Intravenous Immune Globulin (IVIG)
2012 Audit Report

Ontario Regional Blood Coordinating Network

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1.0 Definitions

Approved: In this report, the term approved is used to indicate that the clinical indication in question is approved according to the Ontario IVIG Utilization Management guidelines version 2, March 31 2012.

Hospital classifications
Small (S): Less than 100 bed facility
Community (C): 100 and greater than 100 bed facility
Teaching (T): Over 100 bed facility, associated with academic health science professional programs

IVIG: Intravenous Immune Globulin (IVIG) is a product prepared by several commercial manufacturers who use plasma derived from donors, to extract immunoglobulin subclass gamma (IgG). There were 5 different brands of IVIG products available in Canada at the time this audit was conducted:
Gammagard S/D and Gammagard Liquid both manufactured by Baxter
Gamunex® and IGIVnex™both made by Grifols (IGIVnex™is made from plasma collected from Canadian donors)
Privigen® manufactured by CSL Behring

Infusion: Some patients whose data were part of the data collection were treated a number of times during the data collection period. The analysis is presented both by number of patients (2,246) and number of infusions (6,442).

Labeled Indications: This term refers to indications approved for use in Canada by Health Canada. Together, the 5 brands of IVIG available in Canada at the time this audit was conducted were licensed by Health Canada for the following indications:

Primary Immunodeficiency (PID)
- Congenital agammaglobulinaemia and hypogammaglobulinaemia
- Common variable immunodeficiency
- X-linked immunodeficiency with hyper IgM
- Severe combined immunodeficiency

Secondary Immunodeficiency (SID)
- B-cell Chronic Lymphocytic Leukemia (CLL)
- Allogeneic Bone Marrow Transplantation (for patients at least 20 years of age)
- Pediatric HIV Infection

Idiopathic Thrombocytopenic Purpura (ITP)
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Neonate: age of patient is 0 to 28 days
Pediatric: age of patient is 17 years or less

Recommended Option: In this report, the term “recommended option” refers to the clinical indications identified in the Ontario IVIG Utilization Management guidelines clinical conditions that might benefit from IVIG treatment as an option. This is in contrast to 'approved conditions' that are ones that definitely benefit from IVIG treatment.
Rounding up/down of IVIG doses: Vials containing IVIG for preparation and infusion come in a variety of sizes, and clinicians ordering the product may be uncertain what is available at the time they place an order. Clinicians order the product by specified guidelines per weight of the patient (e.g., 2.0 g/kg). In

some cases, that means that the order actually gets 'rounded up' to make the order understood to those preparing the product. For example, a patient is 97 kg, the order is 1 g/kg, which means 97 grams to be infused, but the order is rounded up to 100 grams. This applies to the preparation of IVIG as well; if vials are available only in certain sizes the Transfusion or Pharmacy personnel may decide, or request, that the order is rounded up or down to accommodate vial size and availability of product.

In other cases, this means that the order actually gets 'rounded down' to make the order understood to those preparing the product. For example, an order is for 5.3 grams, and is rounded down to 5 grams.

Unlabeled indications: Those clinical indications which are not approved by Health Canada and not shown in the manufacturer's product insert. These fall into two categories:

- Unlabeled potentially indicated: There is convincing clinical information supporting use of IVIG in the conditions listed; however, the product is not licensed by Health Canada to be used for the conditions.
- Unlabeled not indicated: There is no convincing evidence of benefit of using IVIG for those conditions.

See Appendix 3 for complete list of Labeled and Unlabeled Indications used for the purpose of analysis.

2.0 Acknowledgements

Ministry of Health and Long Term Care (MOHLTC), Blood Programs Coordinating Office (BPCO)
The Ontario IVIG Advisory Panel (see Membership List in Appendix 6)
Aicha Traore MSc MD, McMaster University, Hamilton ON
McMaster Transfusion Research Program, McMaster University
Data collection and entry staff at participating hospitals

3.0 Executive Summary

IVIG is a blood product made from pooled human plasma, one of a group of products known collectively as Plasma Protein Products (PPPs). The product is administered to patients who either lack appropriate immunity due to immune deficiencies, or who have autoimmune disorders that can be improved by immune globulin infusion. IVIG is provided to hospitals across Canada (with the exception of Québec) by Canadian Blood Services (CBS), free of charge. Each province and territory is required to pay its share of the CBS budget based on units shipped to their respective jurisdiction.

The Ontario Regional Blood Coordinating Network (ORBCoN) was formed in 2006 by the Blood Programs Coordinating Office (BPCO) of the Ministry of Health and Long-term Care (MOHLTC). One of ORBCoN's goals is optimizing blood utilization management, with Intravenous Immune Globulin (IVIG) being a primary focus.

In 2007, a baseline provincial audit of IVIG utilization was conducted, over a 3-month period, involving 25 hospitals. In 2012, an audit capturing the same data points shown below was conducted, and results are presented in this report. Both audits involved the Ontario IVIG Advisory Panel (see Appendix 4), and were managed by ORBCoN.

The following data elements were collected in both audits:

- Hospital site (by code number)
- Patient care area (specialty)
- Date of infusion
- Patient identification by study code number
- Patient weight
- Primary Diagnosis
- Indication for IVIG infusion
- Dose of IVIG ordered
- Ordering physician specialty
- Volume of product issued
- Total volume infused yes/no
- If total volume not infused, indication of reason why not infused

Between 2007 and 2012, several milestones occurred regarding the use of IVIG in Canada and in Ontario.

- 2007: The National Advisory Committee on Blood and Blood Products published national guidelines for Hematology and Neurology indications
- 2008: ORBCoN submitted a report summarizing the 2007 audit results and made recommendations to the Ontario Blood Advisory Committee
- 2009: ORBCoN launched version 1 of the Ontario IVIG Utilization Management guidelines, using the national guidelines for Hematology, Neurology, Immunology and Solid Organ Transplant as primary references
- 2010: The National Advisory Committee on Blood and Blood Products published national guidelines for Immunology and Solid Organ Transplant indications (an "in press" version of the latter was obtained in time to be included as references)
- 2010: ORBCoN launched an IVIG toolkit which, in addition to the guidelines, contained a standard IVIG request form, standard infusion guidelines, adverse events chart and IVIG dose calculator
- 2011: ORBCoN surveyed Ontario hospitals; results suggested only a minority of hospitals had adopted the guidelines and request form
- 2012: MOHLTC launched the Ontario IVIG strategy, which included endorsing the request form

In 2012, an audit tool specifically designed to collect data for IVIG was used and accessed by hospital staff entering data directly into the software program. Sixty-one (61) hospitals, including small, community and teaching hospitals, participated in the 2012 audit. Data collection took place over a 3-month period between September 4, 2012 and November 30, 2012 inclusive. Data entry concluded January 15, 2013.
The audit captured data on 2,246 patients and 6,442 infusions. This corresponded to 301,298.4 grams infused. The increased participation and volume is due to the increased number of hospitals involved. Of the adult patients treated with IVIG, 1, 017 were female and 955 were male. Adult patients comprised 88% of the patients entered. For pediatric patients (17 years or lower), 257 were pediatric patients and 17 were neonates (0 to 28 days).

Data analysis and specialist review allowed the authors to report on usage for fewer than 120 clinical indications. The results are similar to the 2007 audit where over 80 clinical indications were included. Results are analyzed by comparing 2012 to 2007 audit results, and also categorized into labeled vs. unlabeled utilization. The following highlights are included in detail in the body of the report:

- 929 patients received infusions under Immunology specialty clinical conditions; this is the highest number of patients by specialty, which is consistent with the 2007 results
- 125, 290 grams of IVIG were used for patients with Neurology specialty clinical conditions; this specialty is where the highest volume of product was used, consistent with the 2007 results
- Results for labeled vs. unlabeled use categories is very similar to 2007
    - Labeled use comprised 54.7% of the utilization (2007 49.7%)
    - Unlabeled, potentially indicated use is 33.2% (2007, 37.8%)
    - Unlabeled, not indicated use is 11.4% (2007, 10.5%)
- Utilization assessed using the Ontario IVIG Utilization Management Guidelines (version 2, March 31 2012) demonstrated
    - Approved clinical conditions 85.4%
    - Recommended option clinical conditions 1.8%
    - Not approved clinical conditions 12.8%
- Numerical data to establish the precise impact of the dose calculator is not available through data analysis; however anecdotal evidence shared with the Ontario IVIG Advisory Panel indicates that dosing errors are being detected by verifying doses using the calculator

Subsequent to the 2012 audit, a practice survey was circulated to Ontario hospitals to assess aspects of the implementation of the Ontario IVIG strategy. The survey was circulated December 15, 2012 and was closed January 15, 2013.

The response rate was 59%. Ninety (90) % of respondents were from hospitals using IVIG. Small, community and teaching hospitals were represented.

In this survey, 93% of hospitals responding reported that they have implemented the form for IVIG requests, as mandated by the MOHLTC. Another 4% indicated implementation of the form was in progress. Eighty-eight (88) % of respondents reported using the dose calculator. Most use it not only for obese patients as required by the strategy, but for all requests to verify dose accuracy. Seven (7) respondents indicate their hospital is not using any dose adjustment.

Summary details on the survey appear in section 8 of this report.

Upon reviewing a preliminary analysis of audit results, the following recommendations were made by the Ontario IVIG Advisory Panel:

Recommendation 1
Continue to support adherence to Ontario IVIG Utilization Management Guidelines (version 2 March 31 2012).

Recommendation 2
Implement detailed changes to the MOHLTC IVIG request form over 2013-14 and 2014-15.

Recommendation 3
Review or adjudication of requests outside the guidelines need to be further investigated for future phases of the IVIG strategy.

Recommendation 4

Continue to support the practice of dose adjustment using the ideal body weight calculation and provide information to hospital transfusion services, through targeted education and site visits, emphasizing the increased safety realized by identifying errors in dosing.

Recommendation 5
Roll out education based on audit results to identified hospitals over the 2013/14 and 2014/15 fiscal years.

Recommendation 6
Identify best practices for implementation of the evaluation of clinical outcome and need for reassessment strategies.

Recommendation 7
Perform an environmental scan regarding use of subcutaneous immune globulin (SCIG) to assess whether to implement a standard for a provincial home infusion programs.

Recommendation 8
Develop strategies to triage the use of IVIG during IVIG shortages to be included in the provincial contingency plan.

Recommendation 9
Accessibility to alternate therapies should be optimized due to evidence of potential significant improvements to patient care married with more cost effective treatments.

Recommendation 10
Investigate a means to avoid losing data that is being recorded daily on IVIG request forms.

Detailed rationale for the recommendations is included in detail in Section 9.0 of this report.
The recommendations that are approved by the BPCO will inform the next phase of the Ontario IVIG strategy.

4.0 Background

The Ontario Regional Blood Coordinating Network (ORBCoN) is an initiative funded by the Blood Programs Coordinating Office (BPCO), of the Ministry of Health and Long Term Care (MOHLTC). ORBCoN has been in operation since 2006 and the network consists of three regions, using similar geographic divisions to the 2006 Canadian Blood Services (CBS) regions, and are located in Hamilton (Southwest), Ottawa (Northern and Eastern), and Toronto (Central).

ORBCoN's stakeholders include: Medical Directors working in hospital transfusion services, Laboratory and Quality Managers, Medical Laboratory Technologists (MLTs), Nurses, Transfusion Safety Officers (TSO's), physicians ordering blood products and patients. ORBCoN's mandate is to communicate with hospitals about blood issues in conjunction with Canadian Blood Services, improve patient safety through education and standardization of best practices, in addition to improving utilization and inventory management. At ORBCoN's inception in 2006, the BPCO indicated that working on Intravenous Immune Globulin utilization should be top priority.

In 2007, an audit of IVIG utilization was conducted by the Ontario Regional Blood Coordinating Network (ORBCoN). The three-month audit involved 25 hospitals across the province representing about 66% of IVIG use in Ontario for that time period. The audit included 1,345 patients, 4,234 infusions, and approximately 200,000 grams of IVIG and produced the following results:

- 50% of use was for licensed clinical indications
- 40% of use was for unlicensed, potentially indicated clinical indications
- 10% of use was for unlicensed, not indicated clinical indications

To limit use of IVIG to indications with evidence of clinical efficacy, with appropriate dosages and frequencies, ORBCoN and the Ontario IVIG Advisory Panel (IVIGAP) developed the Ontario IVIG Utilization Management Guidelines and Toolkit, which were disseminated to Ontario hospitals in November 2009 and September 2010 respectively. The Toolkit included a Standard IVIG Request Form; IVIG Dose Calculator; Standard Infusion Guidelines; and Adverse Events Chart.

Based on an ORBCoN survey in January 2011, only 23% (29/128) of IVIG user hospitals had implemented the Guidelines, and 20% (26/128) had implemented the Request Form.

To increase adoption of the Ontario IVIG Utilization Management Guidelines and Toolkit, in an effort to mitigate the continued unsustainable increases in IVIG utilization, the Ministry of Health and Long-Term Care (MOHLTC), in partnership with ORBCoN and the Ontario IVIG Advisory Panel, implemented the IVIG Utilization Management Strategy. The IVIG Strategy included 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

The methodology and results are included in this report.

5.0 Methodology

The Ontario IVIG Advisory Panel identified that the data points to be collected be the same as the 2007 audit to allow a comparison to the baseline province-wide audit. For the 2007 audit, a web-based form had been developed enabling ORBCoN staff and some hospital staff to enter data. In 2012, the website audit tool was developed by LixarIT in cooperation with ORBCoN, in the same software framework as the Ontario Plasma and Bedside Blood Administration audit tools. These tools allow hospital participants to enter their data through a password protected data base residing on a secure server and accessed via the internet. Participants were linked to their hospital and allowed to access their own results at any time, but had no access to other participating hospital data. No patient identifying information was entered into the system.

Staff at participating hospitals entered data via a web-based data collection form (*see Appendix 1)*, on infusions done from September 4, 2012 to November 30 2012; however data entry continued until January 15 2013.Two of the 61 hospitals participating sought research ethics board approvals for

participating in the audit. The lead region on the project also obtained local approval for retrospective chart review.

A patient was identified using month and year of birth, gender and a study code number so that patients who received multiple infusions during the audit could be followed. No personal identifiers were entered into the audit data collection software. The variables collected are listed in Appendix 2**.**

Data entered via the Transfusion Ontario website audit software were extracted into an Excel file then transferred to SAS (*Statistical Analysis System*).

