SUPPLY PROJECT
"Strengthening voluntary non-remunerated plasma collection capacity in Europe"

FINAL REPORT:
"Final recommendations to achieve appropriate and prioritised use of immunoglobulins in Europe"

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Work Package 6 Leader
European Hematology Association

Work Package 6 Partners
Centro Nazionale Sangue, Italy
Sanquin Blood Supply, The Netherlands
Assistance Publique-Hôpitaux de Paris, France
International Plasma and Fractionation Association
Deutsches Rotes Kreuz – Blutspendedienst, Germany
Irish Blood Transfusion Service Board, Ireland
Scottish National Blood Transfusion Service, UK
European Blood Alliance, The Netherlands

Contributing Authors
Cynthia So-Osman
Isabelle Durand-Zaleski
Meryl Darlington
Lucie Paulin
Praiseldy Langi Sasongko
Leni von Bonsdorff
Albert Farrugia

Other Work Package Members
Sara Badreh Wirström
Giustina De Silvestro
Augusto Virgini
Aileen Farrelly
Kate Sommerville
Robin Doeswijk
Gauthier Quinonez

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Glossary of acronyms

Acronym	Description
CAR-T	Chimeric antigen receptor T cells
CHESSMEN	Coordination and Harmonisation of the Existing Systems against Shortages of Medicines – European Network
CIDP	Chronic inflammatory demyelinating polyneuropathy
COGS	Cost of goods sold
D6.1	First report of Work Package 6, "A comparative analysis on the current use of immunoglobulins in individual countries: A clinical program"
D6.2	This current report
EAN	European Academy of Neurology
EC	European Commission
EEA	European Economic Area
EHA	European Hematology Association
EMA	European Medicines Agency
ESID	European Society for Immunodeficiencies
ESMP	European Shortages Monitoring Platform
EU	European Union
g	grams
GBS	Guillain-Barré syndrome
GDPR	General data protection regulation (EU)
HMA	Heads of Medicines Agencies
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment – A multi-disciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle with the purpose to inform decision-making in order to promote an equitable, efficient, and high-quality health system.
ICD-10 code	International Classification of Diseases, Tenth Revision
IFR	Individual Funding Request
Ig	Immunoglobulins
IV	Intravenous route
IVIg	Intravenous immunoglobulin(s)
Kg	kilograms
l/L	litres
LTD	Latent Therapeutic Demand
MDSAS	Medical Data Solutions and Services (UK)
mg	milligrams
MS	Member State(s)
PDMP(s)	Plasma-derived medicinal products - example polyvalent immunoglobulins manufactured from whole blood (plasma, red blood cells, platelets) and from apheresis (source plasma)
PID	Primary immunodeficiency
PLEX	Plasma exchange

PNS	Peripheral Nerve Society
QoL	Quality of life
RCT	Randomized-controlled trial(s)
SC	Subcutaneous route
SCIg	Subcutaneous Immunoglobulin
SID	Secondary immunodeficiency
SmPC	Summary of Product Characteristics
SoHO	Regulation on substances of human origin
SPOC	Single Point of Contact Working Party (EMA)
SRIAP	Subregional immunoglobulin advisory panels (UK)
TF AAM	Task Force on Availability of Authorised Medicines for Human and Veterinary Use (HMA/EMA)
UK	United Kingdom
WP	Work Package

Executive Summary

Since demand for immunoglobulins (Ig) in Europe has more than doubled over the past 15 years, the SUPPLY project's Work Package 6 (WP6) was assigned to assess the appropriate use of Ig and on its prioritisation in times of crises amongst European Union (EU) Member States (MS) and the United Kingdom (UK).

This report builds on our first report, D6.1: *A comparative analysis on the current use of immunoglobulins in individual countries: A clinical program.* It assessed the scope of Ig usage across medical specialties and different EU MS, focusing on mitigating and prioritising strategies in times of crisis, particularly on the influence of the COVID-19 pandemic.

This report, D6.2, integrates the feedback of stakeholders and offers a roadmap of final recommendations and concrete actions towards appropriate use and prioritisation of Ig in times of crisis. These are summarized into three main sections, highlighted below.

1. An improved understanding of Ig usage is needed

- Since MS do not have equal capacities to collect information, different steps may be required to systematically collect data about Ig use. A prerequisite would be to agree on governance and responsibilities regarding data jurisdiction, control, maintenance, accessibility, and sustainable resources.
- The first step would be the identification of existing data sources on Ig use within each MS, which includes established registries and databases from reference networks and scientific societies.
- The second step would be the creation of a comprehensive centralised database along with a central analytic hub at the national, or at least regional, level. Aggregated normalised national data would be made available to the upcoming European Health Data Space for global analysis.
- A proposal of variables for a collection of both a *minimum* and an extensive dataset is provided in Appendix II.

2. The development of a structured and harmonised prioritisation and management plan in times of shortages is required

- Since existing EU prioritisation plans and indications are not uniform between countries, a harmonised methodology is recommended as a first step to ensuring that each MS establishes a prioritisation plan for shortages.
- Guidance would include protocols on switching between brands and/or routing, use of alternative treatments, treatment paradigms, best practices, and Europe-wide communication network and shortage awareness systems. Integrating such guidance with existing guidelines and recommendations is crucial.
- Patient representatives are an important part of these decision-making strategies.
- At the EU level, concrete actions can include collaborative groups sharing methods and experiences as the pandemic has resulted in many lessons learned. These lessons learned could be turned into a simple and core set of criteria and actions that can be easily implemented.

3. Collaborative bodies need to ensure linkages between similar initiatives and expert networks

- These recommendations are a starting point to be able to benchmark Ig use on a granular patient level and harmonise the indications for Ig usage within the EU.
- Collaboration with other EU initiatives, such as CHESSMEN, is vital for optimising supply and for the implementation and incorporation into clinical practice for Ig management strategies.
- To ensure adequate linkage and collaboration, collaborative bodies at the national and EU level must be reinforced or created to build necessary partnerships for sharing of data and information to manage Ig supply and demand.

