Audit of Intravenous Immune Globulin (IVIG) Indications and Effectiveness in Ontario Tertiary Care Centres

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1.0 Definitions

IVIG: Intravenous Immune Globulin (IVIG) is a blood product made up of immunoglobulins. It is produced by several commercial manufacturers who extract immunogloblulin subclass gamma (IgG) from plasma derived from donors.

Recommended Criteria: This term refers to clinical indications in the Ontario IVIG Utilization Management guidelines for treatment of clinical conditions through IVIG usage.

Unlabelled Indications: Clinical indications not approved by Health Canada and not shown in the manufacturer's product insert. These fall into two categories:

- Unlabelled potentially indicated: Product is not licensed by Health Canada to be used for the condition, despite clinical information supporting use of IVIG for the condition
- Unlabelled not indicated: No convincing evidence that IVIG use benefits for the condition

2.0 Acknowledgements

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See Appendix 2 for List of Authorship

This initiative was supported by Ontario Regional Blood Coordinating Network (ORBCoN) and funded by Ministry of Health and Long Term Care (MOHLTC).

3.0 Executive Summary

Intravenous immunoglobulin (IVIG) is a blood product made from pooled plasma and used for immunoglobulin replacement or as an immune-modulator. Despite the introduction of a mandatory IVIG Request Form in Ontario and other provinces to reduce inappropriate use, Canada has the highest per capita use of IVIG in the world.

Consecutive adult patients with a new request for IVIG between January and December 2014 were included from each of the four centres. Patients with approved medical conditions where IVIG is indicated, other conditions indicated in Canadian guidelines, and conditions where IVIG is not indicated were categorized separately. The specialty of the ordering physician, the completeness of the form, documentation of diagnostic criteria for the medical condition and indication for IVIG use, and documentation of efficacy were assessed. Diagnostic and IVIG utilization criteria were taken from published guidelines.

Data analysis and specialist review allowed the authors to report on the appropriateness of IVIG usage. For the 179 patients assessed in this audit, the following findings are included in detail in the body of the report:

- Most common indications for IVIG were immune thrombocytopenia (24.2%) and secondary immune deficiency (20.2%)
- Other indications not listed on the form were common, representing 43 cases (24.2%), with the majority not indicated according to current guidelines
- The most frequent users were hematologists (37.6%) and neurologists (10.7%)
- 84 patients (47.2%) did not have IVIG specifically dosed to ideal body weight
- 58 patients (32.6%) did not meet diagnostic criteria for the medical condition for which IVIG was used
- 51.7% of patients did not meet criteria for IVIG utilization and 19.1% had a discrepancy between the indication written on the form and the diagnosis in the clinical record
- Documentation of efficacy was lacking with 39 patients (31.9%) having no documentation regarding IVIG efficacy in clinical records
- 34.2% of patients had subjective improvement recorded by the ordering physician

This audit demonstrates a lack of compliance with IVIG Request Form requirements, inappropriate use of IVIG, and lack of documentation of diagnostic criteria and efficacy. Further interventions should be aimed at increasing appropriate utilization of IVIG and monitoring its efficacy.

4.0 Background

Intravenous immunoglobulin (IVIG) is a blood product containing pooled, polyvalent, mostly IgG antibodies. While initially developed as a replacement product in primary immunodeficiency (PID), its beneficial immunomodulatory effects have led to the expansion of its indications for use.1,2 An audit conducted by the Ontario Regional Blood Coordinating Network (ORBCoN) demonstrated that 44.6% of IVIG is used for unlabeled indications with 11.4% occurring without guideline recommendations or research demonstrating efficacy.[3,4] Because of its frequent adverse effects, high cost and limited availability, some interventions have been employed to ensure appropriate IVIG use, yet Canada still remains the highest per capita user.[5]

In an attempt to limit inappropriate use, the Ontario Ministry of Health and Long-Term Care (MOHLTC) introduced an IVIG Request Form in September 2010 (see Appendix 1). This initiative requires physicians to complete and submit the form to their transfusion medicine department prior to the first dose of IVIG being issued and to resubmit the form every six months for reassessment of ongoing use. The dosage of IVIG must also be adjusted for ideal body weight with a dosing calculator prior to releasing the product.

The introduction of the Request Form has not impacted the continually rising use of IVIG. One reason for this may be that a prescriber can select any of the approved medical conditions for intended IVIG use without being required to demonstrate that the patient meets criteria for diagnosis of the medical condition or for the indication for IVIG use in that condition (Appendix 1). When an indication is not listed on the form, it is classified as “other” and the Request Form is to be reviewed initially by transfusion medicine technical staff then approved by the medical director (when available). This often does not occur or occurs after the IVIG has been administered. In contrast, most drug approval and reimbursement processes require a minimum amount of medical information prior to authorization and many require evidence of benefit for ongoing use. Unlike other drugs associated with the potential for harm and high cost, these principles have not yet been applied to IVIG.

In this study, a retrospective, structured audit in four Ontario hospitals was performed to determine the case mix of new IVIG requests, to authenticate the information provided on the forms, and to determine if clinical efficacy of IVIG treatment was documented.

The methodology and results are included in this report.

5.0 Methodology

5.1 Study Design

A retrospective study was performed at four tertiary care hospitals in Ontario. Research Ethics Board approval was obtained for each of the participating sites, and the study was funded by ORBCoN.

5.2 Patients

Patients were eligible for the study if they met the following inclusion criteria: adult patients (≥18 years); had a new request for IVIG between January 2014 to December 2014 (first time user); and, received at least one infusion of IVIG within six months of the request form being completed. Patients with previous IVIG use were excluded as it was felt that clinical efficacy would be better assessed in patients receiving their first IVIG treatment(s). Consecutive eligible patients were included to avoid selection bias. In the Hamilton hospitals (3 sites), patients who received IVIG during the study period were identified using a local research database (the Transfusion Registry for Utilization Statistics and Tracking) and eligibility was confirmed by reviewing the IVIG Request Forms. At Sunnybrook Health Sciences, eligible patients were identified by reviewing the IVIG Request Forms. Approximately 50 patients from each site were chosen as a convenience sample.

5.3 Data Collection and Management

Data were abstracted from three sources. The IVIG Request Form contained patient demographic data, the ordering physician's specialty, the dose requested, whether a dose calculator was used, whether or not the dose was verified, and the indication for IVIG use. Transfusion laboratory records included the actual dose of IVIG transfused, evidence of a dose calculator being used (a copy of the dose calculator was printed and attached), whether the dose was adjusted after a discrepancy with the dose calculator, and the dates of infusion. Manual chart reviews were used to determine if patients had other medical comorbidities, therapies concurrent with and/or prior to IVIG administration, whether diagnostic criteria for the medical condition requiring IVIG were documented, whether the patient met criteria for IVIG use, and to identify reports of improvement to assess clinical efficacy. A validation exercise was performed prior to commencement of the chart review to ensure that there was accuracy and consistency between data abstractors (A.W.S., E.J, Y.L., C.A., J.D., N.S., C.M.H.). The information collected on the case report forms was entered into a web-based SQL database that was based on a database architecture from a previous audit.[4] The database was designed with built-in discrepancy checks to detect potential errors in data entry.

5.4 Diagnostic Criteria for Medical Conditions Requiring IVIG and Criteria for Utilization of IVIG

The list of conditions for which IVIG is indicated (and listed on the Request Form) and potentially indicated (but not on the Request Form) was adapted from Canadian guidelines as seen in Table 1. These guidelines were developed after a systematic, multidisciplinary review of the literature.[6] Where available, diagnostic criteria for each medical condition were taken from published guidelines. Diagnostic criteria were not evaluated for medical conditions in which IVIG had not been previously studied or recommended for use. Criteria for determining whether or not indications for IVIG treatment were present were taken from Canadian guidelines.[6]

Table 1: Indications for IVIG on Request Form and Canadian Guidelines

Speciality	Condition	IVIG Response Expected Acutely or Chronically	Guidelines Referenced For Diagnostic Criteria and Recommended Criteria for IVIG
Conditions Indicated on IVIG Request Form and Canadian Guidelines			
Hematology	Fetal/Neonatal Alloimmune Thrombocytopenia	Chronic	[19]
	Hemolytic Disease of the Fetus and Newborn	Chronic	[19]
	Immune Thrombocytopenic Purpura (ITP)	Acute	[19,26]
	Post-Transfusion Purpura	Acute	[1,19]
Neurology	Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	Chronic	[8,33,34]
	Guillain-Barre Syndrome (GBS)	Acute	[7,8,35]
	Multifocal Motor Neuropathy (MMN)	Chronic	[8,36,37]
	Myasthenia Gravis (MG)	Acute	[8,38]
Dermatology	Dermatomyositis	Chronic	[1,8,39]
	Pemphigus Vulgaris (PV) and Variants	Chronic	[39,40]
Rheumatology	Juvenile Dermatomyositis	Chronic	[8]
	Kawasaki Disease	Acute	[39]
Infectious Diseases	Staphylococcal Toxic Shock	Acute	[1,39,40]
	Invasive Group Streptococcal Fasciitis With Associated Toxic Shock	Acute	[1,39,40]
Immunology	Primary Immune Deficiency (PID) and Secondary Immune Deficiency (SID)	Chronic	[39,41]
	Hematopoietic Stem Cell Transplant In Primary Immunodeficiencies	Chronic	[39,41]
Solid Organ Transplantation	Acute Antibody Mediated Rejection In Patients Who have Received Living Donor/Deceased Kidney Donor Transplant	Chronic	[1,22]
	Kidney Transplant From Living Donor To Whom The Patient Is Sensitized	Chronic	[1,22]
Conditions Indicated Only On Canadian Guidelines[6]			
Specialty	Condition	Specialty	Condition
Hematology	Acquired Hemophilia	Neurology	Acute Disseminated Encephalomyelitis (ADEM)
	Acquired Red Cell Aplasia		Lambert-Eaton Myasthenic Syndrome (LEMS)
	Acquired von Willebrand's Disease		Multiple Sclerosis (MS)
	Allogeneic Bone Marrow or Stem Cell Transplantation		Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections (PANDAS)
	Autoimmune Hemolytic Anemia		Polymyositis
	Autoimmune Neutropenia		Rasmussen's Encephalitis
	Hemolytic Transfusion Reaction		Stiff Person's Syndrome
	Hemolytic Transfusion Reaction In Sickle Cell Disease	Dermatology	Toxic Epidermal Necrolysis/Stevens-Johnson Syndrome
	Hemolytic Uremic Syndrome (HUS) and Thrombotic Thrombocytopenic Purpura (TTP)	Solid Organ Transplantation	Kidney Transplantation With Donor-Specific Antibodies In Recipient
	Virus Associated Hemophagocytic Syndrome		

5.5 Reports of Improvement to Assess Efficacy

After administration of IVIG, clinical notes were reviewed for up to six months after first administration if given as an outpatient; or until discharge for inpatients. Notes were assessed for both subjective (for example, the patient noting an improvement in symptoms) and objective documentation of improvement (including physical exam findings and improvements in assessment scores). Laboratory results and diagnostic imaging relevant to the medical condition for which IVIG was given were also assessed for up to six months after first administration of IVIG. All reports of improvement were analyzed independently by physicians involved in the study and trained delegates (A.W.S., E.J., Y.L., C.A., J.D., C.M.H.). These reports were categorized as improved, stable, worsened, mixed, or not recorded.

5.6 Data Analysis

A descriptive analysis was performed by specialty and for the overall cohort. Regardless of specialty, patients receiving IVIG for an indication not listed on the Request Form (designated as "Other") were analyzed separately in two categories: a condition in which IVIG is potentially indicated according to guidelines (Table 1) or a condition for which IVIG is not indicated according to guidelines.