A first data validation was performed in October 2012 on 906 infusions and identified 97 discrepancies (related to 41 patients) most of them related to patient demographic data.

A second data validation was performed at the end of data collection January 2013 on 6,442 infusions and identified 514 discrepancies (related to 108 patients) most of them related to patient demographic data (*only 14 on infusions information*). The correction of discrepancies on patient demographics (*gender, height, weight*) was crucial since they are used to identify individual patients, as data is being collected anonymously.

Compared to the 2007 audit, fewer discrepancies (*in percentage*) were identified since the ORBCoN team and the data analyst were involved in the web-form design improving data conformity, completeness and consistency.

The descriptive analysis presented in this report summarizes infusions data captured by this second audit. In addition to a descriptive analysis, some data of this second audit data were also compared to the first audit data.

6.0 Results

A total of **61** hospitals participated in this second IVIG audit, providing data for **2, 246** patients; tracked **6,442** infusions corresponding to **301,398.4** grams infused. Three (3) small hospitals did not have any infusion data to provide. As shown in Table 1, there were more patients, hospitals and grams accounted for in the 2012 audit. Twenty-five (25) hospitals participated in both the 2007 and 2012 audit (40%) and 36 hospitals participated in only the 2012 audit.

Table 1: 2007 Audit vs. 2012 Audit

	2007 Audit	**2012 Audit**	Variation
Hospitals	25	61	144%
Patient	1,345	2,246	67%
Infusions	4,234	6,442	52%
IVIG Grams	199,406	301,398	51%

This audit captured approximately 80% of the IVIG utilization in Ontario hospitals, an estimate based on the CBS shipment amounts from 2011-12.

6.1 Hospitals

6.1.1 IVIG Grams Per Hospital

Hospitals that participated in the 2007 audit were expected to participate in 2012, to allow for a comparison to be done. In addition, any hospital that used 1% or more of the total IVIG shipped to Ontario hospitals was asked to participate. In addition, twenty-three (23) hospitals volunteered to be included.

In Table 2, the total number of grams used at each participating hospital is presented, including a summary of amount used per category of hospital (small, community, teaching) in grams and percentage of shipments.

Table 2: 2012 Audit Participating Hospitals

Type	Hospitals	Total use for 2011-12	% of Ontario IVIG 2011-12
Teaching	Hamilton Health Sciences McMaster	99482	6.0%
Teaching	Hamilton St Joseph's Healthcare	72611	4.3%
Teaching	Ottawa Hospital Civic	89805	5.4%
Teaching	St. Michael's Hospital	69270	4.1%
Teaching	London Health Sciences Centre University	80220	4.8%
Teaching	Kingston General	66220	4.0%
Teaching	UHN Toronto General	51958	3.1%
Teaching	Hospital For Sick Children	41525	2.5%
Teaching	Ottawa Hospital General	65998	4.0%
Teaching	Hamilton Health Sciences Juravinski	40660	2.4%
Teaching	Sudbury Regional Hospital	30688	1.8%
Teaching	Ottawa Hospital Riverside	35345	2.1%
Teaching	UHN Toronto Western	16120	1.0%
Teaching	UHN Princess Margaret	24590	1.5%
Teaching	London Health Sciences Centre Victoria	23070	1.4%
Teaching	Thunder Bay Regional Health Sciences Centre	17945	1.1%
Teaching	Sunnybrook Health Sciences Centre	20584	1.2%
Teaching	Mount Sinai Hospital	16020	1.0%
Teaching	Hamilton Health Sciences General	11258	0.7%
Teaching	Children's Hospital Of Eastern Ontario	16616	1.0%
Teaching	London St Joseph’s Health Centre	918	0.1%
	Teaching Subtotal		**53.5%**
Community	Grand River Hospital-Kitchener-Waterloo	60422	3.6%

Community	Lakeridge Health Oshawa	43562	2.6%
Community	Royal Victoria Regional Health Centre	33192	2.0%
Community	Rouge Valley Centenary	18235	1.1%
Community	Hotel Dieu Grace Hospital Windsor	23235	1.4%
Community	Windsor Regional Metropolitan Campus	18112	1.1%
Community	Niagara Health System St Catharines Site	26680	1.6%
Community	Credit Valley Hospital	30880	1.8%
Community	Trillium Health Centre - Mississauga	32230	1.9%
Community	Mackenzie Health		1.3%
Community	Southlake Regional Health Centre	17290	1.0%
Community	William Osler Brampton Civic	32015	1.9%
Community	Quinte Healthcare Belleville General	16667	1.0%
Community	Joseph Brant	13798	0.8%
Community	William Osler Etobicoke Hospital	9915	0.6%
Community	Orillia Soldiers' Memorial Hospital	22040	1.3%
Community	Grey Bruce Health Services - Owen Sound	10340	0.6%
Community	Markham Stouffville Hospital	18431	1.1%
Community	Cornwall Community, McConnell Site	7270	0.4%
Community	Ross Memorial Hospital	5915	0.4%
Community	Rouge Valley Ajax and Pickering	7320	0.4%
Community	Humber River Regional Hospital Church Street	10065	0.6%
Community	Peterborough Regional Health Centre	25160	1.5%
Community	Humber River Regional Hospital Finch Street	3700	0.2%
Community	Oakville Trafalgar Hospital	12565	0.8%
Community	Northumberland Hills Hospital Cobourg	3298	0.2%
	Community subtotal		**31.2%**
Small	Temiskaming Hospital New Liskeard		0.0%
Small	Tillsonburg District Memorial Hospital	2860	0.2%
Small	Palmerston and District Hospital	3280	0.2%
Small	West Lincoln Memorial Hospital Grimsby	1285	0.1%
Small	South Bruce Grey Health Centre Kincardine	2040	0.1%
Small	Meno Ya Win Health Centre- Sioux Lookout		0.1%
Small	Leamington District Memorial Hospital		0.0%
Small	St Joseph's General Hospital Elliot Lake		0.1%

Small	Louise Marshall Hospital		0.0%
Small	South Bruce Grey Health Centre Walkerton		0.0%
Small	West Parry Sound Health Centre		0.1%
Small	Campbellford Memorial Hospital		0.0%
Small	Dryden Regional Healthcare		0.0%
Small	South Bruce Grey Health Centre Durham		0.0%
	Small subtotal		0.9%
			85.6%

6.1.2 Type of hospital

Fifty percent (50%) of hospitals that provided data were community hospitals (Figure 1). Table 3 compares the 2007 audit to the 2012 audit. The majority (61.7%) of IVIG audited was used by teaching hospitals (Table 2).

The increase in participation by small (5 times higher than 2007) and community hospitals (10 times higher than 2007) in the 2012 audit is relevant; while IVIG use overall is higher at teaching hospitals, ordering physicians in small and community hospitals may not have access to the specialized support consultants teaching sites enjoy. Hence surveillance of the utilization is equally as, or more important, than for teaching hospitals.

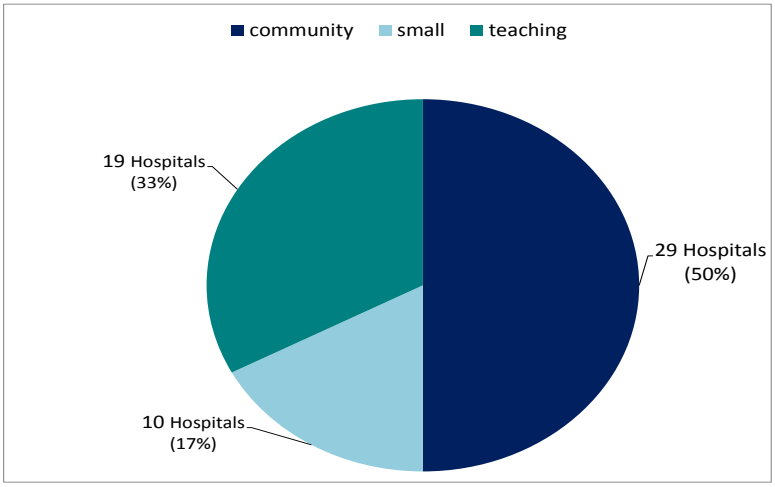


Figure 1: Type of Hospital

Table 3: Hospitals Type: 2007 Audit vs. 2012 Audit

Hospitals Type	**2007 Audit**	**%**	**2012 Audit**	%	Variation
Teaching	18	72.0	19	32.8	+ 6%
Community	6	24.0	29	50.0	x 5
Small	1	4.0	10	17.2	x 10
Total	**25**	**100%**	**58**	**100%**	**x 2**

6.2 Patients

6.2.1 Demographics

The majority (88%) of the 2,246 patients who received IVIG infusions during the audit was adults; gender was almost a perfect split. The proportion of adults compared to other populations is the same in both the 2007 audit and 2012 audit as seen in Table 4.

Table 4: Patients Demographics

Type	2007 Audit				2012 Audit			
	Gender				Gender			
	F	M	Total		F	M	Total	
Adult	632	549	1,181	88%	1,017	955	1,972	88%
Pediatric			141	10%	113	144	257	11%
Neonates			23	2%	5	12	17	1%
Total			**1,345 patients**		1,135	1,111	**2,246 patients**	
					51%	49%		

6.2.2 Specialty

The patients were categorized into nine specialties: Hematology, Immunology, Neurology, Rheumatology, Dermatology, Obstetrics/Gynecology, Infectious Disease, Solid Organ Transplant and Miscellaneous. Since the audit tool for data entry allows for indications to be entered under an 'Other' category (similar to the IVIG request form) this resulted in a total of 540 indications being reported. That list was then examined by specialists from the Ontario IVIG Advisory Panel, and collapsed into the 120 indications included in this report. A comparison of the clinical indications mix in 2012 to 2007 results has not been made.

Audit results enable analysis for patients treated per specialty. Figure 2 summarizes the number of audited patients within each specialty and the proportion of patients included in the audit by specialty. Immunology was the specialty having the highest proportion of patients, 41% (929 patients) which is similar to the 2007 Audit (see Table 3).

In terms of other comparisons to 2007 audit results, while patients treated under the Neurology, Hematology and Rheumatology specialties appeared in the same ranking order, a difference is seen in the ranking of patients treated under other specialties. Of note, the ranking for patients treated under the Dermatology specialty has decreased from fifth rank in the 2007 audit, to seventh in the 2012 audit results. Anecdotal evidence from discussions with Ontario IVIG Advisory Panel members specializing in Dermatology indicate that this change over the last 5 years may be due to increased use of an alternative therapy, which removes these patients from IVIG therapy, but is also seen as a better therapeutic intervention. It is also a less expensive treatment.

One of the issues surrounding the alternative drug therapy is that it is not available to all patients, and is subject to individual insurance coverage. Efforts are being made to lobby government assistance for support enabling universal access to the alternative therapy, which has distinct advantages; it is a better treatment for patients, and it decreases use of a human blood product as a treatment.

Replacing Dermatology specialty in the fifth ranked position is the category of patients treated under the Solid Organ Transplant specialty, moving up from the seventh ranked position in 2007. Table 5 (page 13) presents the ranking that includes percentage of the overall utilization during the audit.

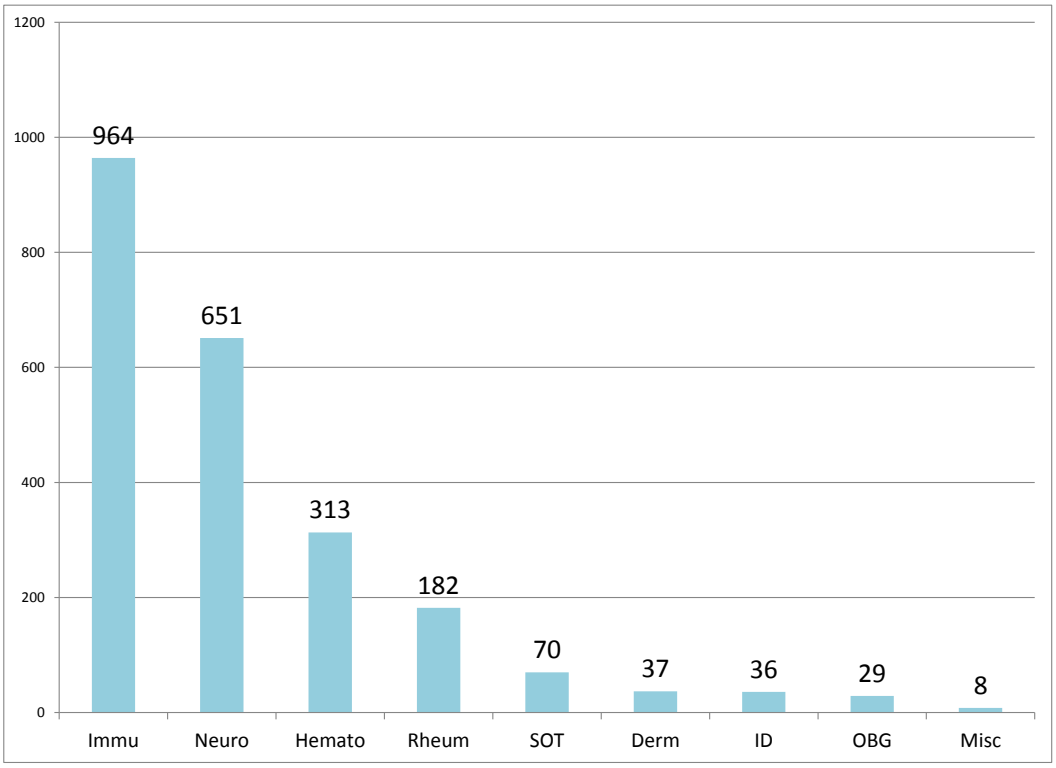


Figure 2: Patients by Specialty*

Immu: Immunology
Neuro: Neurology
Hemato: Hematology
Rheum: Rheumatology
SOT: Solid Organ Transplantation
ID: Infectious Diseases
Derm: Dermatology
OBG: Obs/Gyn
Misc: Miscellaneous**

Table 5: Patients by Specialty

Specialty	2007 Audit		2012 Audit	
	Patients		Patients	
Immunology	504	37%	964	43%
Neurology	349	26%	651	29%
Hematology	238	18%	313	14%
Rheumatology	87	6%	182	8%
Solid Organ Transplantation	22	2%	70	3%
Dermatology	57	4%	37	2%
Infectious Diseases	40	3%	36	2%
Obs/Gyn	13	1%	29	1%
Miscellaneous	35	3%	8	0.4%
Total	**1,345**		**2,290***	

*One of the limitations of the totals shown of the numerical breakdown of patients listed within each specialty is that **41 patients** were categorized into more than one specialty. Details of the breakdown of patients reported in multiple specialties are available in Appendix 4.