Chapter 1: Introduction

1.1. Aim

The aim of Work Package 6 (WP6) is to deliver a set of recommendations on the appropriate use of plasma-derived medicinal products (PDMPs) at baseline and on its prioritisation in times of crisis. Although several PDMPs are manufactured from plasma, emphasis is primarily on polyvalent immunoglobulin (Ig) as this product is the main driver for the volume of plasma collected and needed for European strategic independence.

This report is a follow-up document of the D6.1 report, which provided information on 1) the current indications and usage of Ig and 2) the differences in use of Ig in Europe whilst providing insights on potential reasons for these differences such as clinical practices, product supply and reimbursement, existing guidelines and differences between countries and adherence to the guidelines. Of note, appropriateness (regarding the scientific level of evidence) of the existing guidelines was not under investigation.

After the submission of D6.1, a multi-stakeholder virtual workshop was organized on September 6th, 2023, to present preliminary recommendations and obtain feedback from relevant stakeholders. Forty-seven participants representing patient organisations, clinicians, blood establishments, industry, national competent authorities, the European Medicines Agency (EMA), and the European Commission (DG SANTE) were chosen and invited through the networks of the European Haematology Association (EHA) and the SUPPLY Consortium.

Two breakout sessions of 45 minutes regarding the themes of data collection and harmonisation were organised. Subsequently, all participants gathered for a concluding discussion. The key takeaway points from the breakout sessions were presented and considered along with other topics that had not been discussed until then.

Workshop presentations were sent to the participants along with a brief survey to gather any feedback regarding the content. The survey and responses are found in Appendix I.

Therefore, D6.2, provides our final recommendations, in which we have incorporated stakeholders' input, and offers a pathway for next steps.

Chapter 2: Data Collection Recommendations

The following recommendations have been elaborated based on the conclusions of our previous work (D6.1), as well as the workshop organised in September.

2.1. Steps to follow

One of the key conclusions from D6.1 is that EU MS do not have equivalent capacities to collect data about Ig use. While many MS have digitalised patient management systems, they still do not systematically collect this data centrally/nationally or even at a local/regional level. Moreover, the information in the hospital's electronic patient database is not necessarily collected, processed, and made available.

Looking ahead, there will be the implementation of the European Health Data Space and the single EU market for digital healthcare systems (eHealth Digital Service Infrastructure) that will support more interconnection of data. However, there is consensus that short-term pilot projects to start data collection of Ig use are required and indeed feasible.

2.1.1. Governance and Responsibility

To enhance access to and sharing of data, policy makers face major challenges in setting up the necessary data-governance frameworks taking into consideration privacy protection issues in the light of EU's general data protection regulation (GDPR).[1] Data regarding Ig usage must be owned by the public sector and freely available as it is a crucial tool for a country to be able to measure trends in consumption by organising the data collection, storage, maintenance, and analytics of a national Ig-use database. To be able to anticipate future shortages or supply tensions, it is important for this data to be centralised, if possible. For example, in Germany, the German Transfusion Act states that blood donation services, the pharmaceutical industry, and the health care facilities provide data about plasma collection as well as Ig manufacture, imports, exports, loss and expiry to the Paul-Ehrlich-Institute free of charge.[2] The results are published on a website and are easily accessible.[3]

The determination of governance structures and the identification of key stakeholders at the national level are essential and require the establishment of robust policies and regulations regarding data jurisdiction, control, maintenance, interoperability, and accessibility.[4]

For the successful completion of this step, there is a need to identify sustainable financing mechanisms to support the initiative, as data must be monitored in the long-

term, and connectivity of all the databases at regional, national and EU levels will be a huge challenge requiring significant resources.

2.1.2. First step: Data Identification and Mapping

This step involves the identification of existing data sources on Ig use within each EU MS. This encompasses an assessment of the nature of available data, and the way this data is recorded. Moreover, this process can be accelerated by coordination of established reference networks and scientific societies, many of which have already created relevant registries and databases.

Some challenges to overcome at this step include the limited availability of information in some EU countries, the fragmentation of data across a multitude of sources, and the restrictions on data access in specific MS.

2.1.3. Second step: Database creation at the national level or regional level

Using the results of the gap analysis of the first step, the final step is to create an information system to collect Ig use information, set up a centralised database and central analytics hub. This database should operate at the national, or at least at the regional level, to include Ig usage data from all available sources. Sharing of this information between MS can then facilitate better management of supplies across Europe.

From our work on the French case study in D6.1, the non-specific nature of some ICD-10 codes demonstrated the difficulty in analysing data by underlying disease, even in a system with national data collection protocols and regulation if the system has not been designed with the research question in mind. Thus, we recommend that the data collection should include clear coded information about the indications for all Ig prescriptions since the ICD codes will not be sufficient. Furthermore, collaboration with manufacturers of Ig is pivotal for the success of this initiative as they can provide crucial data about Ig manufacturing, sales, imports, and exports. However, this is likely to be limited since manufacturers will only give information to the National Competent Authorities, or EU Commission, when required. Their data would be aggregated before being published.

To proceed with this step, two approaches are to be taken in parallel:

- In MS with pre-existing databases, it will be necessary to put in place extraction procedures from these identified databases and to create a centralised one at a regional or a national level, while drawing insights from international models.
- Secondly, it will be necessary to analyse the situation of MS who do not have digitalised health data available even at a local level.

This means that even if there are existing databases, there will almost inevitably be missing variables that are not currently uploaded or collected from the original source and information systems will have to be put in place at the local level. Other challenges to overcome have been identified: firstly, the sheer number of different data sources and providers makes it difficult to collect patient-level data, especially in countries with a federal structure. Therefore, in the short term, only data at the product-level may be accessible. Secondly, existing data registries tend to favour certain types of patients, often chosen by specialised clinicians in specialised centres for specific medical conditions and so registers may not exist or may have incomplete information e.g., for certain rare diseases.