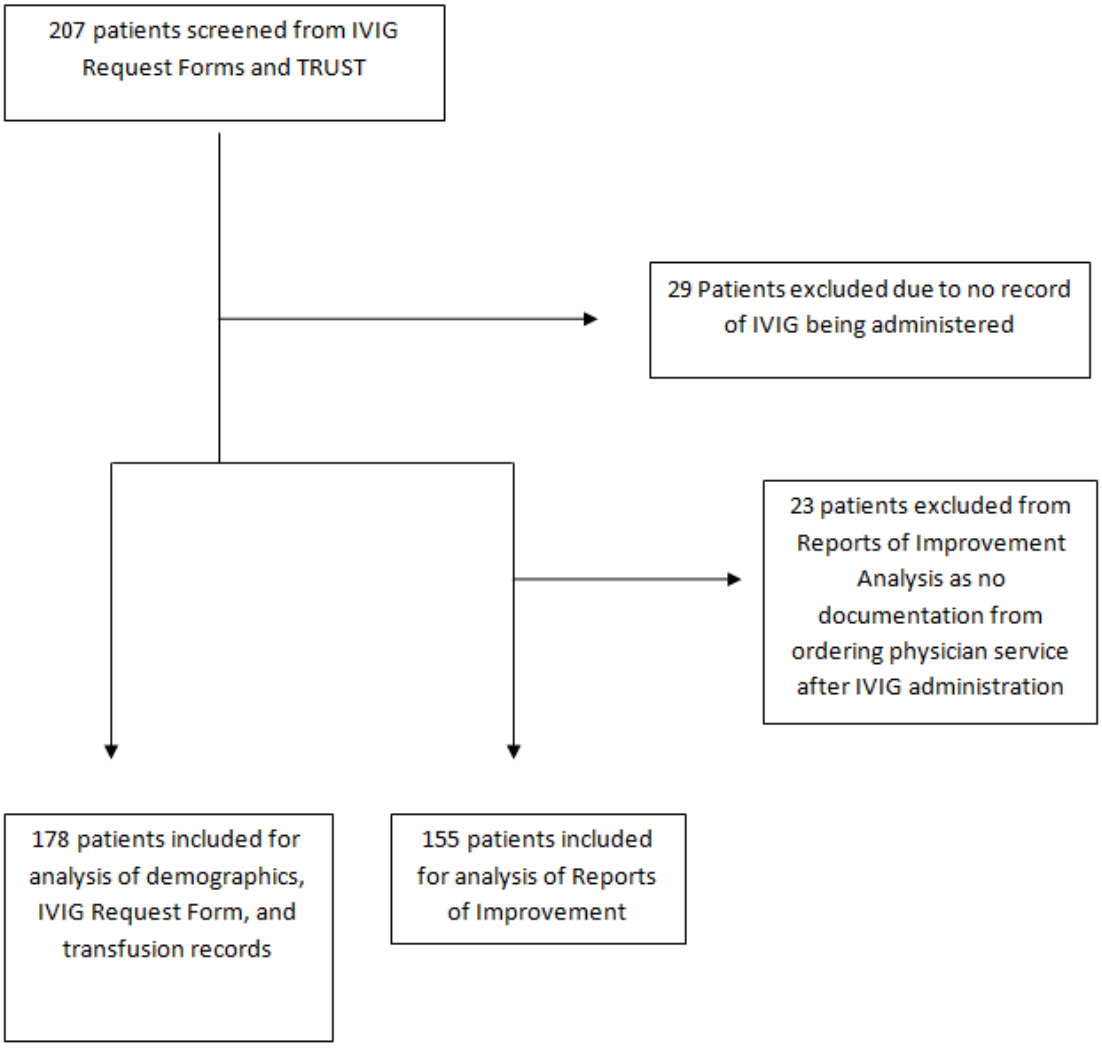
Reports of improvement were analysed by individual patient and not infusion episode, to ensure that patients with multiple reports of improvement contributed equal weighting to those who had fewer reports of improvement. Thus, a patient with multiple episodes of improvement after infusions of IVIG would have shown efficacy equally to someone who had a single infusion of IVIG with one episode of improvement. Patients who did not have any clinical documentation or records after IVIG administration by the physician service who prescribed the IVIG were excluded for the reports of improvement analysis. Pre-specified subgroup analyses included patients meeting and not meeting diagnostic criteria for the medical condition for which IVIG was used, patients meeting and not meeting criteria for IVIG use, patients who had completed IVIG therapy or were continuing IVIG therapy, patients who were receiving or not receiving concurrent therapy, and for those with conditions in which IVIG was expected to be effective either acutely or over a chronic period (listed in Table 1). We also assessed all reports of improvement without averaging them per patient and performed subgroup analyses on reports from patients of hematologists, neurologists, and patients given IVIG for conditions not listed on the IVIG Request Form.

6.0 Results

6.1 Demographics

One hundred and seventy-eight patients were included (Figure 1). At 3 of the 4 sites we enrolled additional consecutive patients to replace any patients initially meeting inclusion criteria who became ineligible based on information obtained from chart review. The mean age of patients was 56.1 years (SD 17.4; 1st quartile: 42; 3rd quartile: 68; range: 18-90), 53% of patients were female, mean height was 167.7cm (SD 11.3; 1st quartile: 160; 3rd quartile: 175; range: 130-211) and mean weight was 79.7 kg (SD 20.7; 1st quartile: 66; 3rd quartile: 90.25; range: 44-160).

Figure 1: Study Flow Diagram

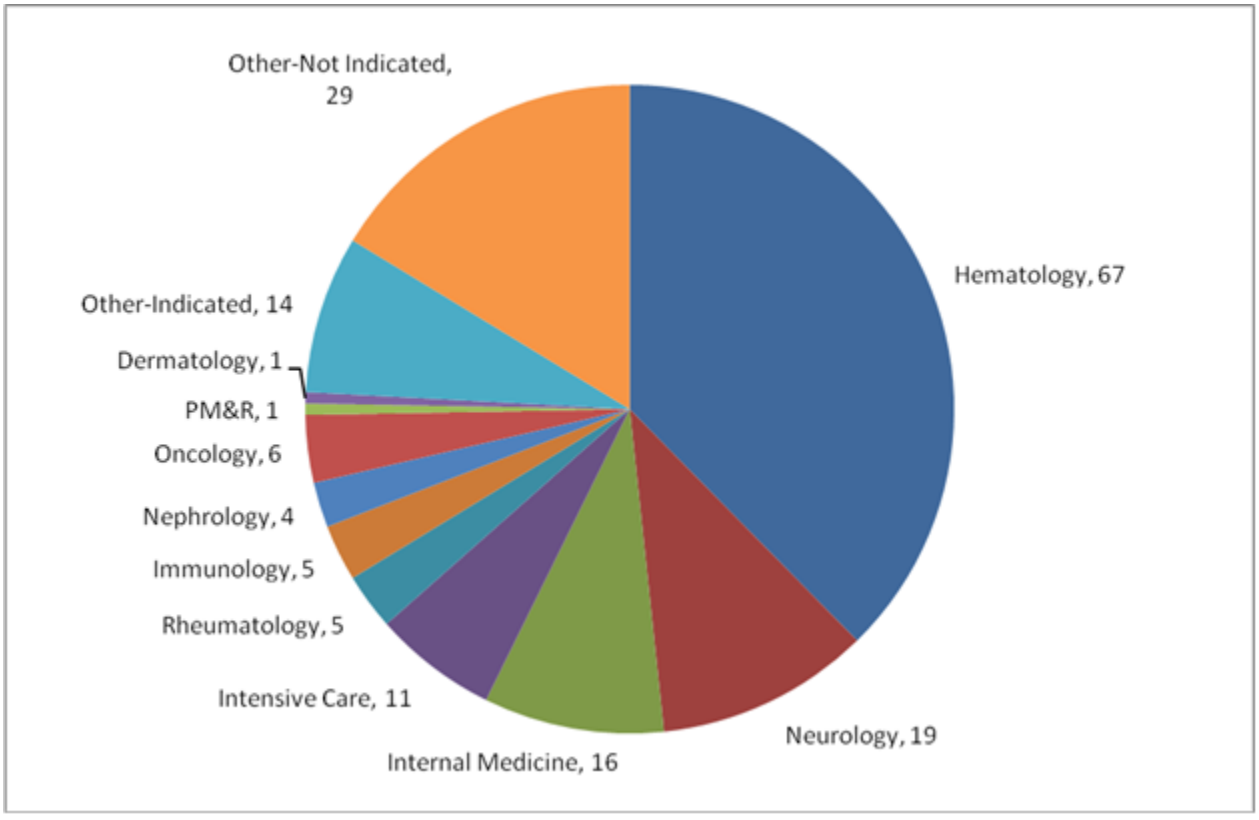


6.2 IVIG Request Form

6.2.1 Physician Speciality and Medical Condition

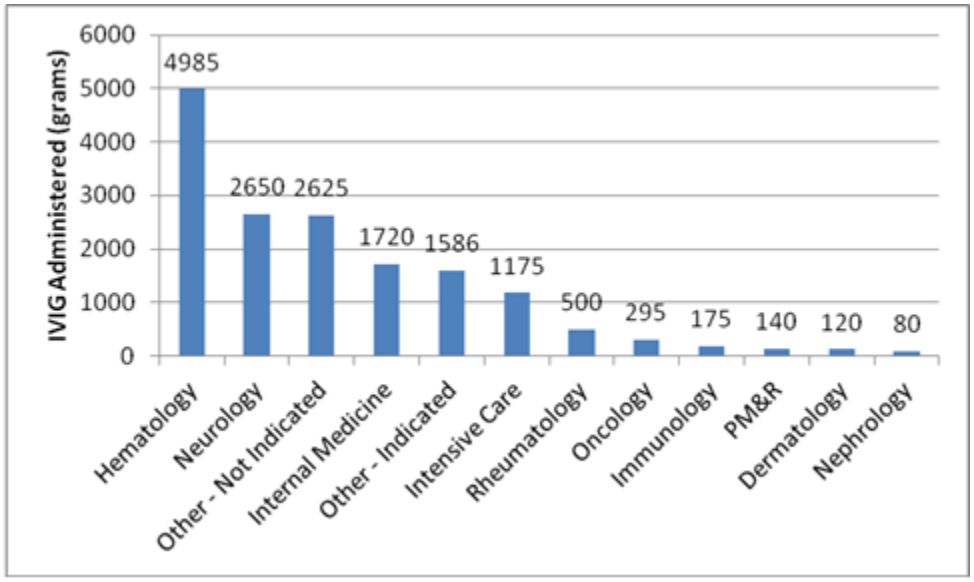
The most frequent prescribers of IVIG were hematologists (37.6%), followed by neurologists (10.7%) and internists (9.0%), as seen in Figures 2 and 3. The most common indications for IVIG included: other indications not listed on the IVIG Request Form (43/178 patients; 24.2%), immune thrombocytopenia (ITP; 37/178 patients; 20.8%), and secondary immune deficiencies (SID; 36/178 patients; 20.2%) as seen in Figure 4. The majority of the patients who received IVIG for other indications not listed on the form did not receive it for a condition indicated by Canadian evidence-based guidelines (29/43 patients; 67.4% of "other" indications; 16.2% (29/178) of all patients). ITP patients had the highest amount of IVIG administered in grams, followed by other indications not listed on the IVIG Request Form as a group, then Guillain-Barre Syndrome (Figure 5).