6.3 Utilization

6.3.1 Top Indications

Data analyzed by indication rather than specialty revealed fifteen (15) different indications that accounted for 86.2% of the total IVIG used during the audit. The top 15 indications that accounted for the most grams (expressed as amount of grams used and percentages of total grams given) are displayed in Table 6. This table further includes which of the top indications fell into the categories of manufacturer labeled/unlabeled use, and approved or recommended option use as per Ontario guidelines. A summary of overall use in those categories appears in sections 6.3.3 and 6.3.4. Furthermore, this table presents comparison ranking to the top 15 indications reported in the 2007 audit.

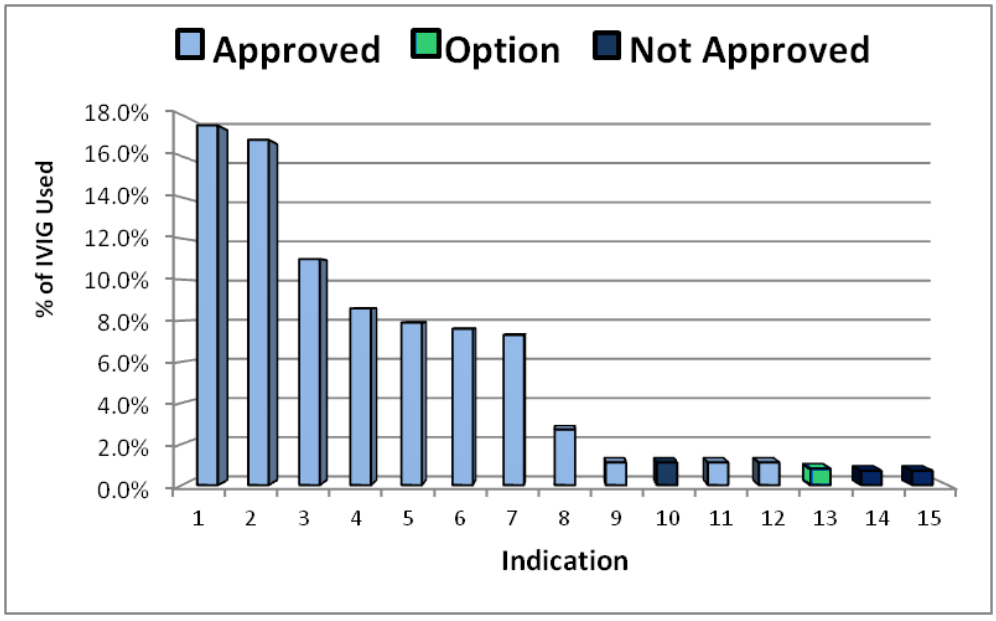
Chronic Idiopathic Demyelinating Polyneuropathy (CIDP) and Primary Immune Deficiency (PID) continue to hold the first two positions in this list; however, CIDP is number one in these 2012 results. In 2007 PID held the first rank. At the time of the 2007 audit, CIDP was not a labeled indication; however it did become a licensed and labeled use in 2008. Both indications are listed as approved indications in the Ontario IVIG guidelines. Twelve (12) of the top indications are in the category of approved indications on the current Ontario guidelines. Figure 3 displays the same information in a graph format.

Table 6: Grams used by Top Indications

Indications	**Labeled**	**Ontario**	**2007 Audit**			**2012 Audit**		
			Rank	**IVIg(g) ordered**	**%**	Rank	**IVIg(g) ordered**	**%**
Chronic Idiopathic Demyelinating Polyneuropathy	Labeled	Approved	2	25,160.9	12.6%	**1**	52,859.6	17.5%
Primary Immune Deficiency	Labeled	Approved	1	31,179.3	15.6%	**2**	50,667.0	16.8%
Idiopathic Thrombocytopenia Purpura	Labeled	Approved	3	19,075.9	9.6%	**3**	33,091.8	11.0%
Secondary Immune Deficiency*	Labeled	Approved	4	15,294.1	7.7%	**4**	28,969.6	9.6%
Myasthenia Gravis	Unlabeled - Potentially Indicated	Approved	5	13,236.3	6.6%	**5**	23,796.3	7.9%
Juvenile Dermatomyositis	Unlabeled - Potentially Indicated	Approved				**6**	22,984.0	7.6%
Multifocal Motor Neuropathy	Unlabeled - Potentially Indicated	Approved	7	9,756.0	4.9%	**7**	21,944.5	7.3%
Guillain-Barré Syndrome	Unlabeled - Potentially Indicated	Approved	9	8,570.3	4.3%	**8**	8,056.0	2.7%
Kidney Transplant	Unlabeled - not indicated	Approved				**9**	3,410.0	1.1%
Connective Tissue Disorder**	Unlabeled - not indicated	Not Approved				**10**	3,330.0	1.1%
Acute Antibody Medicated Rejection	Unlabeled - not indicated	Approved				**11**	3,234.3	1.1%
Hematopoetic Stem Cell Transplant in SID	Unlabeled - not indicated	Approved				**12**	3,228.5	1.1%
Stiff Person Syndrome	Unlabeled - Potentially	Recommended				**13**	2,495.0	0.8%

	Indicated	Option						
Miscellaneous	Unlabeled - not indicated	Not Approved				**14**	2,249.6	0.7%
Unknown	unknown	Not Approved	16	3,934.7	2.0%	**15**	2,219.0	0.7%
Pemphigus Vulgaris	Unlabeled - Potentially Indicated	Approved	6	12,820.0	6.4%	16	2,195.0	0.7%
Dermatomyositis	Unlabeled - Potentially Indicated	Approved	8	8,676.5	4.4%	28	960.0	0.3%
AutoImmune Hemolytic Anemia	Unlabeled - Potentially Indicated	Recommended Option	14	2,173.8	1.1%	24	1,127.0	0.4%
Bone Marrow Transplant	Unlabeled - not indicated	Not Approved	10	8,473.5	4.2%			
Dermatomyositis/Polymyositis	Unlabeled - not indicated	Recommended Option	11	5,254.0	2.6%	53	310.0	0.1%
Desensitization Pre Organ Transplant	Unlabeled - Potentially Indicated	Not Approved	12	3,349.0	1.7%	55	293.9	0.1%
Multiple Sclerosis	Unlabeled - Potentially Indicated	Recommended Option	15	2,016.0	1.0%	59	270.0	0.1%
Sepsis	Unlabeled - not indicated	Not Approved	13	2,150.5	1.1%	60	265.0	0.1%

*Secondary Immune Deficiency includes: BM/PBSCT – CLL - Lymphoma – Leukemia
** Connective Tissue Disorder (Lupus, Relapsing polychondritis, Sjogern's myopathy, Sjogren's dysautomomia, Sjogren's ataxia/neuropathy, Sjogren's sensory ganglionopathy)



1- CIDP
2- PID
3- ITP
4- SID
5- Myasthenia Gravis
6- Juvenile Dermatomyositis
7-MMN
8- GBS
9- Kidney Transplant
10- Connective Tissue Disorder
11- Acute Antibody Mediated Rejection
12-Hematopoetic Stem Cell Transplant in SID
13-Stiff Person Syndrome
14-Miscellaneous
15-Unknown

Figure 3: Summary of IVIG use in Top 15 Clinical Indications (approved, optional or not approved as per the 2012 Ontario Guidelines)

6.3.2 Utilization vs. Specialty

In the 2007 audit results, Neurology patients received the largest portion of IVIG infused. In the 2012 audit, Neurology is still the top user (Figure 4); the proportion went from 35.5% in the 2007 audit to 41.7% in the 2012 audit (Table 7). Rankings for utilization in terms of total grams used in the audit remain the same for the Immunology specialty (2nd) and Hematology (3rd).

Replacing Dermatology specialty in the fifth ranked position is patients treated under the Solid Organ Transplant specialty, moving up from the seventh ranked position in 2007. Potential reasons for this change have been articulated under section 6.2.2.

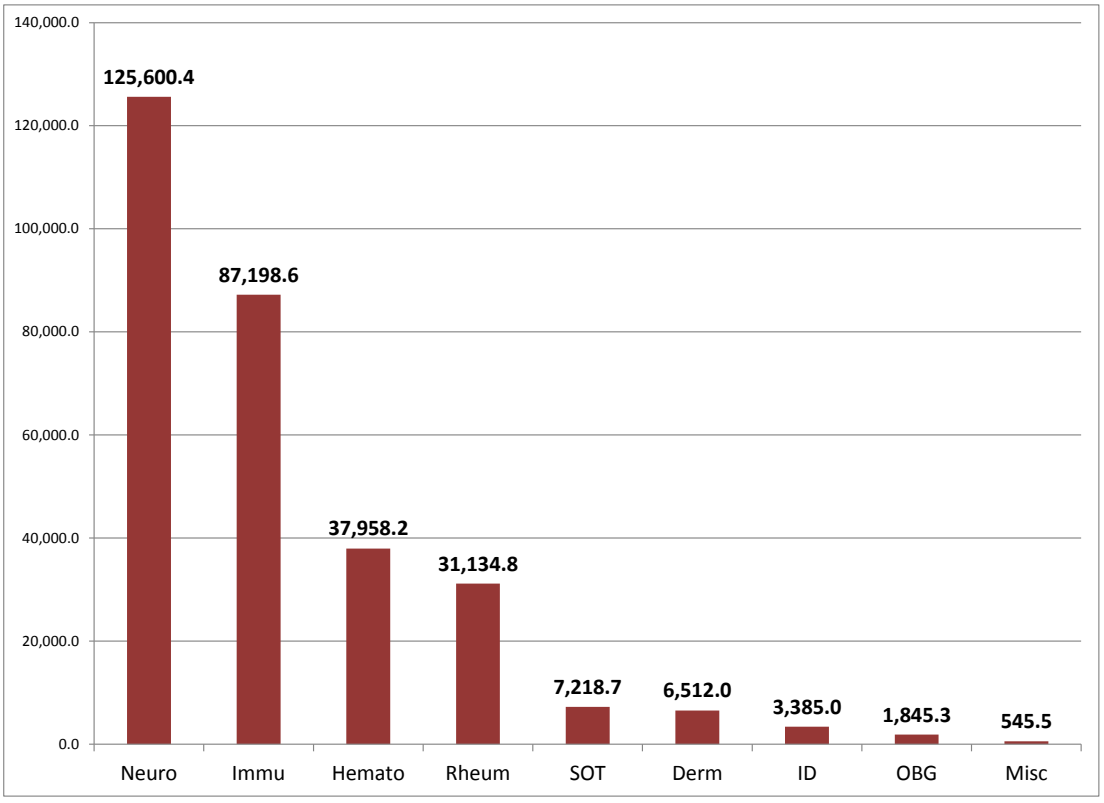


Figure 4: IVIG Use in Grams by Specialty

Neuro: Neurology
Immu: Immunology
Hemato: Hematology
Rheum: Rheumatology
SOT: Solid Organ Transplantation
Derm: Dermatology
ID: Infectious Diseases
OBG: Obs/Gyn
Misc: Miscellaneous

Table 7: Grams used by Specialty: 2007 Audit vs. 2012 Audit

Specialty	2007 Audit		2012 Audit	
Neurology	70,842	35.5%	125,600.4	41.7%
Immunology	49,703	24.9%	87,198.6	28.9%

Hematology	31,812	16.0%	37,958.2	12.6%
Rheumatology	14,672	7.4%	31,134.8	10.3%
Solid Organ Transplantation	3,429	1.7%	7,218.7	2.4%
Dermatology	18,582	9.3%	6,512.0	2.2%
Infectious Diseases	3,677	1.8%	3,385.0	1.1%
Obs/Gyn	2,081	1.0%	1,845.3	0.6%
Miscellaneous	4,325	2.2%	545.5	0.2%
Total	**199,406**		**301,398.4**	

6.3.3 Utilization vs. Labeled

Clinical conditions are categorized into Labeled, Unlabeled Potentially Indicated, and Unlabeled Not Indicated, in order to compare the results to the baseline audit. At that time, no Ontario IVIG guidelines were in place. There is controversy over the conditions included in the Unlabeled categories, and indeed the list used to inform what appears where is sorely out of date (IVIG Consensus Conference 2000), it is the only list the authors have to use that allows a comparison to be made on the results achieved.

The other categorization used is to indicate which clinical conditions are included in the Ontario guidelines. Clinical conditions that appear on the MOHLTC request form are shown as approved. The guidelines also currently list a number of clinical conditions, but do not show on the form, which are recommended as conditions where IVIG might be indicated.

Table 8 shows that the proportion of total labeled indication utilization increased from 49.7% to 54.9%. The unlabeled, potentially indicated category decreased from 37.8% to 33.1%; the unlabeled, not indicated utilization increased slightly from 10.5% to 11.4%. The audit results continue to reveal requests for IVIG are being made with 'unknown' listed as the clinical condition, however in a lower percentage than in the 2007 audit.

Table 8: IVIG Utilization by Labeled and Unlabeled Indications 2007 vs. 2012

Categories	2007 Audit		2012 Audit	
	IVIg(g)	%	IVIg(g)	%
Labeled	99,183.7	49.7%	165,587.9	54.9%
Unlabeled - potentially indicated	75,303.2	37.8%	99,759.6	33.1%
Unlabeled - not indicated	20,984.0	10.5%	33,831.9	11.2%
Indication reported "unknown"	3,934.7	2.0%	2,219.0	0.7%
Total	**199,405.6**		**301,398.4**	

Total Kawasaki (*Unlabeled - Potentially Indicated in Audit 2012*): 1,472.8 g

6.3.4 Utilization vs. Ontario Guideline

A majority of the IVIG requests processed during the audit were reported as being either for the approved or recommended options listed in the Ontario guidelines (86.4%). The IVIG strategy did not require that requests be denied if outside of the guidelines, hence results in the not approved are not

unexpected. Figure 5 and Table 9 display the results of approved, recommended and not approved utilization in grams and percentage of total.