2.2. Minimum dataset to be recorded

2.2.1. National / EU data recorded at the patient level

Whilst the aim is to understand and monitor trends in Ig use (supply and demand), the SUPPLY project has underlined the current absence of granular data or information that would be required to achieve this. To conduct an assessment of appropriate usage, there is a need to collect granular data, ideally at the patient-level using data protection protocols, although clearly this will lead to large datasets over time. An alternative option would be to collect aggregated data on dispensing medicines from hospital and community pharmacists. A proposal for a minimum dataset is provided in the data dictionary found in Appendix II. Analysis of this minimum data set would provide usage data by indication such as the number of patients treated per year and the volume of Ig used which could be crossed with epidemiological incidence, prevalence, and natural history of disease information. In the event of a supply shortfall this would facilitate managing demand within treated populations.

Given the complexity of this task, as discussed with the stakeholders in the workshop, one possibility to initiate this be to pilot data collection - whether it be at a patient level or aggregated data - for a limited selection of pathologies to test the concept and prepare the future of longitudinal follow-up of Ig treatments. It is well known that in addition to the complexity of identifying and collecting the data in the most streamlined fashion possible, the data management aspects, such as data normalisation to standardise and organise the collected data effectively, are challenging. A small pilot to start this process with a minimum data set, with an aim of setting up national or EU Ig information systems, will require decisions to identify the most pertinent pathologies to be covered, minimum data variable requirements, temporal and other technical issues based on the most pressing current information gaps, but also taking into consideration pragmatic issues such as current data availability and the costs of setting up the system.

A more extensive dataset is included in the data dictionary (Appendix II) for research purposes and to forecast trends for prescribing and growth of immunoglobulin as a therapy (see Appendix III).

This data collection is clearly a vast and complex project. The experts consulted in WP6 agree that this initiative may have to be piloted by identifying one or more indications where prescription data collection seems potentially more feasible. An example would be Kawasaki disease that has a clear specific ICD-10 code. For this disease, the French case study, that is currently underway using SNDS data as described in D6.1, will allow to identify the number of patients, number of prescriptions, the percentage of Kawasaki patients treated by Ig and hopefully estimate volumes of Ig prescribed/delivered and hospital Ig costs. In addition, this indication occurs in children under five and, to our knowledge, is always treated in the hospital setting making the identification of patients, at least in theory, possible and exhaustive. Whilst it is audacious to project results at this point, Appendix III contains a simple preliminary draft table demonstrating the kind of information and analysis that could be available should prescription/dispensation data be collected in a future initiative. This would potentially allow comparison of available epidemiological data of the disease with actual Ig usage.

2.2.2. Sales/supply data recorded at the product level

The minimum dataset could also be extended to collect information at the product supply level. Indeed, to accurately monitor volumes of plasma collected/imported, but also Ig quantities produced and used, direction and scale of growth and forecast future trends in Ig use at the national level, sales, and manufacturer data directly at the product supply level is required. Data blood and plasma donation facilities, fractionators, as well as healthcare facilities (e.g., hospital pharmacies) is needed.

Data collection on Ig use in the EU requires the manufacturers to provide data on domestic sales in each country's national market as well as exports in foreign markets. However, since sales data does not entirely equate to dispensed drugs, losses from breakages and expired drugs as well as medicines in stock will also have to be recorded.

This dataset would give an overall picture of the Ig use in EU MS. Data analytics will help assess and anticipate market needs, the impact of any supply disruptions and aid formulation of mitigation plans during supply shortages. It will also allow monitoring of national level spending on Ig. However, this sales or supply product-level information alone would not be sufficient to analyse the usage of Ig: for example, it would not permit assessment of either the clinical effectiveness of a treatment or the extent of deviation

from clinical guidelines (such as off-label use for indications not endorsed in clinical guidelines), as these would require clinical data recorded at the patient level.

Lessons learned from similar approaches in the past should be incorporated by gathering knowledge from existing databases and/or registries (e.g., the European Society for Immunodeficiencies registry).[5] It is crucial that sufficient investment in both manpower and financial resources must be provided to secure the long-term viability, utility and maintenance of the database. Any short-term or half-hearted commitment would severely compromise the purpose and value of the project.

Chapter 3: Harmonisation Recommendations

3.1. Harmonised indications

In D6.1, EMA's Core SmPC indications were compared with approved indications in France, Italy, Spain, Germany, as well as with those in England and Northern Ireland. Across these countries there was agreement for eight indications (Primary immunodeficiency (PID), Guillain-Barré syndrome (GBS), Chronic inflammatory demyelinating polyneuropathy (CIDP), Multifocal motor neuropathy, Idiopathic thrombocytopenic purpura, replacement therapy for Secondary immunodeficiency (SID), Hematopoietic stem cell transplantation, and Kawasaki Disease). However, differences were found when comparing approved, reimbursed indications for Ig per country (see Table 3.1). These differences are due to country-specific factors, such as reimbursement schemes and Ig-related procedures.[6] Interestingly, in evaluating levels of national consumption amongst the five countries in 2021, the lowest level was England and Northern Ireland at 90 g/1,000 inhabitants,[7] though they have the highest number of authorised indications. This can be compared to Germany at 159.6 g/1,000 inhabitants[8] and France at 148.3 g/1,000 inhabitants (from the French case study in D6.1).

The number of approved indications alone does not reflect real Ig usage, whilst off-label usage can be difficult to quantify. Variability in Ig consumption is linked to how Ig is managed, to availability and to utilisation of guidelines – which may differ even at the local level (i.e., across different hospitals) – and to whether an existing system of checkpoints is in place for monitoring and safeguarding Ig. Thus, given that each country has its own guidelines and recommendations, a harmonised approach, beginning with a consistent set of Ig indications for all EU MS that is shared in a structured manner, accompanied by a harmonised prioritisation plan and management plan, is of vital importance.