Figure 2: Physician Specialties of 178 New Requests for IVIG



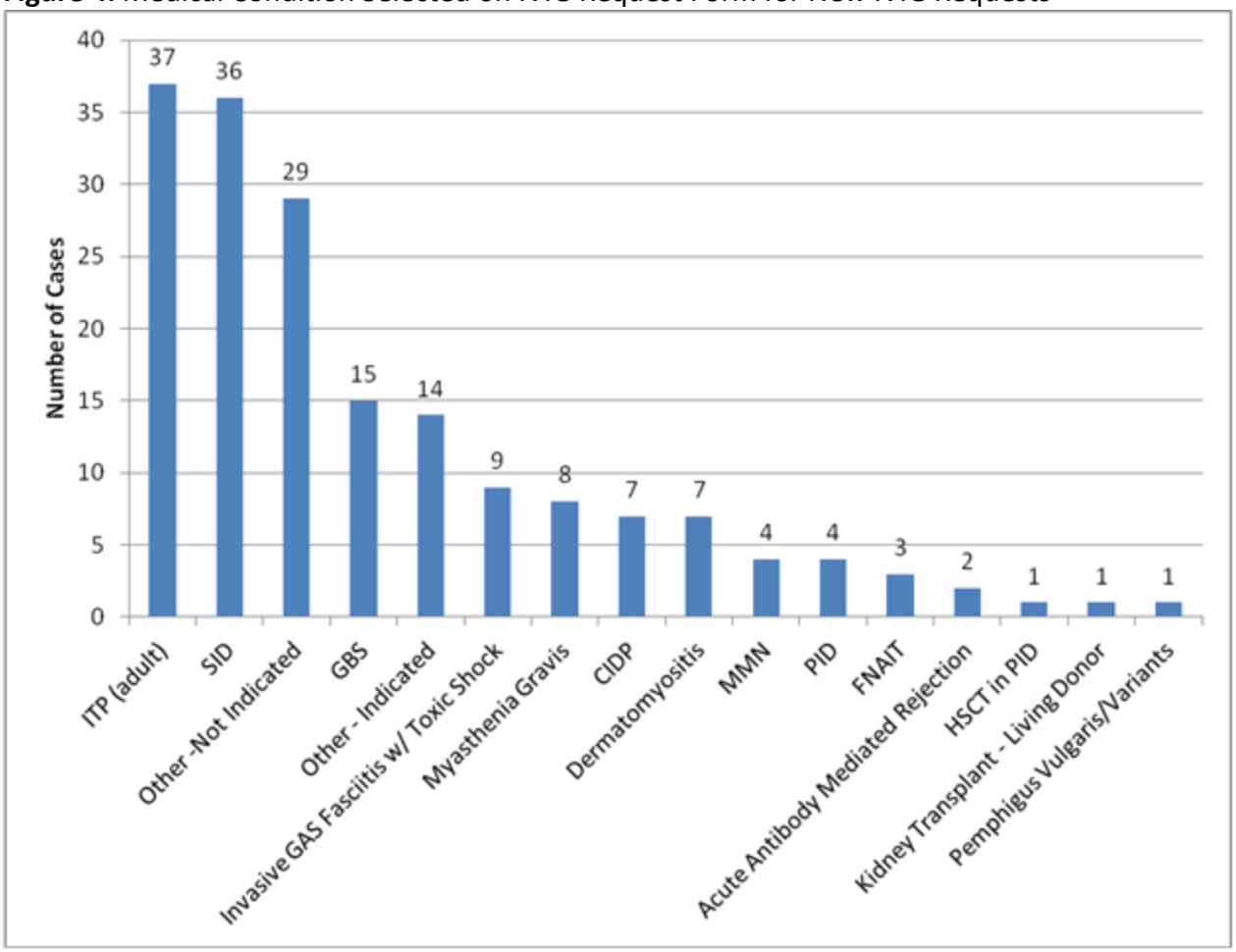
PM&R - Physical Medicine and Rehabilitation
Other - Indicated: Conditions not listed on the IVIG Request Form, but potentially indicated from Canadian evidence-based guidelines
Other - Not Indicated: Conditions not listed on the IVIG Request Form and not indicated from guidelines

Figure 3: IVIG (g) Administered by Specialty in 178 Cases



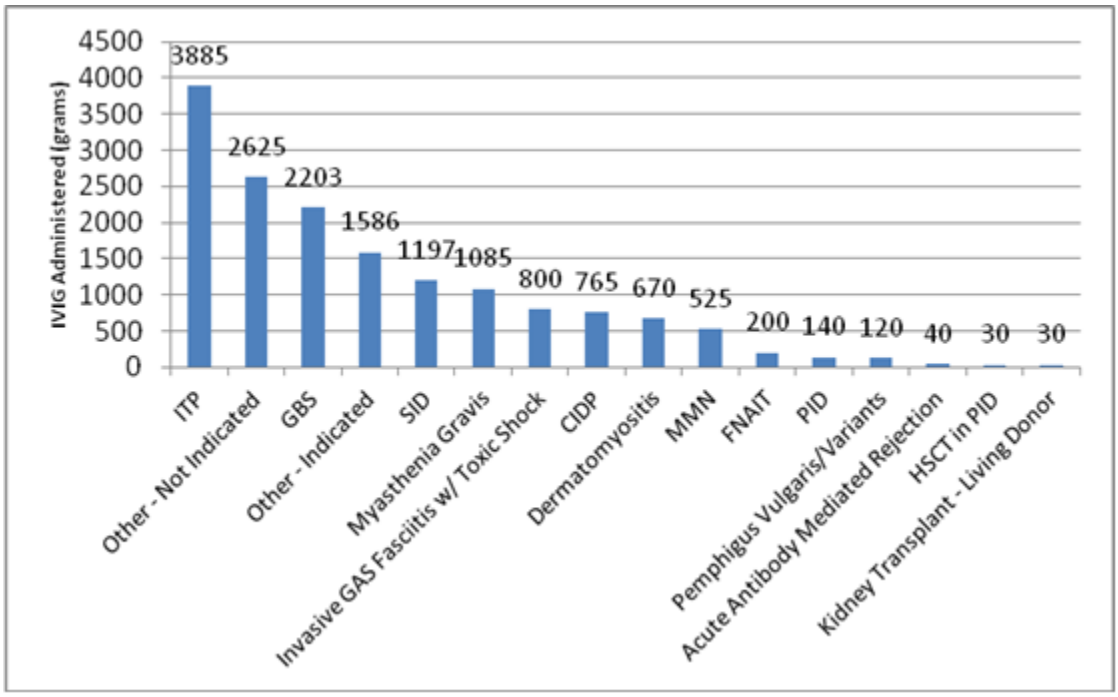
PM&R - Physical Medicine and Rehabilitation
Other - Indicated: Conditions not listed on the IVIG Request Form, but potentially indicated from Canadian evidence-based guidelines
Other - Not Indicated: Conditions not listed on the IVIG Request Form and not indicated from guidelines

Figure 4: Medical Condition Selected on IVIG Request Form for New IVIG Requests



ITP: Immune Thrombocytopenic Purpura, SID: Secondary Immune Deficiency, GBS: Guillain-Barre Syndrome, GAS: Group A Streptococcal, CIDP: Chronic Inflammatory Demyelinating Polyneuropathy, HSCT: Hematopoeitic Stem Cell Transplant, PID: Primary Immune Deficiency, MMN: Multifocal Motor Neuropathy, FNAIT: Fetal/Neonatal Alloimmune Thrombocytopenia

Figure 5: IVIG Administered (g) by Indication in 178 Cases

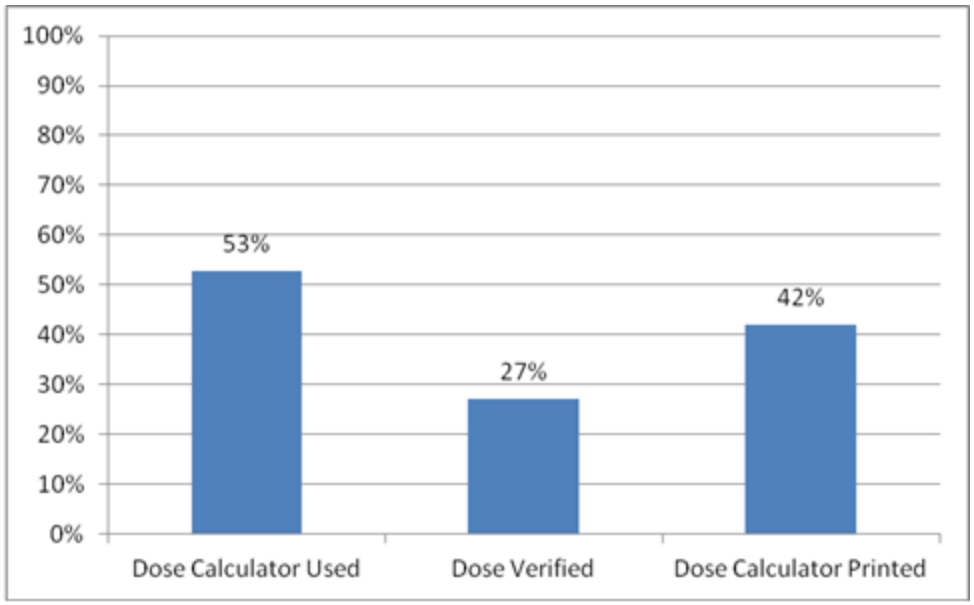


ITP: Immune Thrombocytopenic Purpura, SID: Secondary Immune Deficiency, GBS: Guillain-Barre Syndrome, GAS: Group A Streptococcal, CIDP: Chronic Inflammatory Demyelinating Polyneuropathy, HSCT: Hematopoeitic Stem Cell Transplant, PID: Primary Immune Deficiency, MMN: Multifocal Motor Neuropathy, FNAIT: Fetal/Neonatal Alloimmune Thrombocytopenia

6.2.2 Dose Calculator and Adjustment

According to information available on the Request Form, the dose calculator was not used for 84 cases (47.2%) and 130 cases (73.0%) did not have the dose verified (Figure 6). Documentation such as a printout of the dose calculator was provided for 59 (42%) cases. There were only two cases where a physician was clearly responsible for performing the dose calculation. Dose adjustment was performed for 34 cases (19.1%), with the majority of the cases having no documented reason for the adjustment found in the patient chart or IVIG Request Form.

Figure 6: Documentation of Compliance with IVIG Request Form

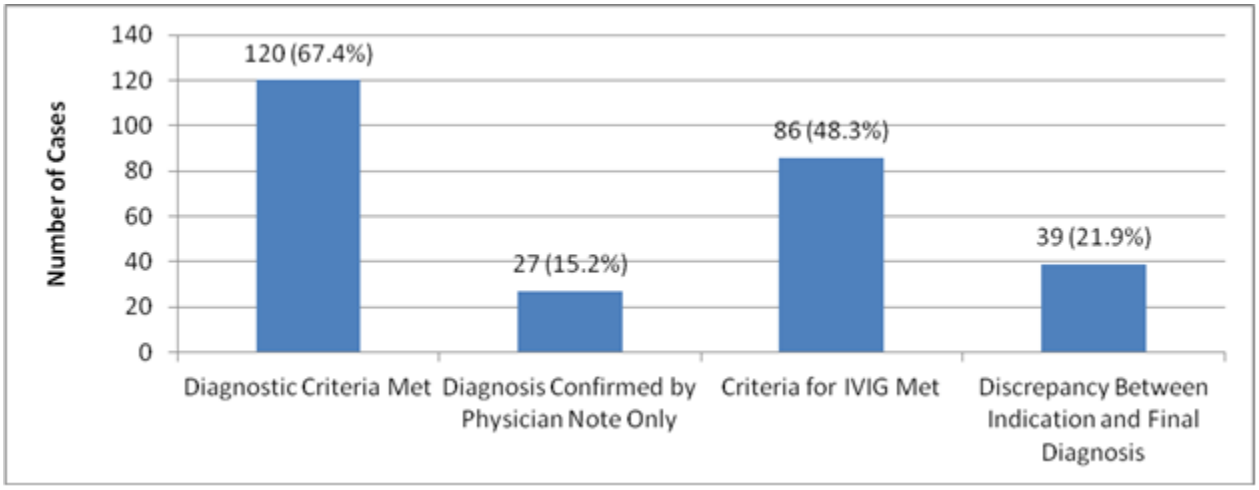


6.3 Chart Review

6.3.1 Patients meeting Diagnostic Criteria and Indications

Based on the chart review, 32.6% of patients did not have adequate documentation to confirm the diagnostic criteria for the medical condition for which IVIG was requested (Figure 7). 15.2% of patients' diagnoses were confirmed by the physician note alone thus did not have documentation of the patient meeting requirements for the diagnosis of the condition for which IVIG was requested. For example, the physician would state that the patient had Guillain-Barre Syndrome, but did not document the patient meeting NINDS Diagnostic Criteria.[7] Over half of patients (51.7%) did not meet criteria for IVIG use for the medical condition indicated on the request form. For example, in Guillain-Barre Syndrome, IVIG is only indicated when the disease is classified as greater than grade 2 severity or for progressive severity within two weeks of symptom onset.[8] Thirty-nine cases (21.9%) had a discrepancy between the indication written on the IVIG Request Form and the final diagnosis in the patient chart.