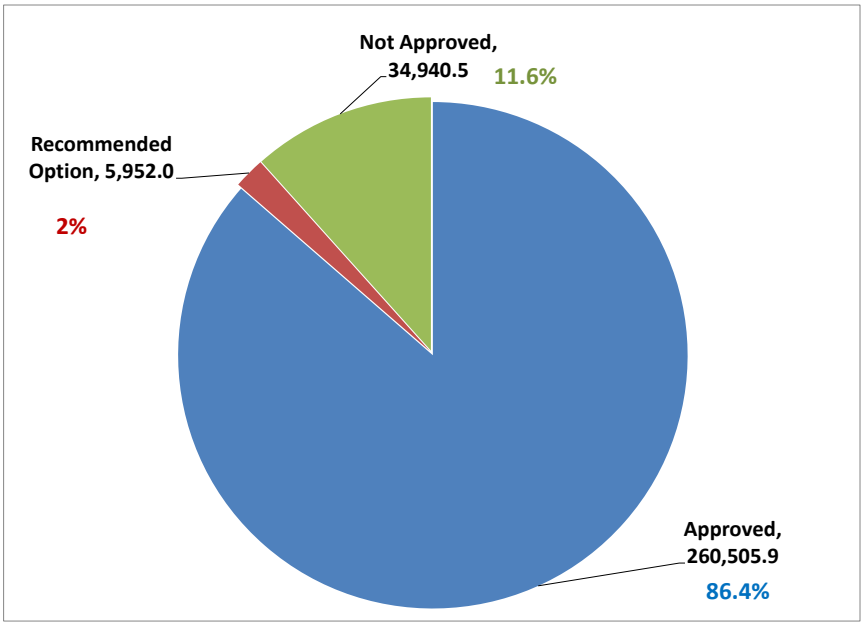


Figure 5: IVIG Utilization based on Ontario Guidelines

Table 9: IVIG Utilization based on Ontario Guidelines

Ontario Guideline	IVIG(g)	
Approved	260,505.9	86.4%
Recommended Option	5,952	1.8%
Not Approved	34,940.5	11.6%

6.3.5 Dose vs. Ontario Guideline

In the 2012 launch of the MOHLTC endorsed IVIG strategy, hospitals were asked to use a dose calculator or similar strategy to adjust doses for obese patients. During the audit, it became clear that the impact of introducing the dose calculator would be impossible to capture accurately. The MOHLTC request form and the audit tool required users to document the total dose and the adjusted dose; however there is no surveillance to ensure this is implemented. Furthermore, the data captured in the audit did not include an accurate measure of adjusted doses.

During the analysis of the audit data, an attempt was made to provide an estimate of dose adjustments, using Idiopathic Thrombocytopenic Purpura as an example. This sub analysis was inconclusive.

Regardless of the data presented, what is clear from the decrease in shipments in 2012-13 (-1.4%), is that a combination of factors, both from the strategy implementation, and from external factors relating to changing therapy, had at least a transitory impact on utilization.

Important anecdotal evidence has been shared at Ontario IVIG Advisory Panel meetings. When using the dose calculator to verify the accuracy of doses requested, physicians and other healthcare professionals have discovered dosing errors that would not have come to light without that step. This confirms the necessity of that part of the IVIG strategy. In 2011, adverse transfusion events (ATE) due to IVIG caused 96% of ATEs due to plasma derivatives, and 15% of overall ATEs (based on preliminary analysis of 2011 Transfusion Transmitted Injury Surveillance System reports, received by personal communication). The dosing errors identified by use of the dose verification step increased patient safety which is the ultimate goal of the IVIG strategy.

6.4 Details per Specialty

The following sections (6.4.1 to 6.4.9) include the various specialties under which patients' clinical conditions are categorized, and display the number and percentage of patients treated for each condition; the total infusions for that condition as well as the minimum, median, maximum number of infusions; the total dose, as well as the minimum, median and maximum dose used.

The legend below describes the short forms used within the tables. Clinical conditions are categorized into Labeled, Unlabeled Potentially Indicated, and Unlabeled Not Indicated, in order to compare the results to the baseline audit, when no Ontario IVIG guidelines were in place. While there is controversy over the conditions included in the Unlabeled categories, and indeed the list used to inform what appears where is sorely out of date (IVIG Consensus Conference 2000), it is the only means the authors have to provide some guidance to the results achieved.

The other categorization used is to denote which clinical conditions are mentioned in the Ontario guidelines. Clinical conditions that appear on the MOHLTC request form are shown with an 'A' for approved. The guidelines also currently include a number of clinical conditions (do not show on the form) which are recommended as conditions where IVIG might be indicated.

Legend
L= Labeled
U-PI= Unlabeled - Potentially Indicated
U-NI= Unlabeled - not indicated
U=Unknown
A= Approved
RO= Recommended Option

Definitions for the terms above appear in section 1.0.

In the tables to follow, rows shown in yellow shading highlight the top indications in that specialty.

6.4.1 Immunology

The majority of patients treated for Immunology indications fall into two (2) categories:

- Primary Immune Deficiency (505/929)
- Secondary Immune Deficiency (361/929)

Both of these indications are labeled indications, and appear as approved indications on the Ontario guidelines (see Table 10). Twelve (12) other indications are reported in the audit results. There is some subjectivity inherent in trying to categorize some of these reported indications, since some of them could presumably fall under either PID or SID. This is a limitation of the audit data collection process.

The major message here is that the patients being treated for immunological disorders comprise the majority of patients receiving IVIG in the province. Furthermore, these patients rely on this replacement therapy for life, not just quality of life. Without treatment they potentially succumb to infections prevalent in the community, which are life-threatening for people with these conditions.

Other data collected from infusions in this specialty category:

- IgG level was done for 45% of the 1,388 infusions for PID; the mean level was 8.61 g/l.
- IgG level was done for 26% of the 821 infusions for a SID; the mean level was 8.9 g/l.

A concern expressed by the Ontario IVIG Advisory Panel members is that this type of clinical outcome evaluation test is not universally available in the province, so using this information as an indicator of evaluation of successful therapeutic outcome for these patients is not widely applicable.

Table 10: Immunology Specialty

Indications	Label	Ontario	Patients		Infusions				Dose(g)			
			N	%	Total	Min	Median	Max	Total	Min	Median	Max
Agammaglobulinemia	U-NI	N-A	1	0.1%	1	1	1	1	40.0	40	40	40
Alpha Globulinemia	U-NI	N-A	1	0.1%	2	2	2	2	120.0	60	60	60
Capillary Leak Syndrome	U-NI	N-A	3	0.3%	13	3	3	7	640.0	30	30	90
HPSCT in PID	U-NI	A	5	0.5%	9	1	2	3	142.5	5	15	40
HPSCT in SID	U-NI	A	60	5.9%	110	1	2	9	3,228.5	5	30	80
Hypersensitivity	U-NI	N-A	1	0.1%	3	3	3	3	150.0	50	50	50
Hypogammaglobulinemia	U-NI	N-A	24	2.4%	47	1	2	3	1,871.0	5	35	75
Keratolimbal Stem Cell Transplant Desensitization	U-NI	A	1	0.1%	1	1	1	1	70.0	70	70	70
Miscellaneous	U-NI	N-A	5	0.5%	5	1	1	1	295.0	25	35	160
Primary Immune Deficiency	L	A	509	50.4%	1,388	1	3	8	50,667.0	3	35	130
Query Schnitzler Syndrome	U-NI	N-A	1	0.1%	7	7	7	7	455.0	65	65	65
Recurrent Optic Neuritis/ Visual Loss	U-NI	N-A	1	0.1%	5	5	5	5	325.0	65	65	65
Severe Asthma	U-PI	N-A	1	0.1%	5	5	5	5	175.0	35	35	35
Secondary Immune Deficiency	L	A	396	39.2%	908	1	2	20	28,969.6	2	30	85
Unknown	U	N-A	1	0.1%	1	1	1	1	50.0	50	50	50
Sub-Total (Some Patients Had More Than 1 Indication)			1,010	100%	2,505	1	3	20	87,198.6	2	35	160
Exact Sub-Total			**964**									

IgG level was done for 45% of the 1,388 infusions for PID; the mean level was 8.61 g/l.
IgG level was done for 26% of the 821 infusions for a SID; the mean level was 8.9 g/l.

6.4.2 Neurology

The majority of patients (545/649) treated for Neurology indications fall into four (4) indications:

- Chronic Idiopathic Demyelinating Polyneuropathy CIDP (267/649)
- Guillain–Barré Syndrome GBS (56/649)
- Multi-focal Motor Neuropathy MMN (94/649)
- Myasthenia Gravis MG (471/649)

Forty (40) other Neurology specialty clinical indications appear in Table 11 as reported by audit data entry. While the list is numerous, the combined total IVIG used under the 40 indications is 8685 grams (7%) of the total used under this specialty (see Table 11).Table 11: **Neurology Specialty**

Indications	Label	Ontario	Patients		Infusions				Dose(g)			
			N	%	Total	Min	Median	Max	Total	Min	Median	Max
Acute Axonal Lumbosacral Plexopathy	U-NI	N-A	1	0.2%	3	3	3	3	120.0	40	40	40
Amytrophic Lateral Sclerosis	U-NI	N-A	1	0.2%	6	6	6	6	570.0	95	95	95
Antibody-Mediated Encephalitis Or NMDA	U-PI	N-A	6	0.9%	23	1	5	5	1,212.5	30	50	70
Autoimmune Autonomic Ganglionopathy	U-NI	N-A	3	0.5%	3	1	1	1	170.0	40	60	70
Autoimmune Encephalitis	U-PI	N-A	5	0.8%	21	2	5	5	1,085.0	30	40	75
Autoimmune Temporal Lobe Seizures	U-NI	N-A	1	0.2%	1	1	1	1	80.0	80	80	80
Cerebellar Syndrome, Anti-GAD	U-NI	N-A	1	0.2%	6	6	6	6	385.0	35	70	70
Chronic Severe Acquired Demyelinating	U-NI	N-A	1	0.2%	5	5	5	5	125.0	25	25	25
Chronic Idiopathic Demyelinating Polyneuropathy	L	A	267	40.0%	968	1	3	25	52,859.6	8	50	160
Connective Tissue Disorder	U-NI	N-A	17	2.5%	60	1	3	9	3,330.0	20	50	100
Diabetic Lumbosacral Plexopathy	U-NI	N-A	3	0.5%	9	2	3	4	690.0	60	75	90
Encephalomyelitis	U-NI	N-A	1	0.2%	6	6	6	6	255.0	40	43	45
Guillain-Barré Syndrome (Miller Fisher Syndrome)	U-PI	A	56	8.4%	198	1	3	10	8,056.0	11	35	180
Hashimoto's Encephalitis	U-PI	N-A	2	0.3%	8	2	4	6	340.0	30	30	70
Idiopathic C8 Radiculitis	U-NI	N-A	1	0.2%	2	2	2	2	130.0	65	65	65
Immune Mediated Necrotizing Myopathy	U-NI	N-A	2	0.3%	3	1	2	2	170.0	50	50	70
Immune Mediated Neuropathy	U-NI	N-A	2	0.3%	7	3	4	4	437.5	28	80	80
Inflammatory Brain Disease	U-NI	N-A	1	0.2%	2	2	2	2	192.0	96	96	96
Inflammatory Paraspinal Myopathy	U-NI	N-A	1	0.2%	3	3	3	3	150.0	50	50	50
Lambert Eaton	U-PI	R-O	1	0.2%	3	3	3	3	150.0	50	50	50

Myasthenic Syndrome												
Lewis Sumner Syndrome	U-NI	N-A	1	0.2%	3	3	3	3	210.0	70	70	70
Limbic Encephalitis	U-PI	N-A	1	0.2%	6	6	6	6	180.0	30	30	30
Miscellaneous	U-NI	N-A	6	0.9%	16	1	3	5	967.0	30	65	100
Multifocal Motor Neuropathy	U-PI	A	94	14.1%	337	1	3	14	21,944.5	15	70	100
Multiple Sclerosis	U-PI	R-O	4	0.6%	9	2	2	3	270.0	20	20	100
Myasthenia Gravis	U-PI	A	128	19.2%	471	1	3	20	23,796.3	2	50	128
Myopathy And Peripheral Neuropathy	U-NI	N-A	1	0.2%	2	2	2	2	140.0	70	70	70
Neuroblastoma	U-PI	N-A	1	0.2%	2	2	2	2	20.0	10	10	10
Neurodegenerative CNS Disease	U-NI	N-A	1	0.2%	3	3	3	3	60.0	20	20	20
Neuromyelitis Optica	U-NI	N-A	1	0.2%	1	1	1	1	50.0	50	50	50
Nonparaneoplastic Anti-N-Methyl-D-Aspartate Receptor	U-NI	N-A	1	0.2%	1	1	1	1	60.0	60	60	60
Opsoclonus Myoclonus Syndrome (Paraneoplastic)	U-PI	N-A	1	0.2%	3	3	3	3	135.0	45	45	45
Optic Nerve Neuritis	U-NI	N-A	2	0.3%	3	1	2	2	105.0	20	20	65
Paraneoplastic Cerebellar Ataxia Syndrome	U-PI	N-A	5	0.8%	11	1	2	5	651.0	45	55	80
Paraneoplastic-Autoimmune Potassium Encephalitis	U-PI	N-A	1	0.2%	3	3	3	3	180.0	60	60	60
Parsonage-Turner Syndrome	U-NI	N-A	1	0.2%	9	9	9	9	270.0	30	30	30
Plexopathy	U-NI	N-A	1	0.2%	1	1	1	1	40.0	40	40	40
Polymyositis	U-NI	R-O	3	0.5%	8	1	3	4	310.0	30	35	70
Rasmussen Encephalitis	U-PI	R-O	3	0.5%	8	2	2	4	390.0	35	40	80
Recurrent CNS Langerhans Cell Histiocytosis	U-NI	N-A	1	0.2%	1	1	1	1	10.0	10	10	10
Refractory Epilectic Encephalopathy	U-NI	N-A	1	0.2%	1	1	1	1	25.0	25	25	25
Sarcoid Neuropathy	U-NI	N-A	1	0.2%	1	1	1	1	45.0	45	45	45
Seronegative Autoimmune Autonomic Gangliopathy	U-NI	N-A	1	0.2%	2	2	2	2	140.0	70	70	70
Small Fibre Autonomic Neuropathy	U-NI	N-A	2	0.3%	4	1	2	3	200.0	40	40	80
Stiff Person Syndrome	U-PI	R-O	15	2.2%	51	1	3	12	2,495.0	15	50	100
Susac's Syndrome	U-NI	N-A	2	0.3%	5	2	3	3	280.0	50	60	60
Unknown	U	N-A	15	2.2%	24	1	1	5	2,119.0	4	69	200
Sub-Total (Some Patients Had More Than 1 Indication)			667	100%	2,323	1	3	25	125,600.4	2	50	200
Exact Sub-Total			**651**									

* Connective Tissue Disorder (Lupus, Relapsing polychondritis, Sjogern's myopathy,

Sjogren's dysautomomia, Sjogren's ataxia/neuropathy, Sjogren's sensory ganglionopathy)

6.4.3 Hematology

The majority of patients treated under the Hematology specialty (264/346) falls into 2 indications:

- Idiopathic Thrombocytopenic Purpura ITP (260/356)
- Hemolytic Disease of the Fetus and Newborn (14/356)

Of these indications ITP is a manufacturer labeled indications (current or past licensed indications, Health Canada approved).