Table 3.1. Comparison of the number of approved indications in different countries

Country	**Number of approved indications for immunoglobulins**
England and N. Ireland	44
Germany	12
France	11
Spain	10
Italy	9

3.2. Harmonised methodology for a prioritisation plan during shortages

Results from D6.1 show that prioritisation plans and indications are not uniform between countries and that varying strategies are in place. Therefore, as a first step to ensuring that each MS has established a prioritisation plan, the creation of a harmonised methodology is recommended. During the workshop, it was discussed that such a methodology would be a process that would include addressing the following elements:

1. High medical need and unmet medical need;

2. Added benefit of Ig (with consideration of alternative treatments);

3. Quality of evidence;

4. Quality of life for patients / patient involvement;

5. Using the EMA list of authorised indications.

As the basis for indications in a harmonised prioritisation plan, workshop participants agreed that the indications authorised by the EMA, outlined in the Product Information of the Core SmPCs,[9,10] is the starting point. During the workshop, participants discussed possible approaches to getting more indications authorised by EMA to update the Product Information. This would entail following a process described in detail in EMA guidelines,[11–13] which includes providing robust clinical data and other applicable regulatory steps.

Since Ig is a scarce product, it is necessary to consider alternative treatments, and to consider these alternatives *first*, i.e. prior to using Ig, if such treatments (e.g., plasma exchange, PLEX) are (high level) evidence-based. Ig should be prioritised for indications for which no alternative treatments are available. One interesting illustration provided during the interviews revealed how a neurologist's hospital, when experiencing an extreme shortage scenario, made significant changes in its treatment paradigms so that steroids or PLEX were used as first-line treatment options. This way, a 50% reduction in Ig usage was achieved, and this practice remains to this day.

Regarding high medical need/unmet medical need, Ig should be prescribed to those who need Ig the most. Additionally, there is a group of patients who remain unrecognised in their need for Ig possibly due to the absence of the appropriate diagnostic tools. This includes rare diseases with the consequence of undertreatment.

Robust clinical evidence is crucial in using Ig wisely and level 1 scientific evidence is preferred.[14] However, it is difficult to obtain this for rare diseases. Hence, workshop participants discussed how real-world evidence can play a role where RCT are challenging. This can be provided by starting registries for rare diseases with details regarding Ig dosing and effectiveness, as described in Chapter 4. International collaboration to this effect is vital, on an EU level, and perhaps even on a global level. With these registries, patient data can be studied using a matched-controlled study design as second-level type of evidence, when RCT are impossible to perform.

3.3. Harmonised (shortage) management plans

Results from D6.1 showed how further work needs to be done on harmonised protocols regarding switching between brands and/or routing, use of alternative treatments, treatment paradigms, best practices, and Europe-wide communication and shortage awareness systems. This is applicable for times of crisis *and* non-crisis.

Therefore, a system of checkpoints for Ig use is highly recommended. The results of expert interviews reported in D6.1 underlined the necessity of such a system during a crisis. Many clinicians described how hospitals that did not have a pre-existing Ig system of checkpoints before the pandemic instated one, which included altering treatment paradigms so that Ig is not always first-line treatment, having an approved list of indications and the establishment of committees or panels for off-label usage. For those settings that already had such a system in place, the pandemic led to stricter implementation of existing guidelines and additional steps (e.g., in the UK, an allocation method to prevent stockpiling was implemented[15]).

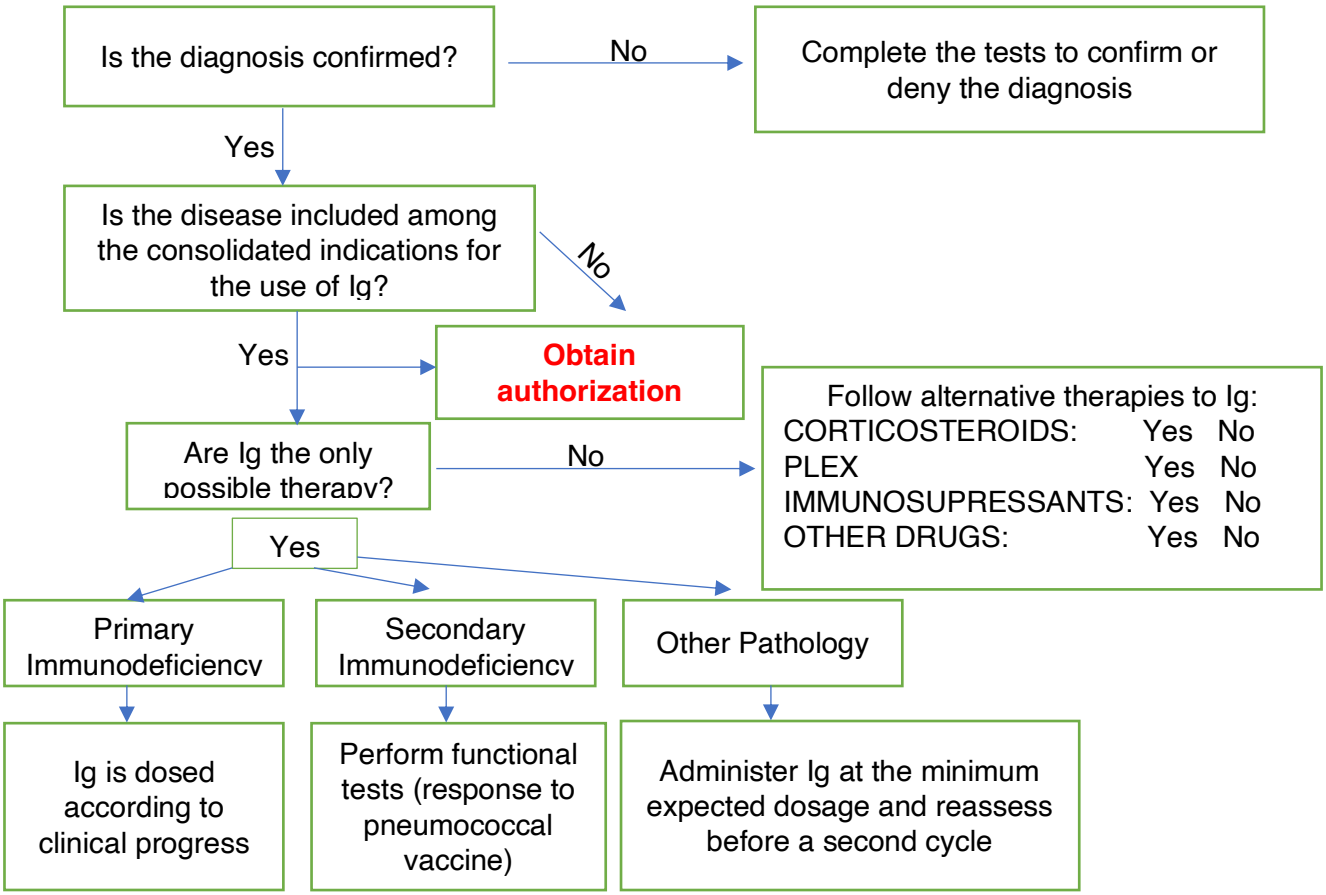
Additionally, clinicians commonly adopted practices of rounding down dosages, using every drop from the vial, assessing if chronic and stable patients could have delayed or decreased dosages, and having reliable consistent methods of communication.