Figure 7: Number of Cases Meeting Diagnostic Criteria and Indications for IVIG in 178 Cases



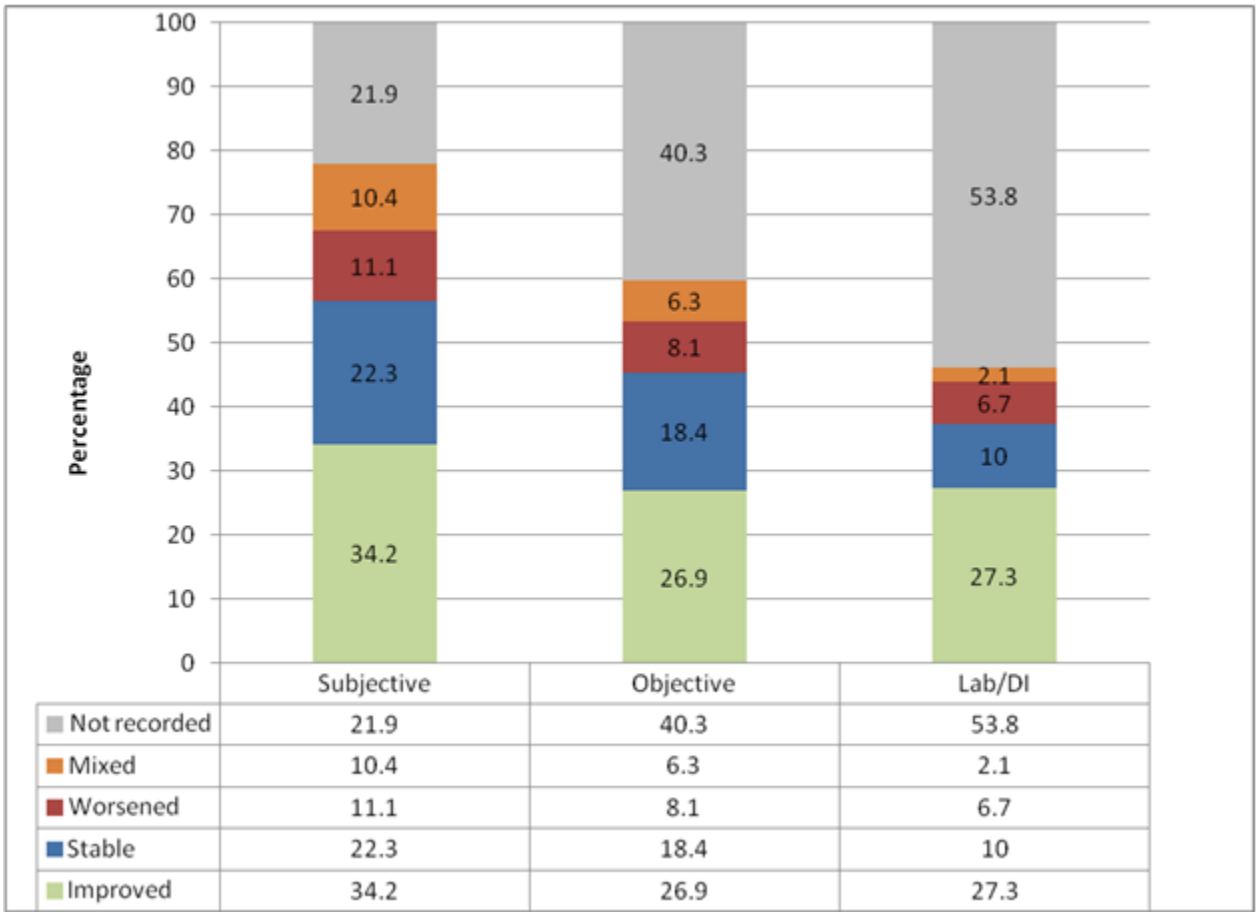
6.3.2 Improvement in Patients

In 155 evaluable patients, 331 reports were available to assess improvement within the six month period following the first administration of IVIG. It was found that 34% of clinical reports documented subjective improvement (Figure 8). Notably, 21.9% of patients reviewed did not have any documentation of efficacy after IVIG administration in the clinical record.

These findings were largely concordant across all subgroups, including patients for which IVIG was given for an indication not in Canadian guidelines (Figure 9), patients that did not meet diagnostic criteria for their condition, patients that did not meet criteria for IVIG administration (although had a medical condition in which IVIG may be used), and patients receiving concurrent therapy or not (see Supplementary Figures). For patients with conditions where IVIG is expected to work acutely, the documentation of improvement appeared to be better compared to conditions where IVIG is expected to be effective in a chronic setting (Figure 10).

When all 331 reports of improvement were considered per infusion, 26.0% of clinical reports documented subjective improvement and 18.7% of clinical reports did not record any mention of efficacy due to IVIG (Figure 11). Reports of improvement from hematologists had higher proportions of clinical records demonstrating laboratory improvement while neurologists had higher proportions of clinical records demonstrating subjective improvement (see Supplementary Figures).

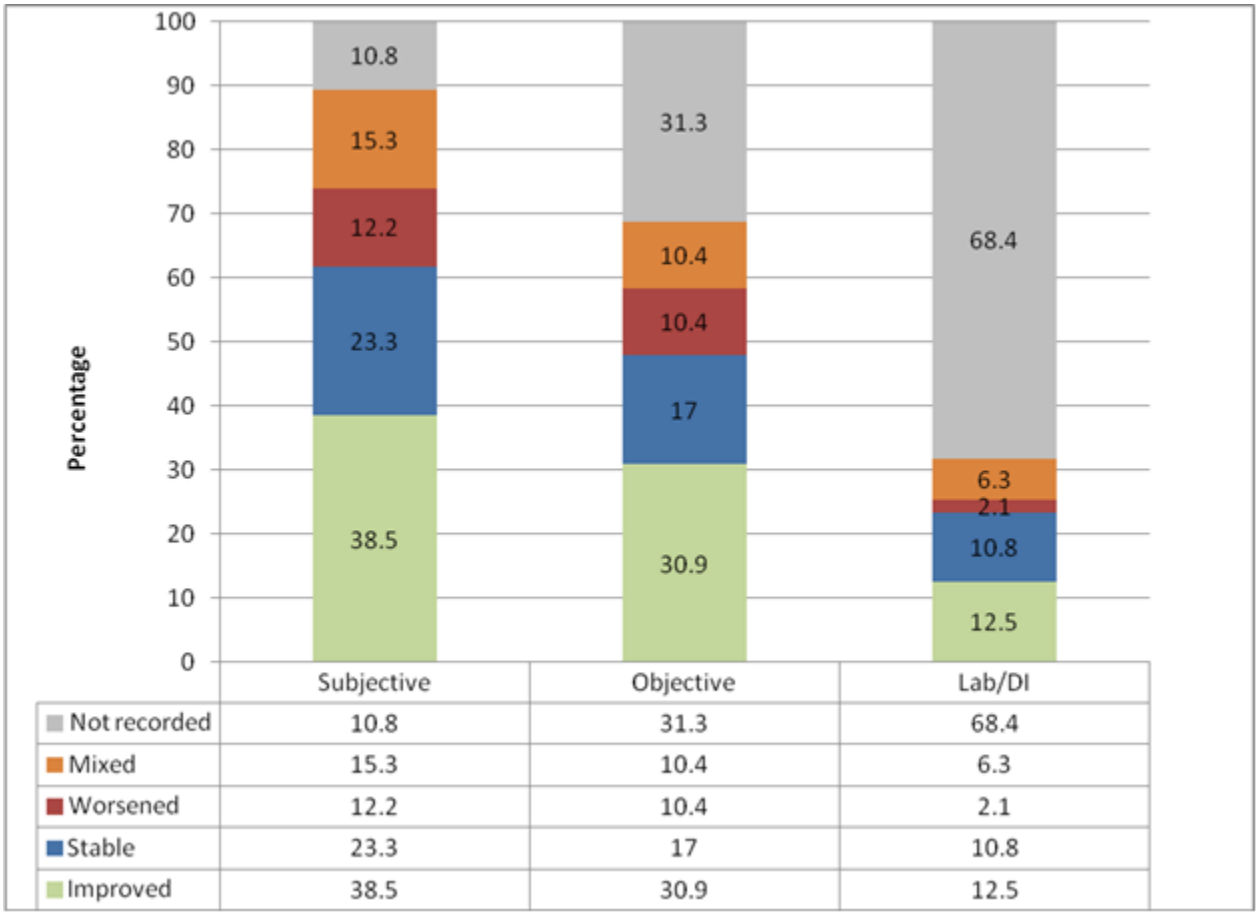
Figure 8: Reports of Improvement in Overall Patient Cohort (Averaged for Each Patient)



	Subjective	Objective	Lab/DI
Not recorded	21.9	40.3	53.8
Mixed	10.4	6.3	2.1
Worsened	11.1	8.1	6.7
Stable	22.3	18.4	10
Improved	34.2	26.9	27.3