Eleven (11) other clinical indications were reported under this category and the combined total IVIG used in grams for these indications in this category is 4612 grams (13%). (See Table 12.)
Other data collected from infusions in this specialty category include that platelet count s were done for 64% of the 543 infusions for ITP, and the mean level was 31.3 x 109/L. Performing a platelet count to assess outcome of the treatment is a norm for clinical practice; however, collecting that information for the audit was not a primary goal of the audit process. Hence, the result may not show conclusively that platelet counts are used to establish clinical outcome, it may be an anomaly of data collection focus not being on this measure.

Table 12: Hematology Specialty

Indications	Label	Ontario	Patients		Infusions				Dose(g)			
			N	%	Total	Min	Median	Max	Total	Min	Median	Max
Acquired Von Willebrand's Disease	U-NI	R-O	3	1.0%	7	1	2	4	485.0	55	70	90
Aplastic Anemia	U-NI	N-A	4	1.3%	11	1	2	6	965.0	30	110	110
Autoimmune Hemolytic Anemia	U-PI	R-O	12	3.8%	25	1	2	5	1,127.0	17	40	100
Autoimmune Neutropenia	U-PI	R-O	3	1.0%	6	2	2	2	390.0	35	80	80
Chronic Graft Versus Host Disease	U-NI	N-A	1	0.3%	1	1	1	1	35.0	35	35	35
Hemolytic Disease Of The Fetus And Newborn	U-PI	A	14	4.5%	20	1	1	3	254.9	1	3	90
Hemophagocytic Lymphohistiocytosis Syndrome	U-NI	N-A	5	1.6%	7	1	1	3	525.5	18	90	98
HLA Alloimmunization	U-NI	N-A	1	0.3%	1	1	1	1	80.0	80	80	80
Idiopathic Thrombocytopenia Purpura	L	A	260	82.8%	543	1	2	15	33,091.8	6	63	132
Langerhans Cell Histiocytosis	U-NI	N-A	3	1.0%	5	1	1	3	94.0	10	24	25
MGUS - Neuropathy	U-NI	N-A	1	0.3%	1	1	1	1	40.0	40	40	40
Miscellaneous	U-NI	N-A	3	1.0%	3	1	1	1	140.0	5	55	80
Red Cell Aplasia	U-NI	N-A	4	1.3%	8	1	1	5	730.0	20	110	140
Sub-Total (Some Patients Had More Than 1 Indication)			314	100%	638	1	2	15	37,958.2	1	60	140
Exact Sub-Total			**313**									

Platelet count was done for 64% of the 543 infusions for ITP; the mean level was 31.3 x 10^9/L.

3.4.4 Rheumatology

The majority of patients treated under the Rheumatology specialty (143/185) falls into 2 indications:

- Juvenile Dermatomyositis (109/185)
- Kawasaki Disease (34/185)

Kawasaki Disease is categorized here as an 'unlabeled, potentially indicated' indication; however, it was a labeled indication at one point in time and continues to be regarded as such in clinical practice. The only reason it is listed as UL, PI is consistency with past reporting of audit results. (See Table 13).

Both Kawasaki Disease and Juvenile Dermatomyositis are approved indications as per the current Ontario guidelines.

Twelve (12) other clinical indications were reported under this category and the combined total IVIG used in grams for these indications in this category is 6678 grams (22%).

Table 13: Rheumatology Specialty

Indications	Label	Ontario	Patients		Infusions				Dose(g)			
			N	%	Total	Min	Median	Max	Total	Min	Median	Max
Felty's Syndrome	U-NI	N-A	1	0.5%	2	2	2	2	60.0	30	30	30
Inflammatory Arthritis	U-NI	N-A	3	1.6%	10	2	2	6	440.0	40	40	50
Inflammatory Myositis	U-PI	N-A	8	4.3%	25	2	3	7	1,507.5	3	70	90
Juvenile Arthritis	U-PI	N-A	1	0.5%	2	2	2	2	60.0	30	30	30
Juvenile Dermatomyositis	U-PI	A	109	59.2%	380	1	3	12	22,984.0	25	60	165
Kawasaki Disease	U-PI	A	34	18.5%	38	1	1	2	1,472.8	15	30	85
Macrophage Activation Syndrome	U-NI	N-A	2	1.1%	2	1	1	1	107.5	48	54	60
Myositis	U-NI	N-A	3	1.6%	8	1	1	6	550.0	60	60	100
Scleroderma	U-NI	N-A	3	1.6%	7	1	2	4	400.0	50	60	60
Scleromyxedema	U-NI	N-A	1	0.5%	6	6	6	6	360.0	60	60	60
Small Vessel Vasculitis	U-PI	N-A	11	6.0%	30	1	3	6	1,820.0	15	70	80
Stevens Johnson Syndrome	U-NI	N-A	3	1.6%	8	1	1	6	563.0	10	80	80
Vasculitis	U-PI	N-A	4	2.2%	11	2	3	3	530.0	25	55	70
Wegener's Granulomatosis	U-PI	N-A	1	0.5%	8	8	8	8	280.0	35	35	35
Sub-Total (Some Patients Had More Than 1 Indication)			184	100%	537	1	2	12	31,134.8	3	60	165
Exact Sub-Total			**182**									

6.4.5 Dermatology

The highest number of patients treated under a single condition in the Dermatology specialty fall into the Pemphigus Vulgaris (13/32) indication.

None of the dermatology indications are labeled indications; however, Pemphigus Vulgaris is an approved indication as per the Ontario guidelines.

Six (6) other clinical indications were reported under this category and the combined total IVIG used in grams for these indications in this category is 4317 grams (66%). Variations in the 2012 results compared to the 2007 audit have been noted in section 6.3.2.

Table 14: Dermatology Specialty

Indications	Label	Ontario	Patients		Infusions				Dose(g)			
			N	%	Total	Min	Median	Max	Total	Min	Median	Max
Dermatomyositis	U-PI	A	5	13.2%	15	1	3	6	960.0	30	70	80
Erythema Multiforma Major Mucosal Only	U-NI	N-A	1	2.6%	1	1	1	1	85.0	85	85	85
Pemphigus Vulgaris	U-PI	A	13	34.2%	35	1	2	6	2,195.0	35	63	100
Polyarteritis Nodosa	U-NI	N-A	1	2.6%	8	8	8	8	640.0	80	80	80
Pyoderma Gangrenosum	U-NI	N-A	7	18.4%	19	1	3	6	997.0	40	55	71
Toxic Epidermal Necrolysis	U-PI	R-O	4	10.5%	5	1	1	2	335.0	10	80	85
Urticaria	U-PI	N-A	7	18.4%	27	1	3	9	1,300.0	20	55	60
Sub-Total (Some Patients Had More Than 1 Indication)			**38**	**100%**	**110**	**1**	**3**	**9**	**6,512.0**	**10**	**58**	**100**

6.4.6 Infectious Diseases

A majority of patients treated under the Infectious Disease specialty fell into the two indications which are approved under the Ontario guidelines:

- Invasive Group A Strep Fasciitis With Toxic Shock (18/37)
- Staphylococcal Toxic Shock (5/37)

Eight (8) other clinical indications were reported under this category (see Table 15) and the combined total IVIG used in grams for these indications in this category is 1053 grams (31%). While all eight indications are shown as unlabeled, not indicated (UL-NI), the authors emphasize that the classification used for this arbitrary categorization is out of date, and as always, clinical situations of a grave nature indicate using any available measure to rescue the patient.

Table 15: Infectious Diseases Specialty

Indications	Label	Ontario	Patients		Infusions				Dose(g)			
			N	%	Total	Min	Median	Max	Total	Min	Median	Max
Atypical Pneumonia	U-NI	N-A	1	2.7%	1	1	1	1	80.0	80	80	80
Clostridium Difficile Colitis	U-NI	N-A	3	8.1%	4	1	1	2	203.5	28	44	88

COPD And Recurrent Infections	U-NI	N-A	1	2.7%	3	3	3	3	90.0	30	30	30
Fourniers Gangrene (Invasive GP A STRP)	U-NI	N-A	1	2.7%	1	1	1	1	150.0	150	150	150
Invasive Group A Strep Fasciitis With Toxic Shock	U-PI	A	18	48.6%	32	1	1	3	1,928.0	23	56	140
Reoccurant Pneumonia	U-NI	N-A	2	5.4%	4	2	2	2	160.0	30	40	50
Sepsis	U-NI	N-A	4	10.8%	6	1	1	3	265.0	20	50	70
Severe CMV Infection/Pneumonia	U-NI	N-A	1	2.7%	1	1	1	1	25.0	25	25	25
Staphylococcal Toxic Shock	U-PI	A	5	13.5%	9	1	1	3	403.5	17	35	80
Toxic Shock Syndrome	U-NI	N-A	1	2.7%	1	1	1	1	80.0	80	80	80
Sub-Total (Some Patients Had More Than 1 Indication)			37	100%	62	1	1	3	3,385.0	17	50	150
Exact Sub-Total			**36**									

6.4.7 Solid Organ Transplant

A majority of patients treated under this specialty fell into two (2) clinical indications:

- Acute antibody mediated rejection (34/73)
- Kidney transplant (31/73)

Both indications are approved as per the current Ontario guidelines; neither is a labeled indication (see Table 16).

Three (3) other clinical not approved indications are reported under this specialty accounting for 574 grams (8%) of the use in this specialty.

Utilization under this specialty is growing as noted in section 6.3.2.

Table 16: Solid Organ Transplant Specialty

Indications	Label	Ontario	Patients		Infusions				Dose(g)			
			N	%	Total	Min	Median	Max	Total	Min	Median	Max
Acute Antibody Medicated Rejection	U-NI	A	34	46.6%	105	1	2	19	3,234.3	3	30	86
BK Virus Infection Post Kidney Transplant	U-NI	N-A	1	1.4%	3	3	3	3	90.0	30	30	30
Desensitization Pre Organ Transplant	U-PI	N-A	5	6.8%	5	1	1	1	293.9	25	65	77
Kidney Transplant	U-NI	A	31	42.5%	87	1	2	17	3,410.0	10	30	100
Lung Transplant	U-NI	N-A	2	2.7%	3	1	2	2	190.5	30	80	81
Sub-Total (Some Patients Had More Than 1 Indication)			73	100%	203	1	2	19	7,218.7	3	30	100
Exact Sub-Total			**70**									

6.4.8 Obstetrics & Gynecology

The majority of patients treated under this specialty fell under one (1) clinical indication:

- Fetal/Neonatal Alloimmune Thrombocytopenia (17/29)

Two (2) other indications for treatment were reported under this specialty, accounting for 1008 grams of the total grams used (55%). One category is Hemolytic Disease of the Fetus/Newborn, and the other is Miscellaneous. Miscellaneous captured: Indications that were entered under the OB/GYN specialty but did not have a definitive indication or primary diagnosis.

Table 17: Obstetrics and Gynecology Specialty

Indications	Label	Ontario	Patients		Infusions				Dose(g)			
			N	%	Total	Min	Median	Max	Total	Min	Median	Max
Fetal/Neonatal Alloimmune Thrombocytopenia	U-PI	A	17	58.6%	21	1	1	2	837.7	2	60	70
Hemolytic Disease Of The Fetus And Newborn (Maternal)*	U-NI	N-A	1	3.4%	3	3	3	3	240.0	80	80	80
Miscellaneous	U-NI	N-A	11	37.9%	22	1	2	4	767.6	5	28	70
Sub-Total			**29**	**100%**	**46**	**1**	**1**	**4**	**1,845.3**	**2**	**45**	**80**

6.4.9 Miscellaneous

Table 18: Miscellaneous

Indications	Label	Ontario	Patients		Infusions				Dose(g)			
			N	%	Total	Min	Median	Max	Total	Min	Median	Max
Autoimmune Inflammatory Bowel Disease	U-NI	N-A	1	12.5%	1	1	1	1	40.0	40	40	40
Bronchiectasis	U-NI	N-A	2	25.0%	8	2	4	6	300.0	30	30	60
Miscellaneous	U-NI	N-A	1	12.5%	1	1	1	1	80.0	80	80	80
Myocarditis	U-NI	N-A	1	12.5%	2	2	2	2	18.0	9	9	9
Nephrotic Syndrome	U-NI	N-A	1	12.5%	3	3	3	3	7.5	3	3	3
Non Specific Interstitial Pneumonia	U-NI	N-A	1	12.5%	2	2	2	2	50.0	25	25	25
Unknown	U	N-A	1	12.5%	1	1	1	1	50.0	50	50	50
Sub-Total			**8**	**100%**	**18**	**1**	**2**	**6**	**545.5**	**3**	**30**	**80**

6.5 Volume Infused, Wastage and Rounding-up/down

Audit data entry required respondents to record whether doses were rounded up or down; whether the total volume of IVIG was infused (and if not, the reason why); and whether any wastage occurred. Some

of this information is readily available to the staff providing the product (rounding up or down). Whether product is entirely infused and/or wasted occurs on the patient care areas, with staff that are not responsible for data entry involved. Hence, the data provided herein are subjective and inconclusive.

Hospitals will round up or down depending on both the vial sizes available and their own site specific policies. A majority of reported infusions was rounded up (see Table 19). The impact of the rounding up is negligible (0.3%) meaning the vial sizes used to meet the dose required did not differ significantly. (See Table 19 and 20)

Table 19: Volume rounding-up/down

Rounded	Infusions		Dose Ordered	Dose Recalculated	
Down	257	4%	15,906.7	10,890.1	-31.5%
Up	6,185	96%	285,491.7	286,389.2	+0.3%
Total	**6,442**		**301,398.4**	**297,279.3**	

Table 20: Wastage

Product wasted	Infusions (N=6,442)	Wasted product volume (N=301,398.4 g)
No	6,416	
Yes	26 (0.4%)	238 (0.4%)

7.0 IVIG Practice Survey 2012/13

Each year ORBCoN conducts a survey inviting all of their regular contacts in hospital Transfusion Services to participate. This year's survey was developed using an Internet tool called LIMESURVEY™. It was piloted in November 2012 with selected hospital staff in the province. Feedback was received and incorporated into the final survey.