One commendable example is the robust system in place in England and Northern Ireland, which includes clearly delineated clinical guidelines ("Commissioning Criteria Policy for the use of therapeutic immunoglobulin England"), a demand management plan, and a national Ig database (MDSAS). When a clinician wishes to use Ig, a referral form must be completed through the MDSAS which indicates whether that action requires prior Panel approval depending on if the indication is 'routinely commissioned' or 'not commissioned routinely.' If it does not require Panel approval, treatment can proceed but a completed application form still needs to be submitted and retrospectively reviewed by the Panel. If the Panel needs to approve it, further processes will be activated. Any indications or clinical scenarios not listed in the Commissioning Criteria requires an Individual Funding Request (IFR) application subject to support by the Sub Regional Immunoglobulin Assessment Panels (SRIAPs),

to be submitted to the national IFR Panel. If the IFR is approved, the diagnosis and locally agreed efficacy criteria are recorded into MDSAS.[16] These digital processes also lead to a potentially exhaustive data collection on Ig prescriptions and use.

Therefore, as part of such a system of checkpoints, a simple flowchart for clinicians to use in decision-making is proposed (Figure 3.3). This flow chart is an example only and does not factor in the complexities of modalities for specific indications described in existing algorithms such as for primary antibody deficiencies,[17] CIDP,[18] or hypogammaglobulinemia.[19] However, it does provide a simple overview of necessary steps prior to administering Ig, which could be integrated into an electronic ordering or prescription system. Additionally, such a system would include a harmonised approach to accommodate for the appropriate usage of off-label indications.

Figure 3.3. Example of a general flow chart to help clinicians determine appropriate Ig use



It is critical that a harmonised prioritisation or management plan should be based on, and integrated into, existing treatment recommendations and/or guidelines from scientific societies. These would certainly include those done by the ESID, European Academy of Neurology (EAN) and Peripheral Nerve Society (PNS), and others that are notable for providing guidance on Ig usage. Such guidelines are updated periodically.

An element to consider in management plans is Ig dosing, based on the ideal body weight. As obesity becomes more prevalent, Ig dosing of obese patients could be calculated, not based on the actual weight, but on the ideal body weight.[16,20] The effect of such a step is described in a study by Roccio et al. of 262 patients, of which 53.6% had secondary hypogammaglobulinemia, leading to a reduction of 20% Ig use in one year after adjusting the dose from actual to ideal body weight.[21]

Additionally, these results support that a coordinated communication and shortage awareness system should be set in place. While many countries already have varying methods and procedures in place, there are benefits in having a coordinated set of actions and communication measures. Reflecting on best practices in terms of communication and sharing these ideas could aid every country. On an EU level, this has already been highlighted by the Heads of Medicines Agencies (HMA)/EMA Task Force on Availability of Authorised Medicines for Human and Veterinary Use (TF AAM),[22] with one of its main action points until 2025 to enhance transparency and communication to prevent and manage shortages, build trust, and frame information appropriately to avoid stockpiling.[23] Additionally, the EC is proposing as part of its revision of the EU's Pharmaceutical legislation that Market Authorisation Holders will be required to have a shortage prevention plan in place and to notify the competent MS authorities and EMA of shortages.[24]

3.4. Considerations for harmonisation

A harmonised approach needs to have the input of patient representatives. The views of users of medicines should be considered for ethical, democratic, methodological and policy principles.[16] It is vital to consider how treatment practicalities affect a patient's quality of life (QoL). Therefore, representatives from European (or global) patient organisations should be included in these discussions, from the beginning or at key stages throughout the project. As shared in the workshop, one interesting example can be seen in the Czech Republic's HTA pathway: for rare diseases and niche oncology, patients have 25% of voting rights in the decision-making.

In terms of implementation, the prioritisation or management plan would have a fixed ‘backbone’ but there would be freedom for each MS to implement it in accordance with the country’s epidemiology, resources, priorities, and needs. As stated above, these prioritisation or management plans must be integrated into existing European medical or treatment guidelines.

At the EU level, concrete actions can include collaborative groups sharing methods and experiences as the pandemic has resulted in many lessons learned. These lessons learned could be turned into a simple core set of criteria and actions that can be implemented when needed. Furthermore, there needs to be a systematic method for monitoring and assessment, which would require long-term commitment and support with sufficient funding and staffing.