Lab: Laboratory Results, DI: Diagnostic Imaging

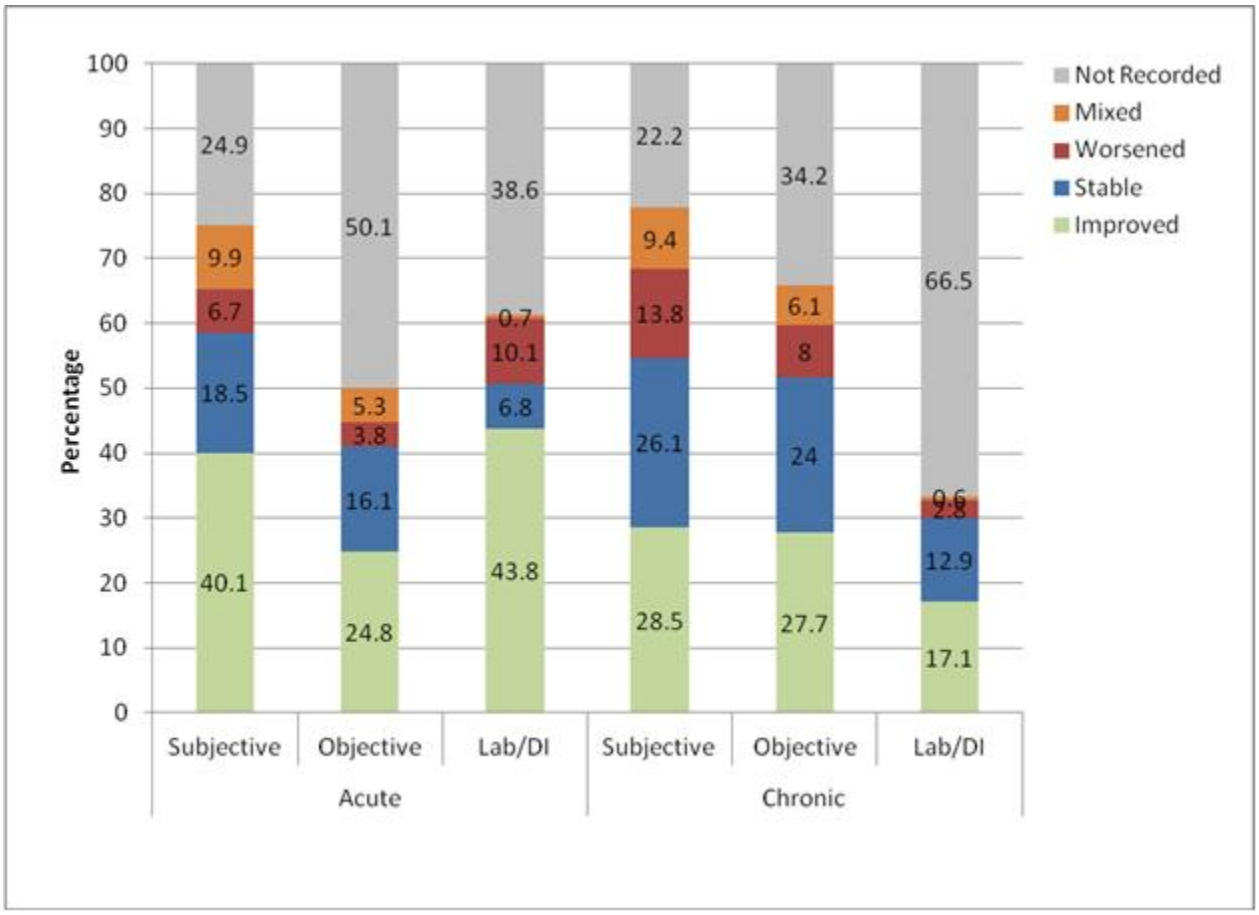
Figure 9: Reports of Improvement in Patients Receiving IVIG for Conditions Not Supported by Canadian Guidelines (Averaged For Each Patient)



	Subjective	Objective	Lab/DI
Not recorded	10.8	31.3	68.4
Mixed	15.3	10.4	6.3
Worsened	12.2	10.4	2.1
Stable	23.3	17	10.8
Improved	38.5	30.9	12.5

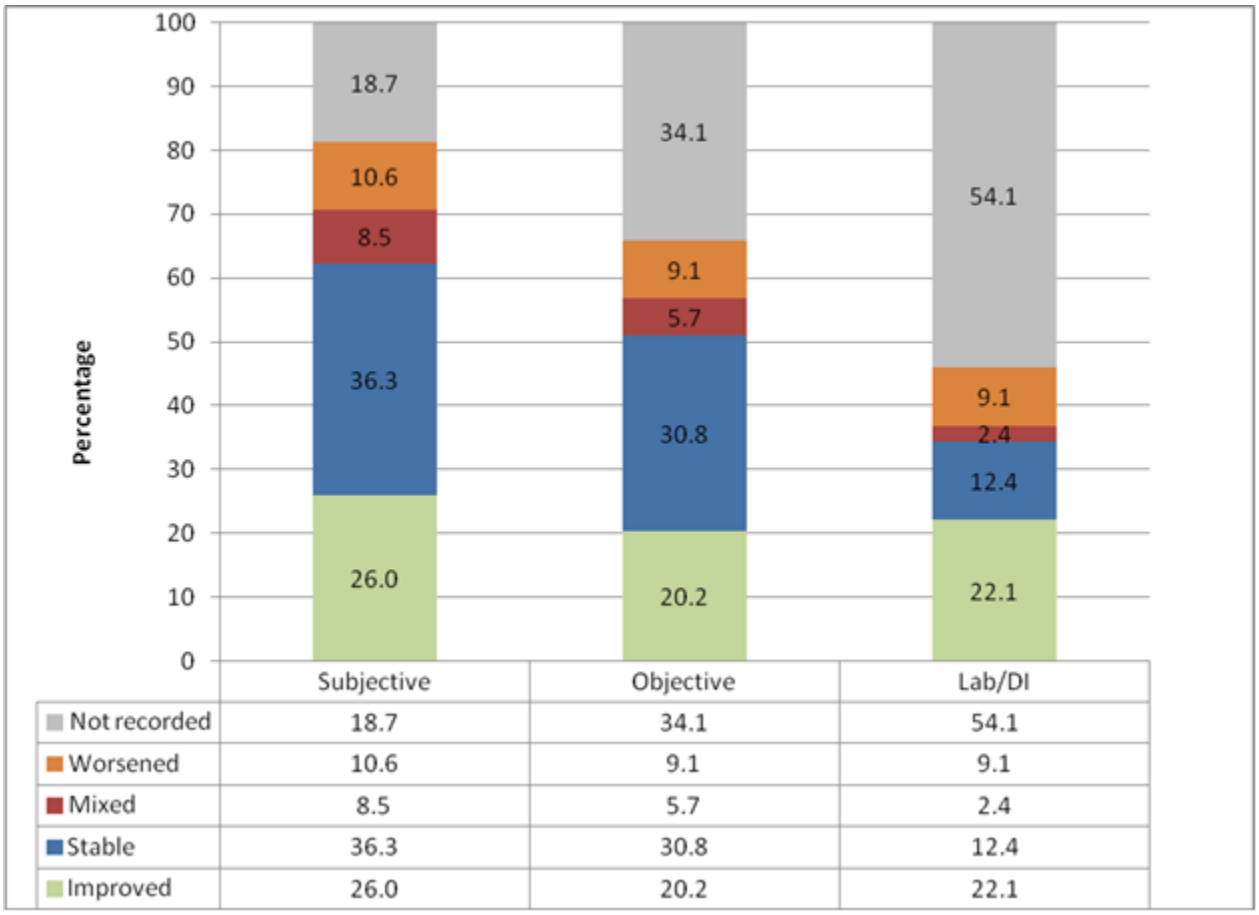
Lab: Laboratory Results, DI: Diagnostic Imaging

Figure 10: Reports of Improvement Following IVIG Administration in Patients Receiving IVIG for Indications Where IVIG Is Expected To Be Effective Acutely and Chronically (Averaged For Each Patient)



Lab: Laboratory Results, DI: Diagnostic Imaging

Figure 11: Reports of Improvement in Overall Patient Cohort (Not Averaged for Each Patient)



	Subjective	Objective	Lab/DI
Not recorded	18.7	34.1	54.1
Worsened	10.6	9.1	9.1
Mixed	8.5	5.7	2.4
Stable	36.3	30.8	12.4
Improved	26.0	20.2	22.1

7.0 Limitations of the Audit Results and Analysis

The limitations of this study pertain to its retrospective nature. This study could only assess the documentation of efficacy and reports of improvement that were explicit in clinical records, which are not necessarily representative of the actual efficacy of IVIG. This could be done more appropriately using standardized tools in a prospective fashion. Similarly, adjudication of appropriateness of IVIG could only be assessed by explicit documentation in clinical records or laboratory findings. Guideline recommendations derived from studies of lower methodological quality may not be a suitable standard for the appropriateness of IVIG and do not take into account individual patient circumstances that may make the utilization of IVIG suitable. However, accountability to the best standard of practice based on available evidence and the proper documentation of efficacy is generally accepted to be the standard for most therapies that are associated with high expense and potential adverse effects. By assessing only new requests for IVIG, this audit cannot provide insight on patients with on-going requests for IVIG.

8.0 Overall Findings and Recommendations

Immunoglobulins are a key mediator of adaptive immunity and deficiencies lead to increased susceptibility to infection. IVIG was developed to replace immunoglobulins in PID, but additional immunomodulatory effects have subsequently been discovered.[9] Despite efficacy in few conditions proven in randomized controlled trials,[10-14] benefit in the majority of conditions in which IVIG is used is less robust, with evidence being derived from studies of lower methodological rigor such as case reports or case-control studies.[3] While it is often trialled in disorders for which there is an immunological basis, many uncertainties remain regarding the mechanism of immunomodulation, making it difficult to identify conditions where IVIG could be effective.[15] Hence, patients are put at risk for adverse events, including fever, thrombosis, aseptic meningitis, and hemolysis without evidence for potential benefit.[16,17]

Rising IVIG expenditures have led to audits of its use,[2,18] evidence-based guidelines to inform appropriate usage,[8,19-22] and utilization control programs.[23-25] For example, ORBCoN created the Ontario IVIG Advisory Panel which subsequently developed the IVIG Utilization Management Strategy, which included consolidated guidelines and the introduction of the IVIG Request Form.[6] This form was developed to allow screening of IVIG requests at the hospital level, but no policy to regulate IVIG has been implemented nor had a formal audit incorporating the information from these forms previously been done. Thus, this retrospective audit served three objectives: to determine the case mix for new IVIG requests at four Ontario tertiary care centres, to authenticate the information provided on the request forms, and to assess the documentation of clinical efficacy of IVIG in previously untreated patients.

Our study demonstrates that the highest prescribers of IVIG in the four Ontario centres audited specialized in hematology or neurology. The medical conditions that were most often listed as indications for IVIG included ITP, SID (mostly from hematological conditions), and neuromuscular and neuropathic diseases. While the case mix represented is consistent with the licensed indications of IVIG by Health Canada (PID, SID, ITP, pediatric HIV infection, and Kawasaki Disease), the category of "other" indications represented the highest number of patients compared to any single listed indication for IVIG. Even in conditions for which IVIG is licensed, indications for IVIG are narrow in scope. For example, in ITP, evidence-based guidelines suggest corticosteroids as first line treatment and treatment with IVIG only if the patient is severely thrombocytopenic (platelet count ≤20-30 x 10^9/L) and a more rapid increase in platelet count is required (such as symptomatic bleeding), or when corticosteroids are contraindicated.[26,27] SID due to chronic lymphocytic leukemia acts as the archetypal disorder for which IVIG is used to reduce clinically documented infections by increasing immunoglobulin levels,[12,28,29] but it has not been associated with an improvement in quality of life or survival, which narrows its scope of use to select patients.[28] The high number of requests for IVIG use in conditions not recommended on the form suggests a potentially high amount of inappropriate use in disorders with limited evidence of benefit. Higher quality studies are needed in these conditions to further clarify the role of IVIG as a treatment strategy.

The IVIG Utilization Management Strategy recommends a dose calculator be used to ensure ideal body weight dosing in obese patients and that the dose be verified by a laboratory technologist or a physician managing the transfusion medicine laboratory. Given that IVIG has little distribution in fat, failing to dose according to ideal body weight may lead to dosages in obese patients that are higher than those studied.[5,30] Evidence is not conclusive as to whether this relative increase in dosage affects efficacy, but this phenomenon has been implicated in reports of adverse effects.[31] There was evidence that a dose calculator was used in less than half of new IVIG requests and the dose was verified in slightly over a quarter of requests, this is concerning for the safety of patients treated with IVIG and for stewardship of a costly therapy.

The chart review was conducted using diagnostic criteria developed *a priori* from guidelines and demonstrated a significant number of cases where the veracity of a diagnosis could not be confirmed using available documentation. In some of these cases, the diagnosis was only confirmed by a physician's note (ie. the physician stated the patient had the condition, but no further information was available to confirm the diagnostic criteria were met), or there was a discrepancy between the indication listed on the IVIG Request Form and the physician's diagnosis in the chart. A significant proportion of cases where the diagnostic criteria were met for an indicated condition did not meet the criteria for IVIG use in that condition. Previous audits done in the province of Ontario showed that the vast majority of IVIG use was appropriate, but only assessed the indication on the completed IVIG Request Form.[4] This audit,

supplemented with thorough chart review, suggests that documentation in medical records does not support this contention. Additionally, the practices described in this audit fall well below what is required in approval processes set by regulatory bodies for other therapeutic drugs.[32] While IVIG is currently similar to other blood products in that it lacks stringent approval processes for its use, parallels could instead be drawn between IVIG and other special access drugs that act as immune-modulators because of the high cost of the product and its associated demands on resources such as hospital infusion facilities.

