be supported with the requisite technology.

13. The external reviewers were anonymous to the hospitals and each other. This provided an objective analysis in the IG review and removal of bias towards ordering or reviewing physicians. However, the collective group of reviewers did not have an opportunity to meet and harmonize reviewing strategies and criteria, nor were the OPs permitted to consult with the reviewers as in British Columbia's model. Having a reviewer training session would have provided a more consistent approach to the review process.

14. Some hospitals complained that the IGSP approved doses were higher than the allowable doses set forth in the hospital's established IG guidelines. It was difficult for the hospital medical directors to negotiate a reduction in dose that aligned with hospital policies when the dosing decision was already made by an expert reviewer. Perhaps the issues discussed in point 10 would assist in addressing problems like this.

Conclusions

The IGSP was successful in that it provided:

1. A standardized approach for reviewing neurology IG requests across the province.
2. OPs and hospitals with access to an expert, external reviewer for questionable orders, which was particularly valuable for hospitals lacking neurology expertise.
3. A potential 72,848g reduction in the amount of IG ordered for a cost savings of over $2M, when the 51% compliance rate is applied and IGSP expenses are taken into account.
4. Validation of the appropriateness of requests for IG in the specialty of neurology with a very low rate of actual refusals.

The IGSP also demonstrated that the manual process in place for this pilot was not sustainable for the EAP group, the OPs or the HTSs due to the many levels of manual work involved. Therefore the maintenance of the IGSP is not recommended for neurology nor should any other specialties be rolled into this current manual system. If requisite technology was developed to support a screening process, this initiative should be revisited with consideration to the "Challenges and Lessons Learned" (page 35).

A streamlined, tested, web-based technology solution needs to be in place to deliver a decentralized, province-wide screening process involving hospital-based and community-based services and service teams. The success of a gatekeeper process to oversee products and services, where decisions have the potential to impact patient care, must be carefully planned, clinically supported by evidence, and optimally delivered with work processes and workflow that are timely, pragmatic and acceptable to impacted stakeholders. An operational process that is under-resourced and relies on manual work processes for the delivery of services, documentation, communication, data collection, and record-keeping is neither efficient nor sustainable. It may serve to disincentivise those who deliver and receive services or to impact patient care.

Appendix A: The Ontario IG Advisory Panel as of January 2017

The Immune Globulin Advisory Panel (IGAP) is a subcommittee of the Ontario Blood Advisory Committee (OBAC) Its initial purpose was to address the unsustainable increase in the utilization and associated costs of IVIG. Subcutaneous Immune Globulin (SCIG) product became more widely used some years later, and is also a responsibility for the IGAP. The IGAP also provides medical, clinical and technical expertise regarding the appropriate use of IG to the PATB of the MOHLTC. The IGAP is also mandated to develop, support and facilitate the implementation of guidelines, policies and utilization management initiatives associated with IVIG utilization.

Name	Specialty	Organization
Dr. Lois Shepherd, Chair	Hematopathologist	Kingston General Hospital
Ms. Lisa Richards, Vice Chair Formerly Dr. Yulia Lin	Acting Charge Technologist Transfusion Medicine Specialist & Hematology	Lakeridge Health Sunnybrook Health Sciences Centre
Dr. Anthony Giulivi	Transfusion Medicine Director	The Ottawa Hospital
Ms. Nancy Heddle	Director, McMaster Transfusion Research Centre	McMaster University
Ms. Jennifer Davis	Manager, Customer Support & Product Distribution	Canadian Blood Services
Mr. Peter Saunders	Associate Director, National Operations	Canadian Blood Services
Ms. Doris Neurath	Manager, Transfusion Medicine, Hematopathology, Tissue Typing / DNA	The Ottawa Hospital
Ms. Laura Aseltine	Transfusion Medicine	London Health Sciences Centre
Dr. Katerina Pavenski	Head of Transfusion Medicine	St. Michael's Hospital
Ms. Lynda Theoret	RN Coordinator of the SCIG Home Infusion Program	The Ottawa Hospital
Dr. Kathryn Webert	Medical Director Utilization	Canadian Blood Services
Dr. Michelle Zeller	Hematologist	Hamilton Regional Laboratory Medicine Program
Ms. Ramona Muneswar	Sr. Policy and Business Analyst	PATB—MOHLTC
Dr. Allison Collins	Clinical Project Coordinator, Medical	ORBCoN
Ms. Laurie Young	Project Coordinator and IG Lead	ORBCoN
Ms. Denise Evanovitch	Regional Manager	ORBCoN
Ms. Wendy Owens	Program Manager	ORBCoN
Mr. Troy Thompson	Regional Manager	ORBCoN
Ms. Sheena Scheuermann	Project Coordinator	ORBCoN

Appendix B: The IG Screening Pilot Working Group (IGSPWG) Membership as of January 2017

The IVIG Screening Pilot/Program Working Group ("ISPWG") is a sub group of the IGAP convened to develop and implement the IVIG Screening Pilot Project.

Name	Specialty	Organization
Dr. Lois Shepherd	Hematopathology & IGAP Chair	Kingston General Hospital
Dr. Yulia Lin	Transfusion Medicine Specialist & Hematology	Sunnybrook Health Sciences Centre
Dr. Steven Baker	Neurology	Hamilton Health Sciences
Dr. Pierre Bourque	Neurology	The Ottawa Hospital
Dr. Vera Bril	Neurology	UHN, Mount Sinai Hospital
Dr. Kurt Kapinski	Neurology	London Health Sciences
Dr. Hans Katzberg	Neurology	University Health Network (UHN)
Dr. Michel Melanson	Neurology	Kingston General Hospital
Ms. Doris Neurath	Manager, Transfusion Medicine, Hematopathology, Tissue Typing / DNA	The Ottawa Hospital
Ms. Laura Aseltine	Transfusion Safety Officer Now: Transfusion Medicine	London Health Sciences
Ms. Donna Berta	ONTraC Nurse Now: Transfusion Safety Officer	London Health Sciences
Ms. Wilma Koopman	NP, RN(EC)	London Health Sciences
Ms. Ramona Muneswar	Sr Policy & Business Analyst	PATB—MOHLTC
Ms. Margaret Wong	Manager IAP Operations	MOHLTC
Ms. Laurie Young	Project Coordinator and IGAP ORBCoN lead	ORBCoN
Ms. Wendy Owens	Program Manager	ORBCoN
Ms. Denise Evanovitch	Regional Manager	ORBCoN
Ms. Sheena Scheuermann	Project Coordinator	ORBCoN