Chapter 4: Affordability of Ig and usage versus demand

4.1. Ig's threatened affordability

Ig represent high expenditures for healthcare systems and can be among the most expensive pharmaceuticals in hospital. The reasons for the high cost of Ig have been presented and discussed in SUPPLY WP4 (D4.5 *Assessment report on Plasma and PDMPs Economics and Tenders*). The main contributor to this is the high cost of manufacturing PDMPs, with a specifically high cost of goods sold (GOGS) which can rise as high as 60-70%, and where the cost of plasma forms the major part.[25] In Europe and the USA, the dominance of Ig as the driver product for the PDMPs adds to the pressure on its price to cover most of these costs and secure a profitable income required by the commercial companies producing them.

Compared with traditional or biotechnological pharmaceuticals, Ig is not under a similar lifecycle span with market prices going down when the patent and other price protection measures come to an end. Patents protecting Ig or its production do not play a major role in the industry and many formulations exist.

As the demand of Ig has increased and is expected to further increase globally, there is a constant pressure on continued market price increases as the supply is depending on the plasma availability. The affordability of Ig products for certain markets are particularly threatened in countries with constrained health care budgets who cannot afford the higher price. Additionally, there are many current signals of increasing Ig supply constraints in Europe, which indicates risks for shortages.[26] To illustrate such a change and its consequences, there is increased use of Ig in SID. The use in this indication is often secondary to new treatment modalities in oncology, causing long-term immunosuppression. Whereas the cost of new pharmaceuticals (including products like monoclonal antibodies, bi-specific antibodies, and CAR-T cell treatments) are properly evaluated according to their main outcomes and their prices are regulated, agreed and approved, the cost of the secondary outcomes, including use of Ig to treat infections, can fall under the radar of such evaluations and may not be evaluated. The impact of the overall use of Ig may not be foreseen when such new drugs are used and may bring an unexpected rise in the demand in Ig, the cost of the treatments, and impact the budget allocated for Ig in different health care systems.

4.2. Usage versus demand

Decision makers charged with Ig procurement should appreciate the difference between usage and demand and plan accordingly. *Usage* represents the demand for Ig at that particular point in time and should not be taken as representing the real demand if all the epidemiological and treatment access factors for the various disease states are optimised.[27] This leads to the concept of Latent Therapeutic Demand (LTD*)*, which can be estimated using decision analysis, a necessary methodology given the uncertainty around several of the parameters shaping demand. This estimation has been published for PID[28,29] and the autoimmune neuropathies.[30]

Figure 4.2. Variables contributing towards Latent Therapeutic Demand[28]

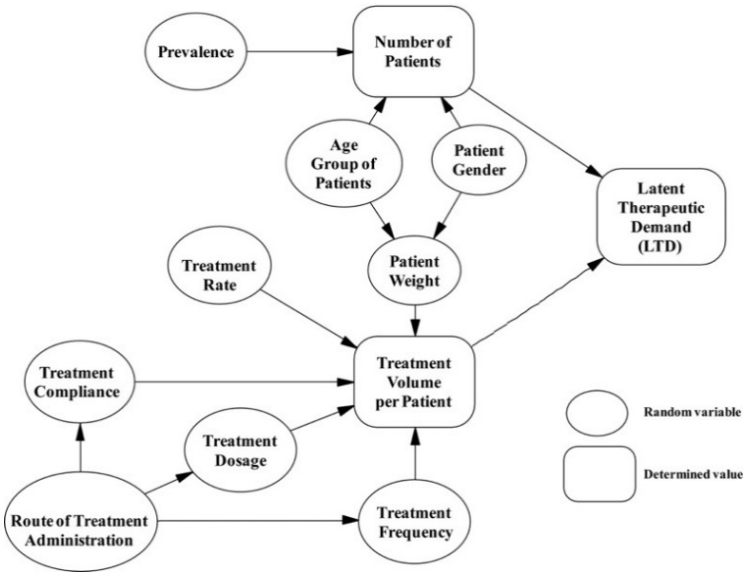


Figure 4.2. shows the variables considered when estimating LTD for a particular disease. The parameters are obtained from available literature and are synthesised into the demand as shown. Since uncertainty surrounds several of these parameters, decision analysis software, such as Excel, can be employed to generate a sensitivity analysis around which the parameters can be arranged hierarchically. (See the references and the detailed online methodology for further information.[28–30])

Several of these variables will shift over time. For example, as diagnostic capacity increases, the prevalence in a particular geography will increase towards values which are globally present. Similarly, as children are successfully treated and survive childhood (e.g., in PID), they will require more Ig as adults since dosage is based on weight. Changes in the demographic of certain diseases (e.g., some haematological cancers are more prevalent at older age), will also affect demand. The estimation of

LTD reveals that other areas of investigation (e.g., geographical variations in prevalence, diagnostic accuracy, personalised treatment) are necessary in some of the contributing parameters.[29,30]

Table 4.2. Latent therapeutic demand for Ig in the USA for PID and neuropathies

Condition	Mean LTD immunoglobulin g/10^3 population	References
Common variable immune deficiency	65.4 ±73.6	(1)
X-linked agammaglobulinemia	25.5 ±27.6	(1)
Severe combined immune deficiency	13.4 ±13.5	(1)
Wiskott–Aldrich syndrome	0.5 ±0.4	(1)
Hyper IGM syndrome	0.3 ±0.3	(1)
Chronic inflammatory demyelinating polyneuropathy	83.05 ±24.5	(2)
Guillain-Barré syndrome	6.1 ±3.2	(2)
Multifocal motor neuropathy	36.1 ±25.5	(2)
Total mean immunoglobulin consumption	230.35	

(1) Stonebraker, J.S., Hajjar, J. and Orange, J.S. (2018), Latent therapeutic demand model for the immunoglobulin replacement therapy of primary immune deficiency disorders in the USA. Vox Sang, 113: 430-440.