The survey was developed and distributed to 139 contacts at hospitals having a Transfusion Service throughout the province of Ontario on December 15, 2013 via email with an embedded link. Respondents were asked to answer the 24 questions on the survey directly online.

The survey was to be completed on or before January 15, 2013 and addressed the following aspects of the Ontario Intravenous Immune Globulin (IVIG) Strategy launched in 2012:

- The IVIG request form
- Dose calculator
- Approval process
- Audit experience

The target population for the survey was hospitals within the province having a Transfusion Service.

Response Rate

A total of 82 (59%) complete responses were received. Incomplete responses were not analyzed for this report. Since all respondents did not identify themselves, the analysts cannot report how many hospitals this represents precisely. Of the respondents, 74 (90%) identified themselves as a hospital site where IVIG was infused. Of these, 30% (25/83) were small hospitals (≤ 100 beds), 43% (35/83) were community hospitals (100 or ≥ 100 beds), and 16% (13/83) as teaching/academic hospitals. Classifications used are based on MOHLTC hospital classifications. (Eleven percent of respondents answered 'other' or did not answer).

MOHLTC IVIG Request Form version 2

The survey post implementation of version 1 of the Ontario IVIG Utilization Management guidelines and IVIG Standard Request form, conducted in January 2011, showed only 23% (29/128) of IVIG user hospitals had implemented the Guidelines, and 20% (26/128) had implemented the Request Form.

In this survey, 93% of hospitals responding reported that they have implemented the form for IVIG requests as mandated by MOHLTC. Another 3 (4%) of hospitals reported that they are in the process of implementation.

The survey also requested information in what format the request form will be offered. Sixty-eight (68) use the paper format, one (1) site reported using computer assisted physician order entry, and three (3) hospitals are using both formats. Two (2) hospitals reported they have not implemented the form at the time of the survey.

Respondents were also asked for suggestions to improve the form. Several are being considered for a future revision of the form in 2014-15. One suggestion, listed below, has been implemented in April 2013:

- Have an electronic form with the required fields so physicians can fill it out properly prior to submitting for approval

A PDF fillable and savable version of the form has been made available, in English and French, on the www.transfusionontario.ca website under IVIG.

Dose Calculator

Respondents were asked to indicate whether they had implemented the dose calculator, and how they did so if they had been successful. Of the respondents who used IVIG at their hospital, 65/74 (88%) are using the dose calculator. Two (2) are using an "alternate" method for correcting doses. Fifty-five (55) used the dose calculator for all patients in their hospital; five (5) use it for overweight/obese patients only. Seven (7) reported they are not using any dose adjustment process.

Approval Process

In order to assess the implementation of the approval process, the following questions were posed.

Who is responsible for the initial screening process at your facility?

The majority (77%) of healthcare professionals responsible for screening IVIG requests are medical laboratory technologists as shown in Figure 6. Seven (7) % of respondents reported Transfusion Medicine directors screened requests at their hospital; pathologists and transfusion safety officers were each reported as the initial screening professional by 3% of respondents. Responses in the 'Other' category (11%) mostly referred to another job position category within the laboratory service (manager, charge technologist, laboratory director).

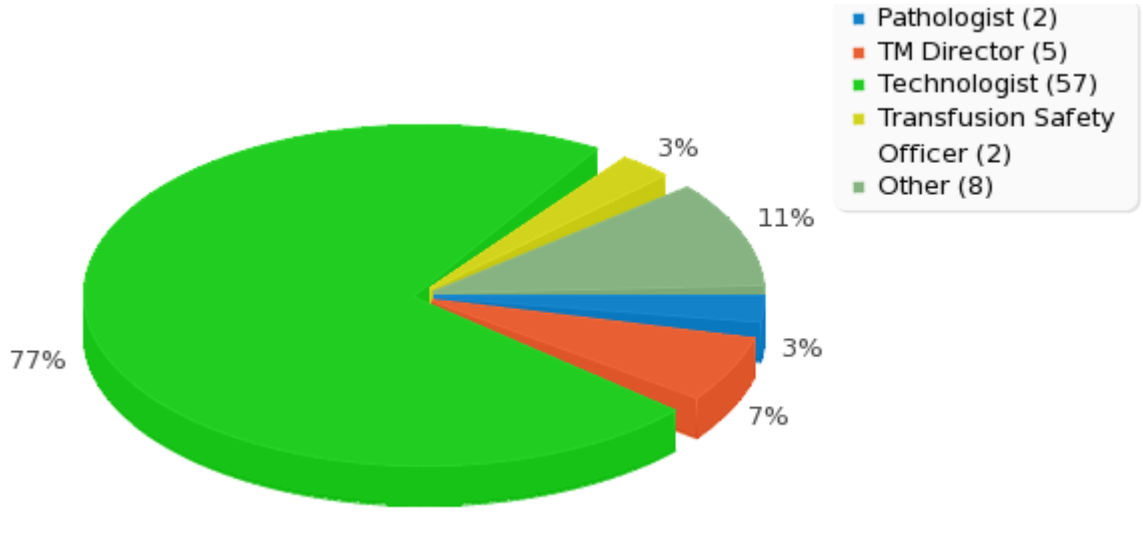


Figure 6: Healthcare professionals responsible for screening IVIG requests

Who is responsible for the final approval/denial of IVIG requests?

In terms of responsibility final approval of the IVIG requests, medical laboratory technologists were in the minority (7%). A similar percentage of responses indicated a pathologist was responsible (35%), or a transfusion medicine director (32%). Hematologists were reported by 9% of respondents, and 16% reported using the 'other' category.

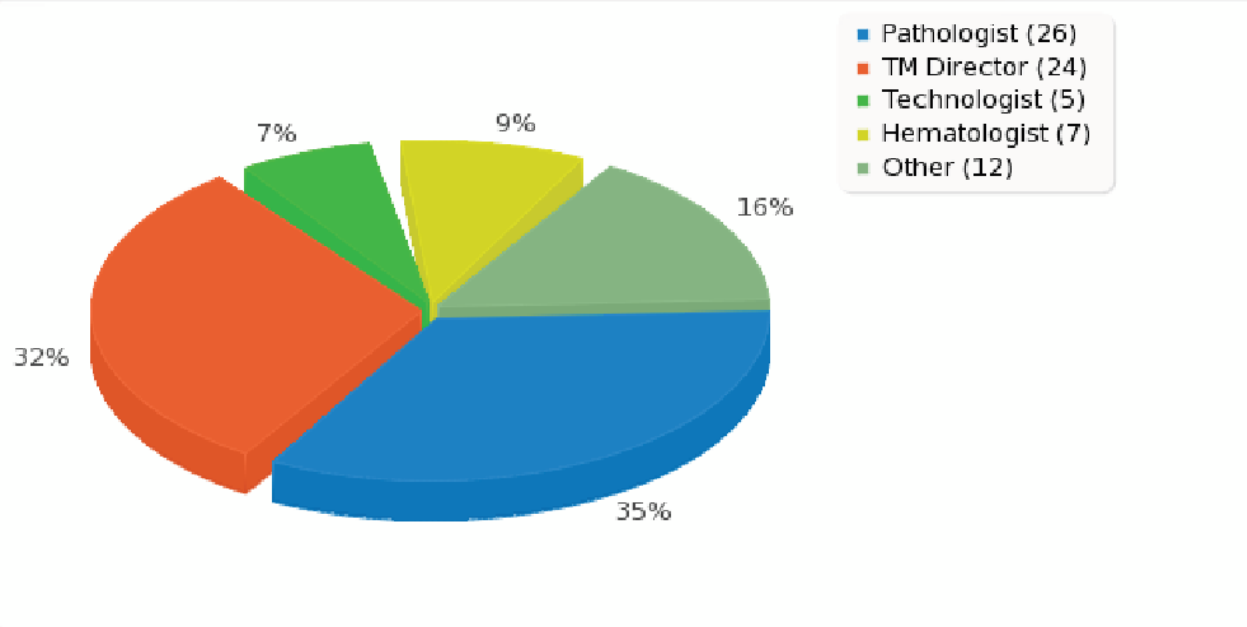


Figure 7: Healthcare professionals responsible for the approval of IVIG requests

The following list shows a sampling of the results that were provided under the Other category:

- Chief of staff when indication is outside guidelines (2 responses)
- Ordering physician will be the approving physician. They should provide documentation of subspecialist consultation in these situations.
- Lab Supervisor
- TM lab physician
- Senior technologists signs on behalf on TM consultant
- Internist

Have you denied any requests? List any requests that were denied.

Very few requests for IVIG for patients were denied as reported by respondents to this survey. Only 3 (4%) respondents indicated a denial of a request. All 3 responses did not report the clinical indication for which the request was denied because the respondent did not review the requests for the purpose of answering the survey. One reported denying a usually high dose request for a critical care patient; however again, the clinical indication was not reported.

Do you currently have an appeal process for denied requests?

Twelve (16%) respondents indicated some form of appeal process had been implemented at their facility. The methods were informal and formal:

- Discuss/talk over the request
- Approve the request on a trial basis
- Take to Transfusion Committee for approval

Evaluation of Clinical Outcomes

How often are clinical outcomes being evaluated?

Most indicated that they were following the recommended timeframes for clinical outcome evaluation. In some cases, hospitals chose to implement a policy for evaluation every 6 months; some for every 12 months; and some, a combination of the two, based on the population of patients served. A wide variety of comments were received, and in some hospitals, the policy is to evaluate on a case by case basis. The table below summarizes the results. Some of the responses may be subjective, based on respondent understanding of the question. There may be some confusion about whether this question was asking about the process approval of requests, or the process for evaluation of clinical outcome by the ordering physician.

Table 21: Summary of responses received regarding evaluation of clinical outcomes

Response	Number of responses
6 months request for new form (evaluation assumed)	20
12 months evaluation	9
6 or 12 month review/evaluation as per MOHLTC form	16
Each use evaluated	3
Never/no policy for evaluation	5
Physician dependent	1
Don't know/uncertain	6
Not applicable (hospitals not handling IVIG requests at this time)	3
Still in development	1
Other/comments only	5

Audit experience

Towards the end of the survey, respondents were asked questions about their experience doing the audit, and given the option of identifying themselves and their institution for follow-up.

The first question simply asked whether the respondent's hospital had participated in the audit. Thirty-nine (39) of the respondents, 52%, had participated.

The second question asked for an estimate of how much time had been spent entering data for the audit; answers ranged from 5 minutes to 10 hours a week. There was little correlation to how many

infusions was taking place at the hospital that reported the estimate; no conclusions about average time spent entering a patient's results can be made.

The third question asked for respondents to provide any overall comments or suggestions about the audit process. Twenty-two (22) comments were received, which fell into the following themes:

Improvements required for the audit tool

- 7 comments related to the need for an auto-fill function to be added to the audit tool such that patient demographic information on repeat patients would appear. This option was requested during the initial development of the tool, and not provided by the developer. Subsequent to the audit, based on user feedback, *this function has now been incorporated into the audit tool* 3 comments related to the requirement to enter physician specialty, which is problematic for many users to obtain and enter, since it does not properly coincide with the clinical condition (ordering physician is not from the same specialty as the patient's clinical condition would suggest e.g. hematologist ordering for a patient with a immunological disorder). This design issue with the tool can be addressed in future redesign.

Time consuming nature of the data collection process

- 3 comments referred specifically to the resource demands of staff and impact on workload resulting from their participation in the data collection process

Positive comments about the audit process

- 3 comments were received relating to how organized the audit process was, and the help received during the data collection and entry period

Hospital Specific Information

A series of questions in the final section of the survey asked respondents to provide information about the handling of IVIG and SCIG, to report the size of the hospital, and to voluntarily identify the hospital and the contact information of the respondent.

Which department at your hospital issues IVIG requests?

The majority of respondents (87%) indicated that the Transfusion Medicine department issues IVIG; one (1) respondent answered 'Core laboratory'. Two (2) answers indicated the Pharmacy issues IVIG. (See Figure 8)

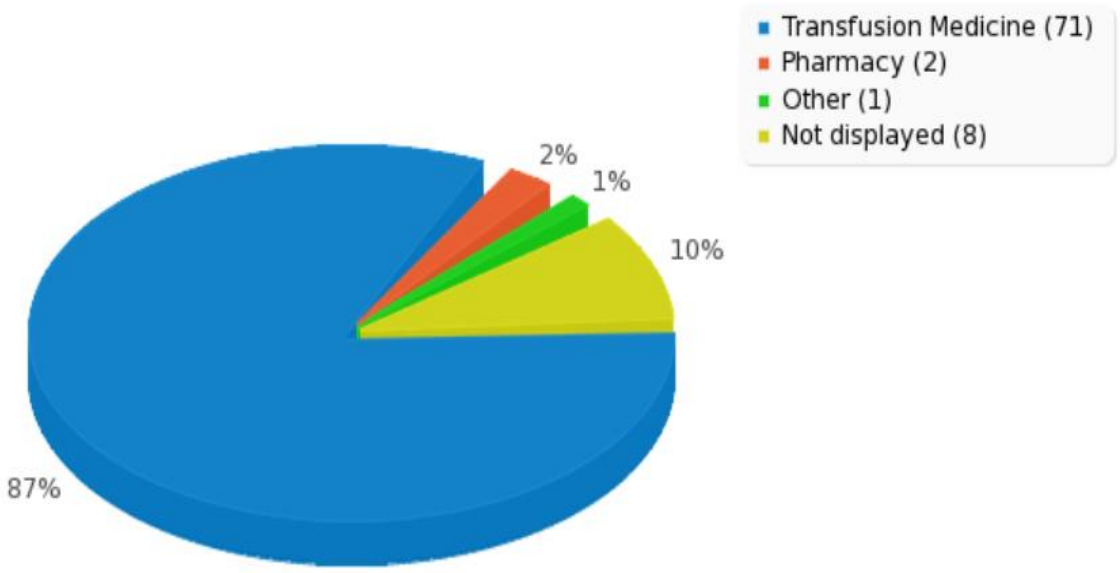


Figure 8: Department that issues IVIG at responding hospitals

Does your hospital issue SCIG for home infusion?