Previous audits have not assessed the efficacy of IVIG, given the diversity of the conditions in which it is used. However, even when using minimal criteria for determining improvement such as a subjective report in a clinic note, only one third of reports showed improvement after IVIG administration. When more stringent criteria were applied, for example, requiring objective improvement to be noted on exam or based on diagnostic testing, findings were often not documented at all, or testing was not used appropriately to guide treatment. This is concerning as any drug should not only be monitored but also have ongoing assessments of efficacy to determine if the risks and costs of administration are worth the potential benefit. Documentation of efficacy was lower in conditions where IVIG is expected to be effective in a chronic setting, suggesting that improvement may be particularly difficult to assess in these conditions or that physician documentation practices may be deficient in this group of patients. Assessment of the efficacy of IVIG was difficult in this retrospective design, due to information and selection bias (only patients in tertiary care centres receiving IVIG for the first time) as well as confounding by other disease processes and treatments, and was further complicated by a lack of consistent documentation of response to IVIG treatment. Overall, this audit demonstrates a need for accountability of IVIG prescribers similar to other drug therapy access and reimbursement programs which require documentation of ongoing monitoring and benefit.

The findings of this study support the need for a comprehensive, evidence-based approval process to ensure that patients are protected from inappropriate use of IVIG. Not only are patients put at risk of adverse effects of IVIG, but ease of access to IVIG as a therapy may prevent patients from receiving more appropriate therapy which may be more difficult to obtain. A rigorous IVIG approval process that requires prescribers to justify its use and document ongoing efficacy may potentially be useful in ensuring appropriate IVIG utilization, reducing costs, and freeing up limited resources to be used elsewhere.

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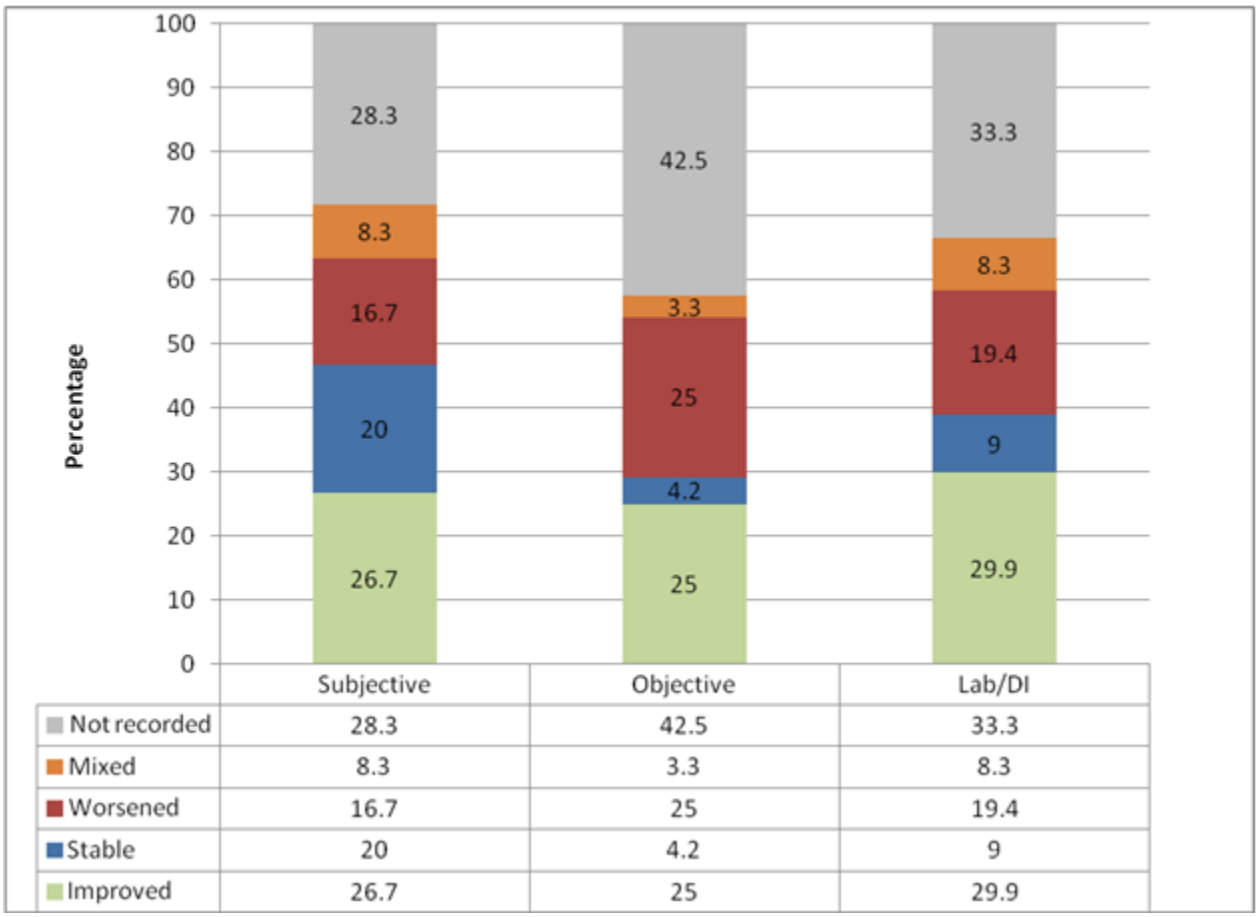
Supplementary Index: Audit of IVIG Indications and Effectiveness in Ontario Tertiary Care Centres

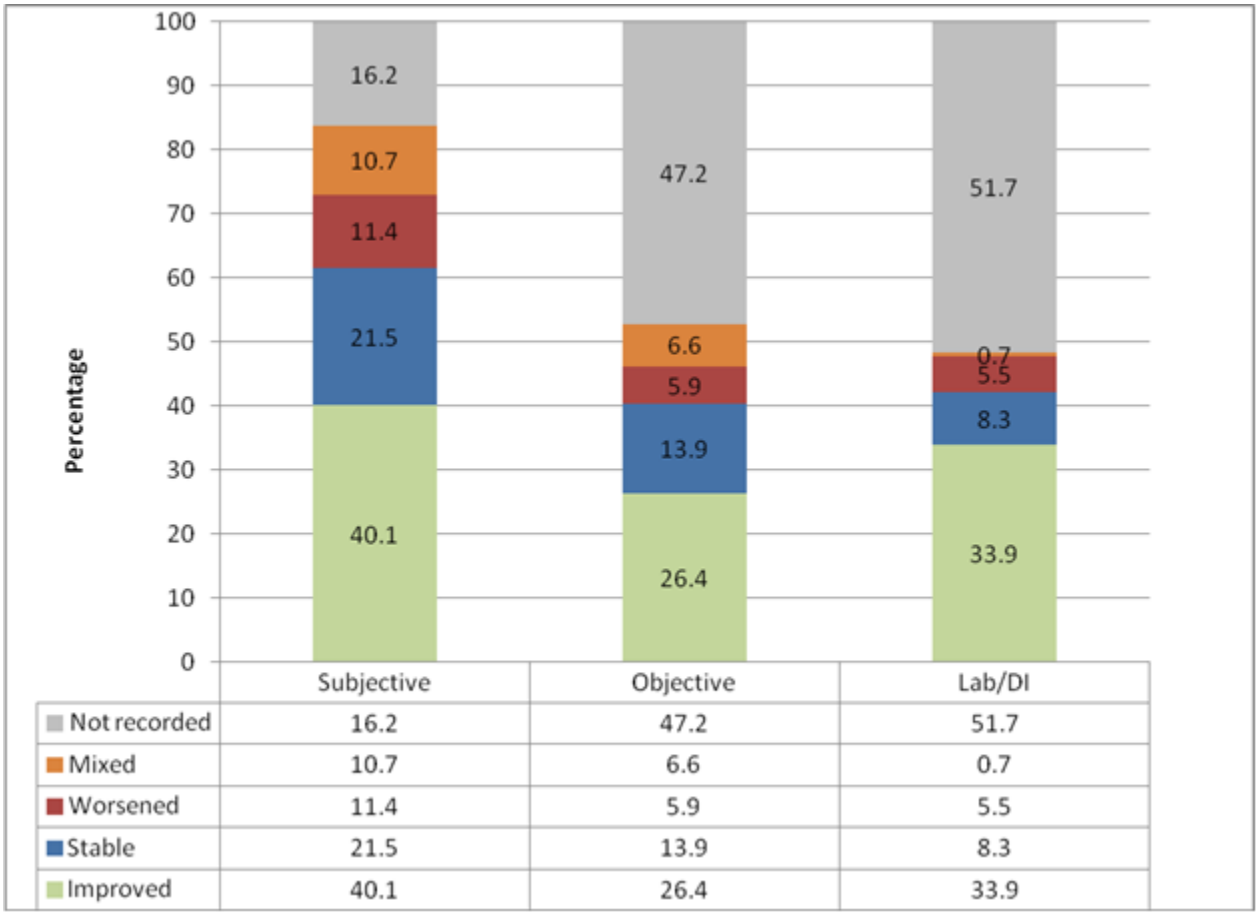
Supplementary Figure 1: Reports of Improvement in Patients Receiving IVIG for a Condition Indicated By Canadian Guidelines but Not on the Request Form (Averaged For Each Patient)



	Subjective	Objective	Lab/DI
Not recorded	28.3	42.5	33.3
Mixed	8.3	3.3	8.3
Worsened	16.7	25	19.4
Stable	20	4.2	9
Improved	26.7	25	29.9