(2) Farrugia, A, Bansal, M, Marjanovic, I. Estimation of the latent therapeutic demand for immunoglobulin therapies in autoimmune neuropathies in the United States. Vox Sang. 2022; 117: 208–219.

Hence, it is not surprising that the *usage* of Ig in European jurisdictions is increasing. As an example, Table 4.2 summarises the results of the three studies cited above. It will be seen that for these indications, which are all level 1 indications, the total mean LTD exceeds the mean EU Ig usage of 112 g/1,000 inhabitants in 2020. (EU Ig usage was calculated from the total amount of Ig used[31] divided by the EU population[32] in 2020.) Note that these studies have not included SID, which has been approved relatively recently in Europe. Estimating LTD for SID is very challenging, but some work is underway.

In conclusion, it is important to emphasise that plasma procurement in Europe has to consider not just current usage, but the usage predicted when LTD is gradually fulfilled.

Chapter 5: Connections and collaborations with existing EU initiatives and entities

SUPPLY's outputs should be connected and combined, if appropriate, with the works of other similar EU initiatives and groups.

The first is the EMA Single Point of Contact (SPOC) Working Party, which is associated with the HMA-EMA taskforce on shortages (TF AAM[22]) and ensures effective coordination with the national competent authorities. This subgroup was established in January 2022 to monitor Ig shortages as part of its responsibility to monitor and report events that could affect the supply and availability of medicines in the EU/EEA.[33] Within this context, the WP conducted a survey in 2022 on the availability and the shortages of intravenous Ig (IVIg) and subcutaneous Ig (SCIg) in the EU/EEA. It was also intended to understand the marketing situation, stock level info, historical consumption, and forecast demand. Their results were presented as part of a multi-stakeholder workshop in March 2023, and corroborates our results and recommendations for future actions.[26] The SPOC is the WP of the Executive Steering Group on Shortages and Safety of Medicinal Products, an executive body that coordinates urgent actions within the EU to manage medicine supply issues in a public health emergency or major event and in preparation of a crisis.

Secondly, in January 2023, the Coordination and Harmonisation of the Existing Systems against Shortages of Medicines – European Network (CHESSMEN) project began. This project aims to support European MS to provide a harmonised response to mitigate medicines shortages and to contribute to an appropriate and timely availability of medicinal products. CHESSMEN will be running for three years, bringing together a total of 22 countries participating as beneficiaries (21 EU MS and 1 EEA country) and 5 affiliated entities. Their eight WPs have aims that overlap with those of SUPPLY, such as identifying the root causes of observed shortages of medicines, identification of best practices to address medicines shortages, digital information exchange for monitoring and reporting medicine shortages, and reducing the likelihood of medicines shortages via preventive and mitigation strategies.[34] Of importance, this initiative is aiming to develop actual strategies, which will complement our work, and be the next steps in developing concrete materials, protocols, and mitigating measures.

Thirdly, the EC's Communication from October 24, 2023 "Addressing medicine shortages in the EU"[35] sets a good foundation with a reference to a future "Critical Medicines Act" and the creation of a "Critical Medicines Alliance" to address shortages of medicines. On December 12, 2023, the EC, HMA and EMA published the first version of the Union list of critical medicines, which includes several PDMPs.[36]

The planned work includes assessing supply chains, procurement processes, and possible future legislation on the topic.

Past initiatives include the industry-sponsored Green Paper on the “Appropriate use of immunoglobulins”, which was written by Vintura with input from an expert advisory committee. Their work has resulted in a consensus framework that includes dimensions and criteria for assessing unmet medical need, innovativeness assessment, and the quality of evidence.[37]

Chapter 6: Amendment to the first report

We would like to make a correction to the description of the UK prioritisation plan listed in Table 3.4.3.2 of D6.1 (pages 47-48). There, it was described as the “national” prioritisation plan but it is the *regional* plan from the “Clinical guideline for immunoglobulin treatment by the East of England Immunoglobulin Assessment Panel.” There is a National Demand Management Plan from 2008[38] but it has an outdated classification system for prioritisation. Therefore, we continue using the East of England’s prioritisation classification system.[39]

Chapter 7: Discussion

7.1. Final recommendations

Our final recommendations are presented in Table 7.1, which summarise the contents of the previous chapters, and outlining a roadmap of steps ahead for the appropriate use and prioritisation of Ig, including in times of crisis.

Table 7.1. Final recommendations and pertinent actions

Recommendations	**Concrete actions**
We recommend the creation of a comprehensive **national database** that includes information (at a minimum) on consolidated Ig use at the patient level, discharge summaries with specific indications (e.g., PID, CIDP), and clinical efficacy of Ig use.	• List/ map all available registries / data sources in each country • Data ownership must be public • Governance must be public • Ensure a core data set common in each country • Re-allocate funding for data collection and maintenance
We recommend the **sharing of information** in a structured manner, with the aim of maintaining a **consistent set of indications** in all EU MS as a prerequisite to the harmonisation of Ig use.	• Agree on a limited number of indications, beginning with EMA's authorised indications for Ig[9,10] • Include and share data on each MS' approved indications • MS can decide on which other indication(s) to include
We recommend the creation of a harmonised European **prioritisation plan methodology** with a common backbone that can be adjusted to the country's organisation, epidemiology, and resources.	Process would include: • Starting point would be EMA's authorised indications for Ig; for more indications to be authorised by EMA, follow the process described in applicable EMA guidelines[11–13] • Elements such as epidemiology, high unmet need, robust evidence, high medical benefit, and QoL data should be considered • Collaborate with existing scientific societies / clinical groups • Long-term adherence should be monitored