Twenty-four (24) respondents indicated their hospital issues SCIG for patients on home infusion.

Select the category that best describes your hospital:
Small (100 beds or less)
Community (Over 100 beds)
Teaching/Academic

The majority of respondents were from community hospitals (43%), small hospitals reporting were 30%, and 16% were teaching hospitals. (See Figure 9)

Hospital identification

A majority of respondents (70%) provided the name of their facility and their own contact information.

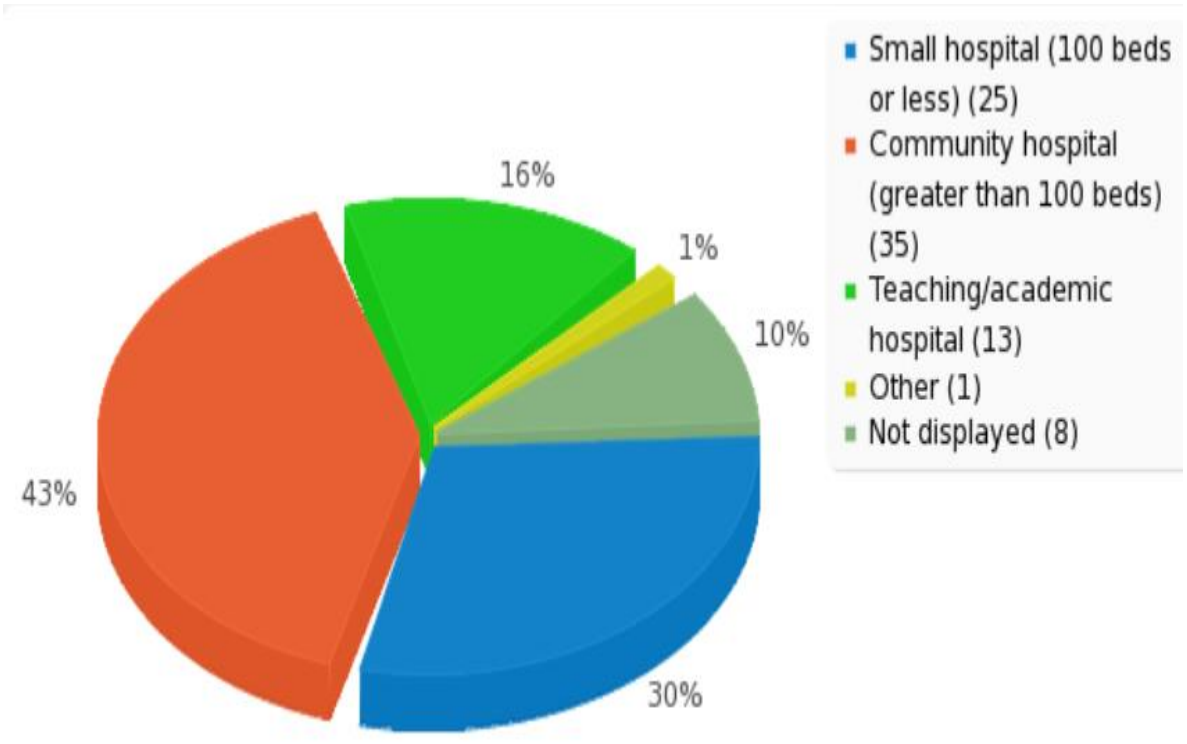


Figure 9: Responding Hospitals by MOHLTC Category

8.0 Limitations of the Audit Results and Analysis

A standard audit software program was provided to hospital staff entering data. Orientation to the process of data entry was provided by the ORBCoN staff, in the format of a user guide. Webinars held throughout summer 2012 to augment understanding of the contents of the user guide were offered as well. During the audit, one of the ORBCoN staff was available continuously during normal business hours to answer questions, and to liaise with the IT company supporting the audit software for any questions requiring their support.

Despite these measures, and the implementation of a standard MOHLTC IVIG request form from which to gather data, collection of data remains a subjective process involving numerous data entry personnel and questionable consistency of entries. Sixty-one (61) hospitals were involved, meaning at least 61 data entry personnel were involved overall. In fact, the audit involved many more staff entering data.

Identification of the specific clinical indication for IVIG infusions continued to be an elusive data point in the 2012 IVIG audit. Much more readily found is the patient's primary diagnosis. Height, as well as a recently obtained weight, which are crucial to the use of the dose calculator, tended to be the data points most often missing. Hospital feedback did suggest that as clinicians became more familiar with the data points required on the MOHLTC request form this problem was greatly reduced. IgG levels were often missing or out of date for Primary and Secondary Immune Deficiency patients. This was also true of platelet counts for patients with ITP. The investigators cannot be certain whether this audit captured all of the instances of dose adjustment, as it was identified that clinicians at some hospitals more familiar with the screening process were efficiently making dose adjustments before submission of requests.

Finally, data were only collected for a three month period; hence the total dose given per patient, per indication could not be determined. Some patients entered into the data base would have been mid-treatment at the onset of the audit and others would be unable to complete a course of treatment before the conclusion of the audit. It also remains uncertain whether three months of data collection was long enough to check if patients are being adequately dosed, and is certainly not sufficient to determine if re-assessment is taking place.

9.0 Recommendations

1. Continue to support adherence to Ontario IVIG Utilization Management Guidelines (v2.0 Mar 31, 2012).

Rationale:

To reduce IVIG use for those indications that is not approved in the Ontario Guidelines.

- Ontario guidelines will not be revised until 2015 or until Canadian guidelines are revised and published.
- The National Advisory Committee on Blood and Blood Products (NAC), who led the development of the Canadian guidelines, has indicated that they will not be revising guidelines for IVIG utilization in Hematology, Immunology and Solid Organ Transplantation at this time.
- The NAC will be revising Neurology guidelines, due to new evidence, which may not be published for another year or more.

- ORBCoN will concentrate instead on what changes need to be made to the form and process, and prepare a process document that includes, for example, the practical information contained in the FAQ document.

2. Implement detailed changes to the MOHLTC IVIG Request Form over 2014-15.

Rationale:
To clarify and streamline the use of the form. Feedback from users has been plentiful, and some of the changes to the MOHLTC IVIG Request Form for 2013-14 have been completed. A PDF fillable savable version of the form launched in 2013 (v 2.0 Mar 31 2012).

What will stay the same?

- Keeping 1 form, double sided – for simplicity. Rationale: A system with multiple forms, in the absence of resources for screening and technology with which to manage the process, would be onerous. The number of suggested changes that can be implemented will depend upon what fits within the 1 form, double-sided format.
- Do not implement physician signature requirement. Rationale: this confuses the intent of the form (which is a request form, not an order form) and increases steps in the process.

<u>Recommended Changes for version 3.0 of the form, to be launched 2014-15</u>

- Involve hospital pharmacists and other key hospital representatives (e.g. risk managers) in the form review process
- Investigate for possible inclusion a means of collecting the dose pre and post use of the calculator

<u>Dose & Duration of Treatment</u>

- Making a space to indicate if treatment is for initial or maintenance therapy
- Clarifying language to better address maintenance therapy as opposed to initial therapy
- Clarifying language around duration of therapy (clarify treatments, frequency e.g. reassessments)
- Create a section to document that ordering physician approved adjusted dose / person verifying dose checks with ordering physician first before changing dose (add to bottom of form)

<u>Indication</u>

- Allowing the option to select Specialty
- Address any changes to the guidelines
- Revise the Clinical Indication box so that 'Other' section captures consistent diagnoses.

3. Review or adjudication of requests outside the approved indications is further investigated for future phases of the IVIG strategy.

Rationale:
To reduce unlicensed use for indications that are not approved or recommended in the Ontario IVIG Utilization Management Guidelines (v2.0 Mar 31, 2012), a formal review process should be implemented to adjudicate these requests whether at a regional or provincial level. ORBCoN and the Ontario IVIG Advisory Panel fully realize the implications of the recommendation, and that currently, funding is not available through the MOHLTC for additional resources for the screening process.

Also, to continue to change the culture from automatic approval of requests to one of a collaborative approach involving a conversation about requests outside of the approved guidelines, ORBCoN will promote that message through site visits and other communication opportunities.

Finally, when physicians ordering IVIG outside of the 'approved medical conditions' can provide evidence (e.g. published article) that their request conforms to current best practice, there should not be a modification or denial of the request

4. Continue to support the practice of dose adjustment using the ideal body weight calculation, and provide information to hospital transfusion services emphasizing the increased safety realized by catching errors in dosing.

Rationale:
A pronounced decrease in IVIG shipments occurred in 2012-13. Shipments of Ig, including both IVIG and SCIG, to Ontario hospitals decreased by 1.4% from 2011/12. Although use of dose calculator (or alternative strategy) is mandatory only for obese patients, there might be a combination of factors in addition to the introduction of the tool that resulted in that impact. However, it is worth reinforcing the rollout of the dose calculator tool as a key factor.

Instances where use of the dose calculator to verify doses has caught errors have been reported to ORBCoN and the Advisory Panel. Increased safety has been observed at some sites where errors in dose calculation (high doses being inappropriately requested) have been detected before patients came to harm, due to the use of the dose calculator.

5. Roll out education based on audit results to targeted hospitals over the 2013/14 and 2014/15 fiscal years.

Rationale:
Twenty-five (25) of the participating hospitals were involved in both 2007 and 2012 province wide audits. These hospitals will be provided with comparison data on their progress with IVIG utilization patterns (to be completed by September 30, 2013). Where indicated, education tailored to identify areas for improvement will be offered by ORBCoN; also included will be emphasis on key points from the 2012 strategy (e.g. evaluation of clinical outcomes and need for reassessment.)

Preferably this can take place using the expertise of a physician affiliated with the ORBCoN program as well as other staff support. A pilot site or sites will be conducted, in 2013/14, to assess approach prior to full launch in 2014/15.

6. Identify best practices for implementation of the evaluation of clinical outcome and need for reassessment strategies.

Rationale:
The need for reassessment by the ordering physician, on a regular basis, for patients on long-term IVIG therapy, continues to be a priority of the IVIG strategy to ensure clinical efficacy. Hospitals have reported successful introduction of policies to evaluate clinical outcomes and need for reassessment. Whether or not the policies are working is unknown at this time.

Most survey respondents (79%) indicated that they were following the recommended timeframes for evaluation of clinical outcomes. A variety of approaches were reported in the Survey. They ranged from evaluating every 6 months, to every 12 months, to a combination of 6 and 12 months, depending on a patient's medical condition. Some hospitals reported doing this on a case by case basis.

Review of the survey results, using the respondents who have provided their name and location, can be further utilized to identify examples of best practices. That information can be built into the targeted education program explained in Recommendation 4.

7. Perform an environmental scan regarding use of SCIG to assess whether to develop and implement a standard for provincial Home Infusion Programs.

Rationale:
Although overall shipments of Ig, including both IVIG and subcutaneous IG (SCIG), have decreased by 1.4 per cent in 2012/13 from 2011/12, SCIG use has doubled over the same time period. To date, the Ontario IVIG Advisory Panel and ORBCoN have not included SCIG in its mandate given that the product was relatively new at the time and ad hoc members from Immunology (major specialty prescribing SCIG for patients) had not yet joined the IVIGAP. Moving patients to this product is one of the factors contributing to the decreased use of the IVIG product. If the use of SCIG increases over time, the impact on the use of IVIG will be even greater.

To date there is no standardization for the management of SCIG patients when it comes to training, recognition and management of adverse events or record keeping. From a patient safety perspective, standardization of policies might be indicated. Some basic information has been collected by ORBCoN through a recent survey (e.g. if a site provide SCIG for home infusion). An environmental scan will determine: the number of patients, where they are being treated, extent and methodology of training, record keeping, costs of consumables and other issues. If results of the scan identify a gap in current SCIG programs, consideration should be given to initiating a working group assigned to create a standard program. The working group could commence work in 2014-15 if the scan can be completed in 2013-14.

Existing SCIG packages from other provinces should be leveraged. Liaising with the Factor Concentrate hemophilia home infusion program staff and product manufacturers (to provide training, consumables) would likely be an advantage, again, to avoid duplication of efforts.

8. Develop strategies to triage the use of IVIG during shortages to be included in the provincial contingency plan.

Rationale:
The current Ontario Plan for the Management of Blood Shortages does not contain specific information to address shortages of IVIG. To mitigate against a shortage, a triage plan should be investigated by ORBCoN and the Advisory Panel over the next 2 years. Following that, a proposal for an IVIG triage plan will be made to the Ontario Contingency Planning Working Group (CPWG), with the goal of having a model ready for a future version of the provincial contingency plan. Examples from other nations where a triage type categorization for requests already exist and, will be utilized to avoid duplication of effort. Amongst the considerations for triage strategies are the differences

between requiring Ig for replacement therapy versus therapeutic therapy. A desirable outcome would be a national collaboration on this subject or even an international policy.

9. Accessibility to alternate therapies should be optimized due to evidence of potential significant improvements to patient outcomes married with more cost effective treatments.

Rationale:
One of the observations from the 2012 audit is that the utilization for dermatology specialty indications dropped significantly. In the 2007 audit, 18582 grams were used in the 3 month period, which accounted for 9.3% of the overall utilization. The 2012 audit shows 1.8% of the overall utilization.