Lab: Laboratory Results, DI: Diagnostic Imaging

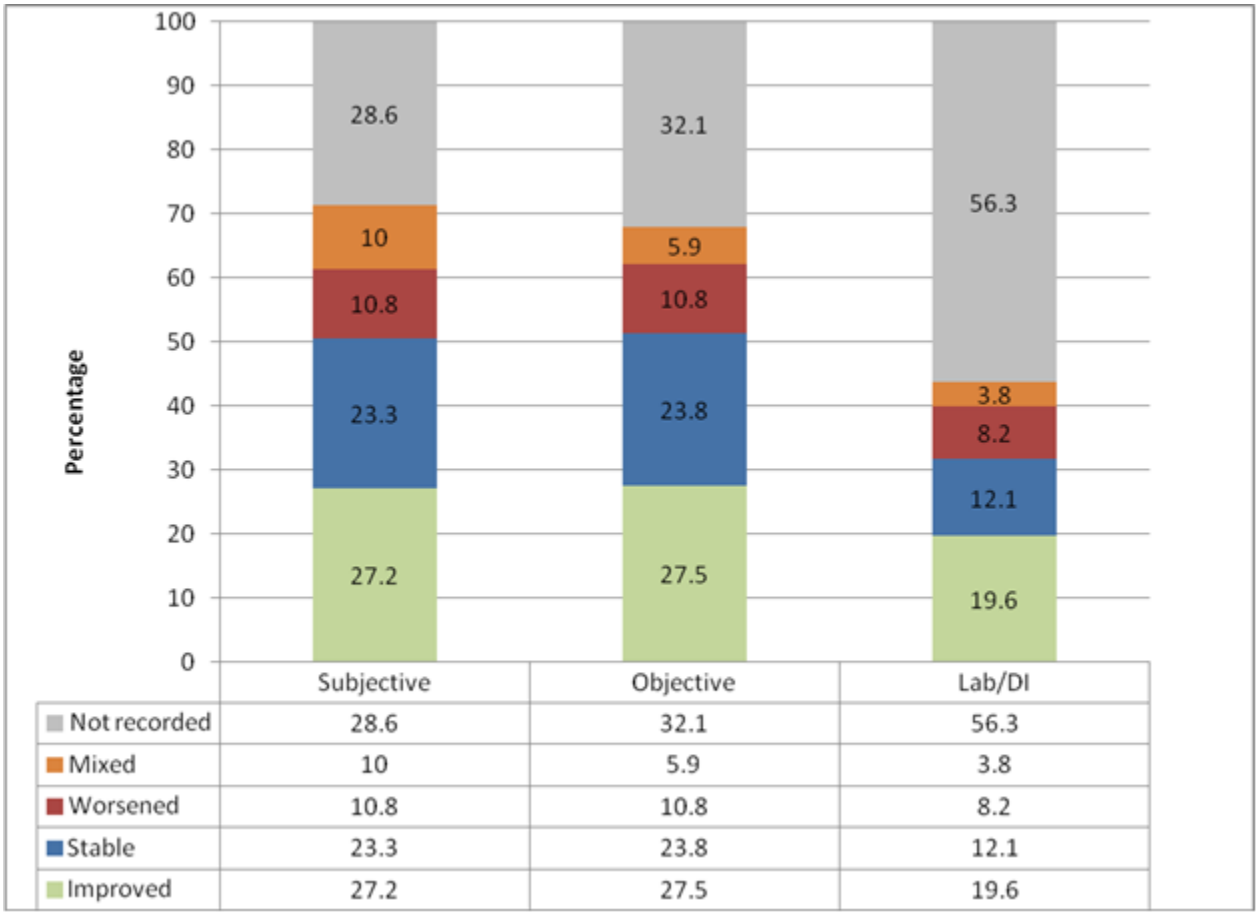
Supplementary Figure 2: Reports of Improvement in Patients For Which IVIG Administration Is Indicated by Canadian Guidelines (Averaged For Each Patient)



	Subjective	Objective	Lab/DI
Not recorded	16.2	47.2	51.7
Mixed	10.7	6.6	0.7
Worsened	11.4	5.9	5.5
Stable	21.5	13.9	8.3
Improved	40.1	26.4	33.9

Lab: Laboratory Results, DI: Diagnostic Imaging

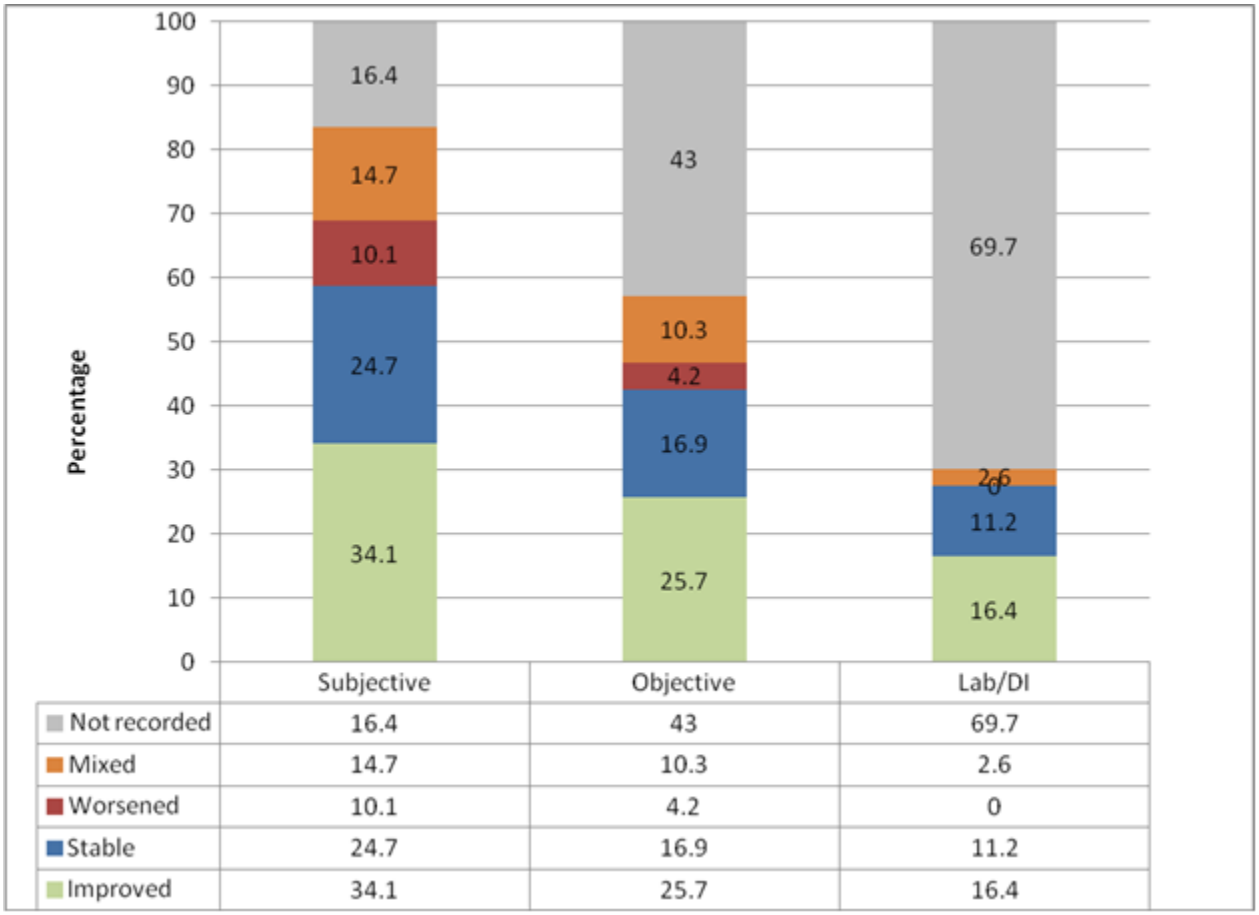
Supplementary Figure 3: Reports of Improvement in Patients For Which IVIG Administration Is Not Indicated by Canadian Guidelines (Averaged For Each Patient)



	Subjective	Objective	Lab/DI
Not recorded	28.6	32.1	56.3
Mixed	10	5.9	3.8
Worsened	10.8	10.8	8.2
Stable	23.3	23.8	12.1
Improved	27.2	27.5	19.6

Lab: Laboratory Results, DI: Diagnostic Imaging

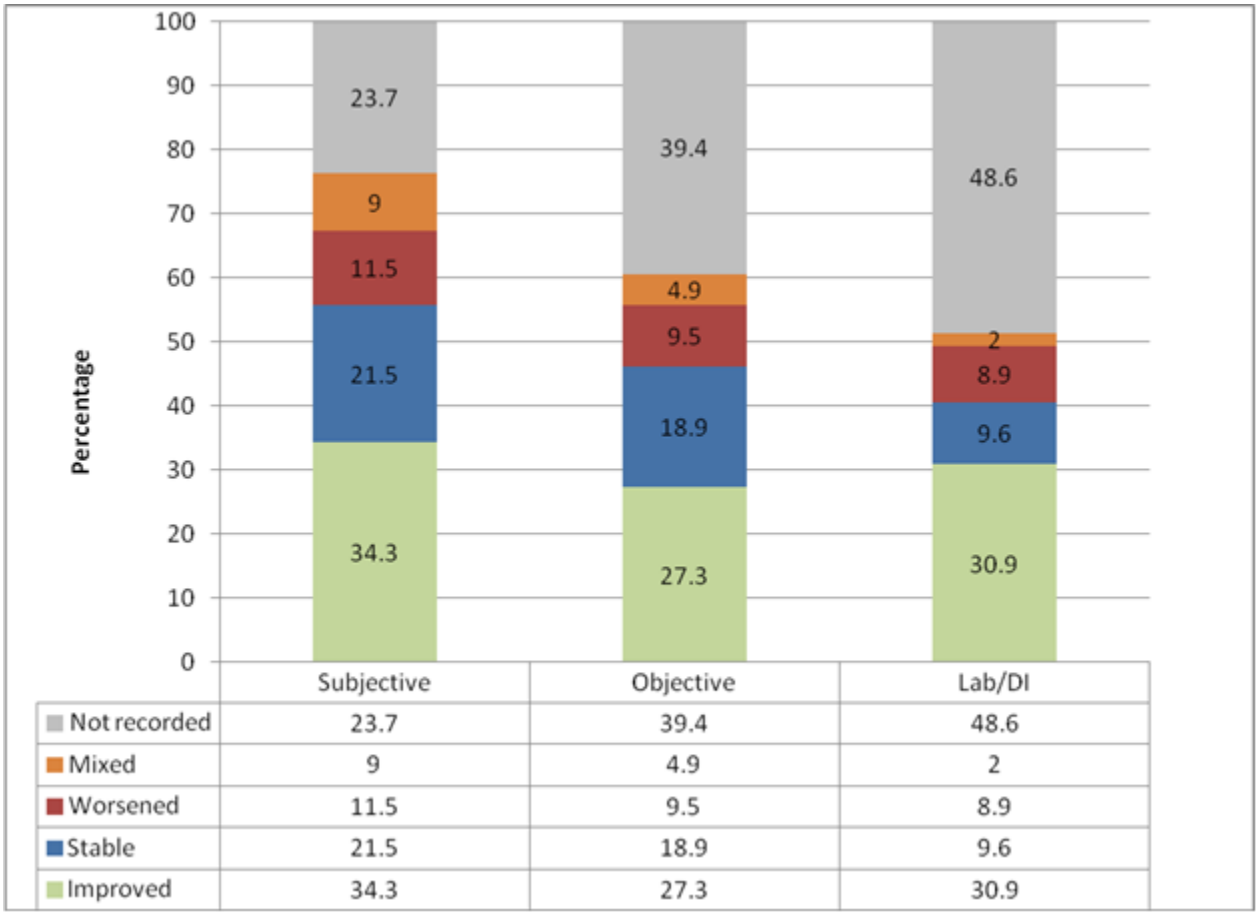
Supplementary Figure 4: Reports of Improvement in Patients Not Meeting Diagnostic Criteria for Conditions Where IVIG Is Used (Averaged For Each Patient)



	Subjective	Objective	Lab/DI
Not recorded	16.4	43	69.7
Mixed	14.7	10.3	2.6
Worsened	10.1	4.2	0
Stable	24.7	16.9	11.2
Improved	34.1	25.7	16.4