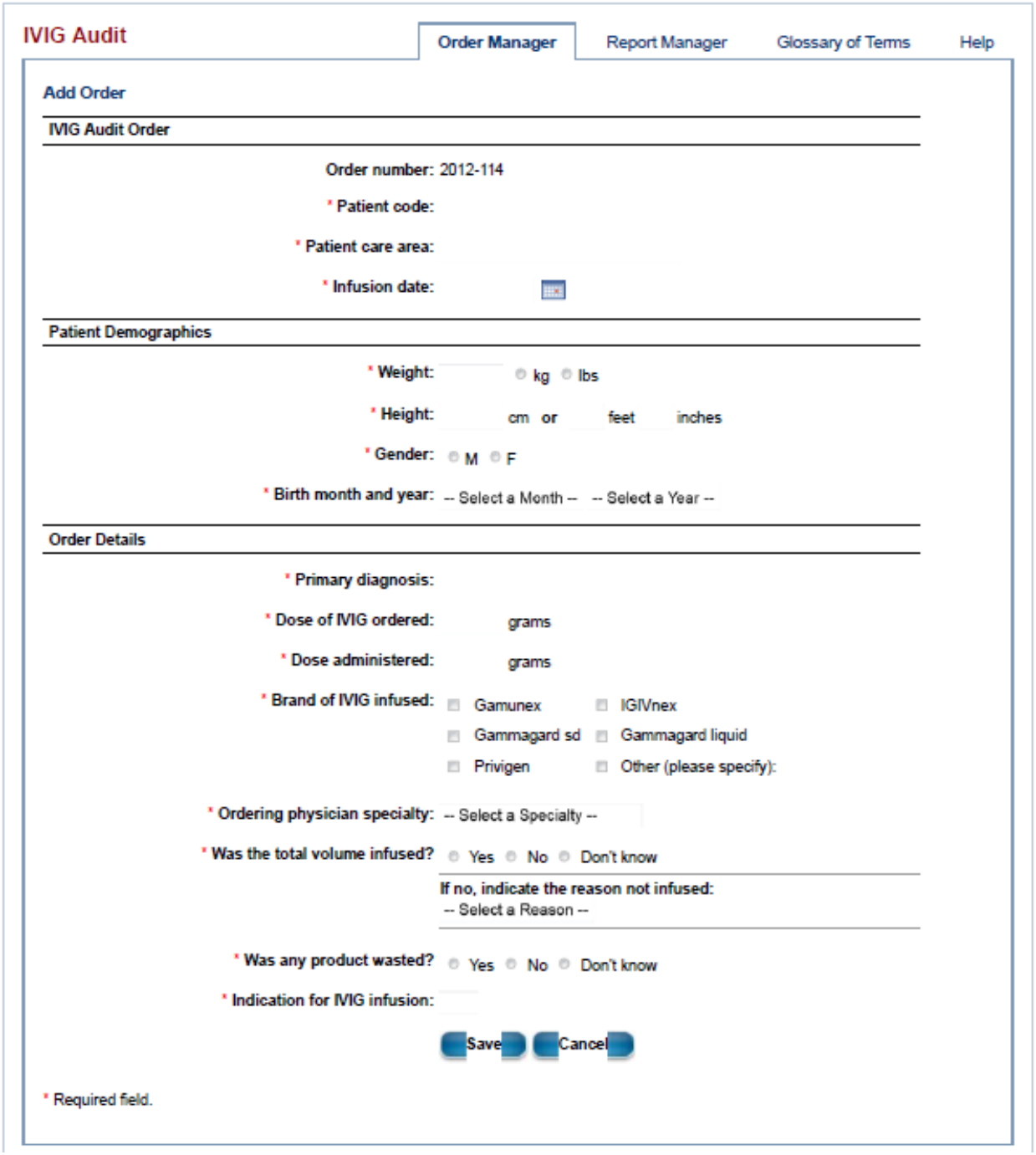
Since the alternate therapy (Rituximab) may play a factor in treatment of certain clinical conditions, it is desirable to help promote increased accessibility. Furthermore, since the drug therapy is potentially more beneficial to patients, and avoids use of an expensive blood product, the IVIGAP supports this recommendation to the MOHLTC. Further investigation of the option of plasma exchange can also be pursued if the recommendation is accepted.

10. Investigate a means to avoid losing important data that is being recorded daily on IVIG request forms across the province.

Rationale:
A wealth of data is being collected via the MOHLTC IVIG request form. Hospitals continue to collect valuable information but currently have no means to collect the aggregated data from the forms over time.
Potential avenues to investigate include:

- Leverage data strategy if implemented beyond pilot stage
- Use existing audit tool to continue to collect data at sentinel sites
- Identify best practices for collecting IVIG data in other jurisdictions

Appendix 1: ORBCoN 2012 IVIG Audit Electronic Data Collection form



IVIG Audit

Order Manager | Report Manager | Glossary of Terms | Help

Add Order

IVIG Audit Order

Order number: 2012-114

* Patient code:

* Patient care area:

* Infusion date:

Patient Demographics

* Weight: kg lbs

* Height: cm or feet inches

* Gender: M F

* Birth month and year: -- Select a Month -- -- Select a Year --

Order Details

* Primary diagnosis:

* Dose of IVIG ordered: grams

* Dose administered: grams

* Brand of IVIG infused: Gamunex, IGIVnex, Gammagard sd, Gammagard liquid, Privigen, Other (please specify):

* Ordering physician specialty: -- Select a Specialty --

* Was the total volume infused? Yes No Don't know

If no, indicate the reason not infused:
-- Select a Reason --

* Was any product wasted? Yes No Don't know

* Indication for IVIG infusion:

Save Cancel

* Required field.

Appendix 2: List of Variables

- Hospital data:
  - ✓ Name
  - ✓ Mak code
- Patients data:
  - ✓ Study code
  - ✓ Weight
  - ✓ Weight unit
  - ✓ Height metric
  - ✓ Height feet
  - ✓ Height inches
  - ✓ Gender
  - ✓ Birth year
  - ✓ Birth month

- Infusions data:
  - ✓ Order number
  - ✓ Infusion date
  - ✓ Dose ordered
  - ✓ Dose recalculated
  - ✓ Primary diagnosis
  - ✓ Primary care area
  - ✓ Physician specialty
  - ✓ Infusion indication
  - ✓ Was total volume infused
  - ✓ Reason not total infused
  - ✓ Was any product wasted
  - ✓ Wasted product volume
  - ✓ Primary IgG level
  - ✓ Primary IgG level date
  - ✓ Secondary IgG level
  - ✓ Secondary IgG date
  - ✓ Platelet count
  - ✓ Platelet count date
  - ✓ Brands

Appendix 2: Summary of Labeled and Unlabeled Indication Categories

Labeled Indications
Primary Immune Deficiency (PID)
Secondary Immune Deficiency (SID)
B-cell Chronic Lymphocytic Leukemia (CLL)
Idiopathic Thrombocytopenic Purpura (ITP)
Allogeneic Bone Marrow Transplantation (for patients at least 20 years of age)
Pediatric HIV infection
Chronic Inflammatory Demyelinating Polyneuropathy*

*labeled as of 2008

Unlabeled, Potentially Indicated (as per IVIG Consensus Conference, 2000)
Anti-Phospholipid Antibody Syndrome
Myasthenia Gravis
Guillain–Barré Syndrome
Multifocal Motor Neuropathy
Polymyositis
Multiple Sclerosis
Stiff Person Syndrome
Encephalitis
Neuroblastoma and Opsoclonus Myoclonus Syndrome
Opsoclonus Myoclonus
Paraneoplastic Syndrome
Lambert Eaton Syndrome
Auto Immune Hemolytic Anemia
Hemolytic Disease of the Newborn
Autoimmune Neutropenia
Wegener's Granulomatosis
Dermatomyositis
Kawasaki Disease
Juvenile Dermatomyositis
Juvenile Rheumatoid Arthritis
Leukocytoclastic Vasculitis
Vasculitis
Pemphigus Vulgaris
Toxic Epidermal Necrolysis
Pemphigoid
Necrotizing Fasciitis
Staphylococcal Toxic Shock
Desensitization Pre-Organ Transplant
Fetal/Neonatal Alloimmune Thrombocytopenia
Infertility/Multiple Miscarriages not secondary to chromosomal or structural abnormalities
Acquired Factor VIII Inhibitor
Chronic Urticaria/Urticaria

Unlabeled, no apparent indication (as per IVIG Consensus Conference 2000), or insufficient information
Asthma
Acquired Von Willebrand's Disease
Angioedema
Autoimmune Enteropathy
Autoimmune Polyendocrinopathy
Scleroderma
MGUS Neuropathy
Ataxia Telangiectasia
Inclusion Body Myositis
Lewis Sumner Syndrome
Amyothrophic Lateral Sclerosis
Erythema Multiform
Hashimotos Encephalopathy
Issacs Syndrome
Mononeuritis Multiplex
Myopathy
Myotropic Neuralgia of the Diaphragm
Status Epilepticus
Unclassified Connective Tissue Disease
Pure Red Cell Aplasia
Thrombotic Thrombocytopenic Purpura
Aplastic Anemia
Cryoglobulemia
Hyperhemolytic Syndrome (Sickle Cell Disease)
Myelodysplastic Syndrome
Post Transfusion Purpura
Rheumatoid Arthritis
Churg-Strauss Syndrome
Polyarthritis Nodosa
Polymyalgia Rheumatica
Sjogren Disease
Pyoderma Gangrenosum
Inflammatory Myopathy
Hailey-Hailey Skin Disease
Pemphigus Foliaceus
Sepsis
Parvovirus B19 Infection
Post-Transplant Lymphoproliferative Disease
Systemic Lupus Erythematosus
Chronic Obstructive Pulmonary Disease
Immune Mediated Lumbosacral Plexopathy

Appendix 3: Summary of Patients with Multiple Specialties

In the Patients by Specialty results presented in Figure 2 of the report, the authors noted that 41 patients were reported under two or more specialties. The table below shows the detail of that summary.

Combination of Specialties	**Number of Patients**
Dermatology/Neurology/Rheumatology	1
Dermatology/Rheumatology	4
Hematology/Immunology	6
Hematology/Neurology	2
Hematology/Obstetrics/Gynecology	1
Hematology/Rheumatology	1
Hematology/Solid Organ Transplant	1
Immunology/Infectious Disease	4
Immunology/Miscellaneous	1
Immunology/Neurology	8
Immunology/Neurology/Rheumatology	1
Immunology/Neurology/Obstetrics/Gynecology	1
Immunology/Obstetrics/Gynecology	1
Immunology/Rheumatology	2
Miscellaneous/Obstetrics/Gynecology	1
Neurology/Rheumatology	3
Neurology/Solid Organ Transplant	1
Total	**41**

Appendix 4: Summary of Approved and Recommended Options Ontario IVIG Utilization Management Guidelines

Ontario Approved Indications	
Hematology	Fetal/ Neonatal Alloimmune Thrombocytopenia (F/NAIT)
	Hemolytic Disease of the Fetus and Newborn (HDFN)
	Idiopathic Thrombocytopenic Purpura (ITP) Adult
	Idiopathic Thrombocytopenic Purpura (ITP) Pediatric
	Post transfusion Purpura
Neurology	Chronic Inflammatory Demyelinating Polyneuropathy(CIDP)
	Guillain-Barré Syndrome (GBS) including Miller-Fisher syndrome and other variants
	Multifocal motor neuropathy (MMN)
	Myasthenia gravis (MG)
Dermatology	Dermatomyositis
	Pemphigus Vulgaris (PV)and Variants
Rheumatology	Juvenile Dermatomyositis
	Kawasaki disease
Infectious Diseases	Staphylococcal toxic shock
	Invasive Group A streptococcal fasciitis with associated toxic shock
Immunology	Primary Immune Deficiency (PID)
	Secondary Immune Deficiency (SID)
	Hematopoietic Stem Cell Transplant in primary immunodeficiencies
Solid Organ Transplantation	Kidney transplant from living donor to whom the patient is sensitized
	Acute antibody mediated rejection in patients who have received living donor/deceased kidney donor transplant
Ontario Optional Indications	
Hematology	Acquired hemophilia
	Acquired red cell aplasia
	Acquired Von Willebrands disease (AvWD)
	Allogeneic bone marrow or stem cell transplantation
	Autoimmune Hemolytic Anemia (AIHA)
	Autoimmune neutropenia
	Hemolytic transfusion reaction (HTR)
	Hemolytic transfusion reaction in sickle cell disease (HTRSCD)
	Hemolytic uremic syndrome (HUS)and Thrombotic Thrombocytpenic purpura (TTP)
	Virus associated hemophagocytic syndrome (VAHS)
Neurology	Acute disseminated encephalomyelitis
	Lambert-Eaton Myasthenic Syndrome (LEMS)
	Multiple Sclerosis (MS)
	Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections (PANDAS)
	Polymyositis
	Rasmussens's Encephalitis
	Stiff Person's Syndrome
Dermatology	Toxic Epidermal Necrolysis (TENS)/ Stevens Johnson Syndrome
Solid Organ Transplant	Kidney transplantation with donor-specific antibodies in recipient

Appendix 5: **Ontario IVIG Advisory Panel Membership as of June 2013**

Core Panel

Dr. Jeannie Callum, Director, Transfusion Medicine Sunnybrook Health Sciences
Ms. Julie Ditomasso, Transfusion Safety Officer, Hamilton Health Sciences, Hamilton St. Joseph's
Ms. Kathleen Eckert, Transfusion Safety Officer, London Health Sciences, London St. Joseph's
Dr. Anthony Giulivi, Transfusion Medicine Director, The Ottawa Hospital
Ms. Nancy Heddle, Director, McMaster Transfusion Research Program
Ms. Elenore Kingsbury, Manager, Plasma Products and Services, Canadian Blood Services
Dr. Yulia Lin, Hematologist, Sunnybrook Health Sciences, *Vice Chair*
Ms. Doris Neurath, Manager, Transfusion Medicine, The Ottawa Hospital
Dr. Katerina Pavenski, Division Head Transfusion Medicine, St. Michael's Hospital
Dr. Elianna Saidenberg, Hematopathologist, The Ottawa Hospital
Dr. Lois Shepherd, Hematopathologist, Kingston General Hospital, *Chair*
Dr. Kathryn Webert, Medical Director, Utilization, Canadian Blood Services

Ad Hoc Members

Dr. Stephen Betschel, St. Michael's Hospital (Immunology)
Dr. Vera Bril, University Health Network and Mount Sinai (Neurology)
Ms. Wilma Koopman, London Health Sciences (Neurology)
Dr. Jeff Lipton, University Health Network (Allogeneic Bone Marrow Transplant)
Dr. Michel Melanson, Kingston General Hospital (Neurology)
Dr. Chaim Roifman, Hospital for Sick Children (Pediatric Immunology)
Dr. Neil Shear, Sunnybrook Health Sciences (Dermatology)
Dr. Rachel Shupak, St. Michael's Hospital (Rheumatology)
Dr. Andy Thompson, London Health Sciences and London St. Joseph's (Rheumatology)
Dr. Scott Walsh, Sunnybrook Health Sciences (Dermatology)

Staff Support

Ms. Denise Evanovitch, Regional Manager, ORBCoN Southwestern
Ms. Kate Gagliardi, ORBCoN Southwestern
Ms. Ramona Muneswar, Senior Policy and Business Analyst, BPCO MOHLTC
Ms. Debbie Lauzon, Regional Manager, ORBCoN Central
Ms. Wendy Owens, Program Manager, ORBCoN
Ms. Sophie Yang, Project Coordinator, BPCO MOHLTC
Ms. Laurie Young, Regional Project Coordinator, Southwestern