Lab: Laboratory Results, DI: Diagnostic Imaging

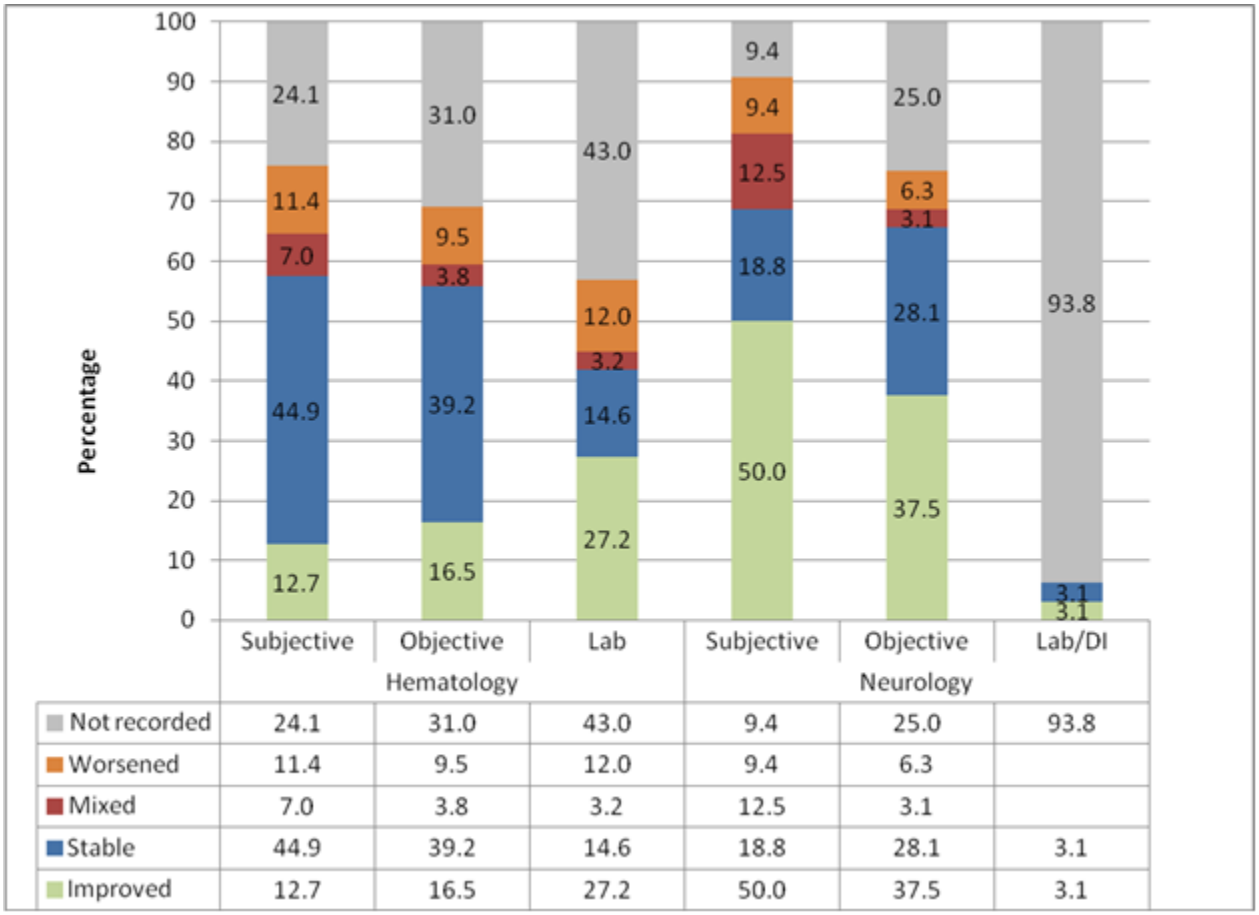
Supplementary Figure 5: Reports of Improvement in Patients Meeting Diagnostic Criteria for Conditions Where IVIG Is Used (Averaged For Each Patient)



	Subjective	Objective	Lab/DI
Not recorded	23.7	39.4	48.6
Mixed	9	4.9	2
Worsened	11.5	9.5	8.9
Stable	21.5	18.9	9.6
Improved	34.3	27.3	30.9

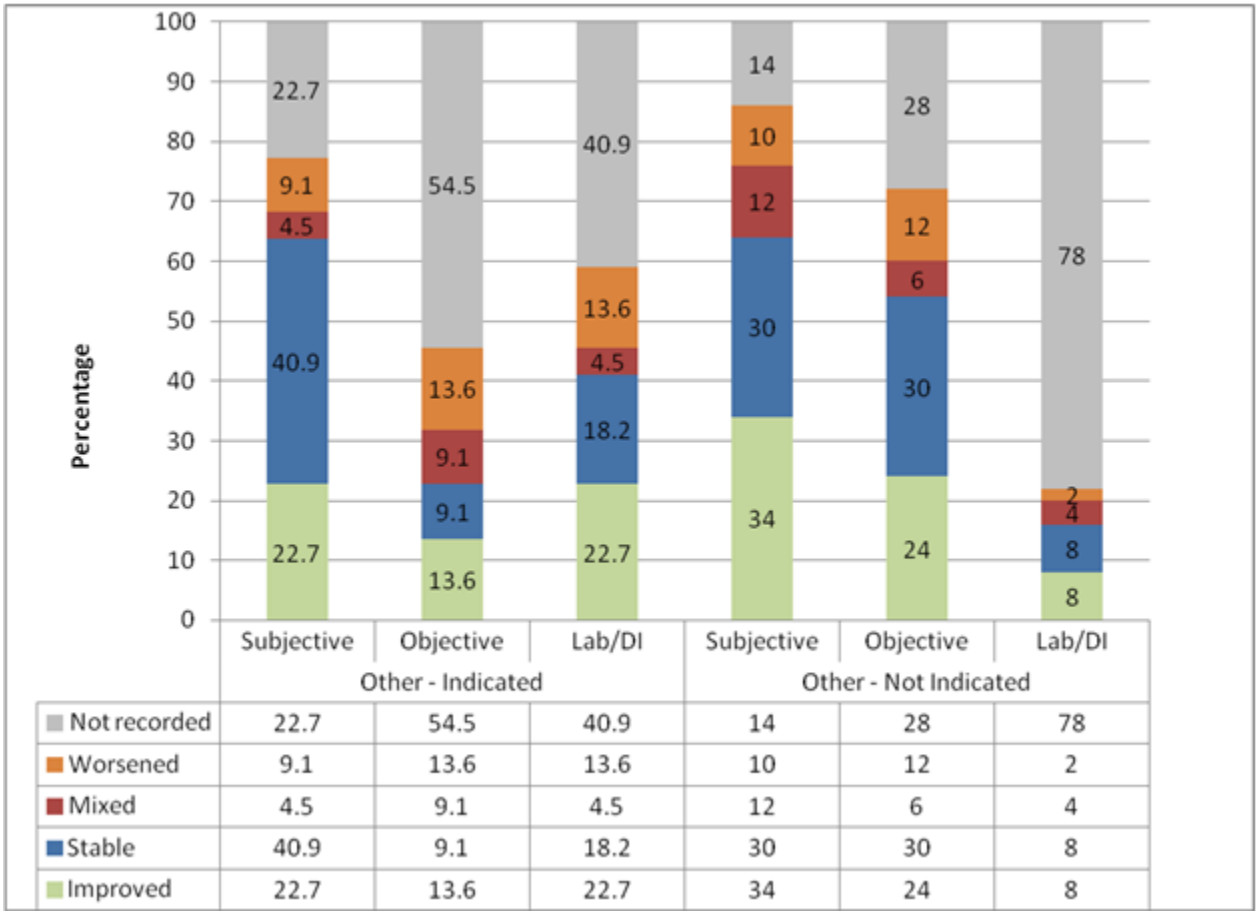
Lab: Laboratory Results, DI: Diagnostic Imaging

Supplementary Figure 6: Reports of Improvement after IVIG Administration by Hematologists and Neurologists (Not Averaged For Each Patient)



Lab: Laboratory Results, DI: Diagnostic Imaging

Supplementary Figure 7: Reports of Improvement after IVIG Administration in Conditions Not Listed on the IVIG Request Form (Not Averaged For Each Patient)



	Other - Indicated			Other - Not Indicated		
	Subjective	Objective	Lab/DI	Subjective	Objective	Lab/DI
Not recorded	22.7	54.5	40.9	14	28	78
Worsened	9.1	13.6	13.6	10	12	2
Mixed	4.5	9.1	4.5	12	6	4
Stable	40.9	9.1	18.2	30	30	8
Improved	22.7	13.6	22.7	34	24	8

Lab: Laboratory Results, DI: Diagnostic Imaging
Other - Indicated: Conditions not listed on the IVIG Request Form, but potentially indicated from Canadian evidence-based guidelines
Other - Not Indicated: Conditions not listed on the IVIG Request Form and not indicated from guidelines

Appendix 1: Ministry of Health and Long Term Care Ontario IVIG Request Form

Ontario

MOHLTC IVIG Request Form

Patient Name
ID #
D.O.B.
Gender Female
Location
HC#
ALL FIELDS MANDATORY

Date Requested: (YYYY/MM/DD)	Date Required: (YYYY/MM/DD)
Patient weight: kg Patient height: cm	Treating Physician:
	Physician Specialty:

Indicate dosage required and duration of request

☐ Induction dose: _____ g/kg = _____ g total dose* _____ g per day X _____days ☐ Maintenance dose: _____ g/kg = _____ g total dose* _____ g per day X _____ days, q _____ weeks Duration of request: _____ months (max 6 months - exception PID, max. 12, then new approval form required)	☐Dose calculator used. ☐Not required (Maintenance dose) *Verification of dosage using Dose Calculator tool is recommended. Refer to http://www.transfusionontario.org/dose/ IgG level/Platelet Count/other relevant test results. Result: Date:

Clinical Indication for use must be recorded below

Medical Condition	Suggested initial dose and duration
☐ Acute antibody mediated rejection	0.1 g/kg/treatment day or as a set dose of 2 g/kg total
☐ Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	Initial dose: Adult: Total dose of 2 g/kg divided over 2 to 5 days. Pediatric: Total dose of 2 g/kg divided over 2 days. Maintenance dose: A systematic approach should be taken to determine the minimum effective dose, and continued use of IVIG should be based on objective measures of its sustained effectiveness.
☐ Dermatomyositis	
☐ Multifocal Motor Neuropathy (MMN) initial treatment	
☐ Myasthenia Gravis (MG) initial treatment	
☐ Fetal/Neonatal Alloimmune Thrombocytopenia (F/NAIT)	Maternal dose: weekly 1 g/kg. Infant: an initial dose of 1 g/kg.
☐ Guillain–Barré Syndrome (GBS) including Miller- Fisher Syndrome and other variants	Adult: Total dose of 2 g/kg divided over 2 to 5 days. Pediatric: Total dose of 2 g/kg divided over 2 days.
☐ Hematopoietic Stem Cell Transplant in primary immunodeficiency	0.4-0.6 g/kg every 4 weeks; requirements may increase and should be based on clinical outcome.
☐ Hemolytic Disease of the Fetus and Newborn (HDFN)	0.5 g/kg over 2 hours; if necessary repeat in 12 hours.
☐ Immune Thrombocytopenia Purpura (ITP) Adult ☐ Immune Thrombocytopenia Purpura (ITP) Pediatric	Adult: Acute ITP with bleeding or no response to steroids: 1 g/kg daily for 2 days. Chronic ITP Post splenectomy 0.5 g/kg every 4 weeks. Pediatric: One dose of 0.8 to 1 g/kg with a second dose given within 48 hours if the platelet count has not increased to >$20x10^9$/L.
☐ Invasive Group A streptococcal fasciitis with associated toxic shock ☐ Staphylococcal Toxic Shock	1 g /kg on day one and 0.5 g/kg per day on days 2 and 3 OR 0.15 g/kg per day for 5 days.
☐ Juvenile Dermatomyositis (JD) initial treatment	Total dose of 2 g/kg divided over 2 days.
☐ Kawasaki Disease (KD) initial treatment	2 g/kg for 1 day.
☐ Kidney transplant from living donor(recipient de-sensitization)	2 g/kg/month for 4 months.
☐ Pemphigus Vulgaris and variants	Total dose of 2 g/kg divided over 2 to 5 days.
☐ Post-transfusion Purpura	1 g/kg daily for 2 days.
☐ Primary Immune Deficiency (PID) ☐ Secondary Immune Deficiency (SID)	Adult: 0.4-0.6 g/kg every 4 weeks Pediatric: 0.3-0.6 g/kg every 4 weeks.
**Other Requires Approval Clinical diagnosis and/or indication for IVIG request:	

** For Transfusion Medicine use only

☐ Dose verified	☐ Dose adjusted to:	By (signature req'd):
☐ Confirmed with ordering physician		Date:
☐ Approved		☐ Denied
Signature of Approving Physician:		Date:

Please fax/send to

Version 3.0 November 6, 2014

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