We recommend a harmonised approach on the **management of Ig use** across Europe that includes protocols on switching between brands and/or routing, use of alternative treatments, treatment paradigms, best practices, and Europe-wide communication and shortage awareness systems.	• Create a standardised system of checkpoints • Collaborate with existing scientific societies/clinical groups who already have protocols/ guidelines • Systematic method for monitoring and assessment should be done
We recommend the **inclusion of patients and patient advocacy groups** in all discussions regarding the therapeutic value of current and future Ig use.	• Embed/include representatives at the beginning of the project and/or at key points in the process

Our recommendations link with that of SUPPLY WP4's recommendations, which advocate that strategies for the appropriate allocation and usage of Ig need to be based on best practice evidence and real-world experience. Relevant research needs to be supported and conducted, which includes real-world experience, drawing on larger post-registration surveys, assessments of patient Health Related Quality of Life (HRQoL) and estimates of LTD.[29,30] Such studies are needed to construct a holistic picture of the real and projected demand for the various indications of Ig. These should be accompanied by HTA taking into account current and future alternatives to Ig.

7.2. An improved understanding of Ig usage

One major finding of this report is the lack of existing comprehensive databases about Ig use on a granular patient level in the analysed countries, covering all indications, while Ig are listed among the critical medicines in the MS.[36] Therefore, as current available data on Ig use cannot inform on possible unmet needs, this goal will only be achieved by the comparison of population sizes by country and by indication.

Regarding the anticipation of future shortages with prioritisation plans, either at the EU or MS level, data is again required to have information on current Ig volumes used and current indications:

- at the MS level, identification of the indications of Ig usage is necessary to undertake HTA for each indication, and to populate economic evaluation and budget impact models,
- at the EU level, information on differences in Ig indications and use will be necessary to the joint clinical assessments of innovations for which Ig are possible comparators.

7.3. The development of a structured and harmonised prioritisation and management plan in times of shortages is required

Our recommendation for a harmonisation of prioritisation plans for shortages and harmonised management plans is not new as previous work has highlighted this need.[40] We also acknowledge the past and present efforts of many countries worldwide to create effective programs for Ig utilisation, which, to be successful, requires a robust monitoring system with various checkpoints that are not cumbersome, adherence to guidelines, and an attitude of judicious use. A current international example includes the Canadian "National Ig Shortages Management Plan Project" which aims to provide the necessary framework and guidance for appropriate allocation of Ig products to patients in the setting of short-term or more prolonged shortage situations. By March 2024, an ethical framework, alternative therapy recommendations, triage and adjudication criteria and an operationalisation plan are expected.[41] The pandemic has emphasised the need to have a shortage management plan, which was lacking in 11 of 22 MS as found in a survey by SUPPLY WP4 (see D4.2 report). To this end, we advocate for the sharing of methods and experiences between collaborative groups to help ensure that the many lessons learned throughout this pandemic are translated into a simple set of criteria and actions that can be implemented in emergency situations. Such lessons should also be collected from the "hidden figures" who are embedded in, and crucial for, Ig clinical management such as the nurses, lab technicians, pharmacists, and other hospital or regional actors involved. Their insights could be valuable in making implementation more practical and feasible.

While it may not be feasible to harmonise indications for all MS, there could be harmonisation of the prioritisation *process*. Each MS can learn from the experiences of others in dealing with shortages. Also, any harmonised prioritisation or management plan must be integrated with existing guidelines and recommendations, coupled with the input of patient representatives. Efforts to do this eases the complexity of harmonisation, which, we acknowledge, is a multi-factorial issue. It would require ai consensus between the legislators at the European Parliament, the Council, and commitments from the MS at a national level for European cooperation. It would require significant efforts of all relevant stakeholders to agree on a common framework and way of working.

7.4. Collaborative bodies need to ensure linkages between similar initiatives and expert networks

Since there is no need to “reinvent the wheel,” an assessment of how we can build off existing initiatives and collaborate with relevant stakeholders is the first step. It should be explored how linkages between such initiatives and expert networks can be established or reinforced, and/or if collaborative bodies can be created where needed, both on the national and the EU level. Of note, work has begun at the European level, with new governance structures and tools foreseen under EMA’s extended mandate. Further milestones will include the introduction of the European Shortages Monitoring Platform (ESMP) which will be a key tool used both by MS and pharmaceutical companies to report shortages and provide supply and demand data for critical medicines during crises.[26] Scheduled to go live in 2025, the platform's primary objective is to institute a unified approach for monitoring and reporting information on available stocks and shortages, especially during public health emergencies and significant events with potential impacts on public health. This platform represents a crucial initial step in establishing a centralised mechanism for monitoring and managing essential medicinal products and medical devices, as outlined by the European Institutions.[42] This also aligns with our recommendations on Ig data collection, emphasising the need for a similar centralised approach, at least at the national level.

7.5. Next steps and points to consider

Further continual collaborations with other overlapping projects have been agreed (HMA-EMA and CHESSMEN) and could help to achieve optimal success in translating some of the SUPPLY recommendations into actual strategies. It is vital to look for more possibilities for collaboration between SUPPLY and other overlapping EU projects.

Additionally, the EU institutions reached a political agreement on the SoHO Regulation although, as of December 2023, the agreed text is not yet available. This move is a significant step towards both enhancing the safety and quality of these substances (which includes blood, tissues, and cells, but also breast milk and microbiota) and safeguarding the well-being of donors and recipients.[43]

And finally, the demand of immunoglobulin for indications which are currently based on the highest level of clinical evidence may be expected to increase in all European MS, especially when LTD comes into play. LTD factors include improved diagnostic capacity, increased survival rates for paediatric patients, and the increasing demand of Ig in relevant patient populations (e.g., haematological cancers in older age groups).

Decision-makers should remember these factors and recognise that current usage levels may not accurately reflect the domestically-sourced plasma volumes for plasma for fractionation to ensure strategically-independent supply. Continued investment in the public blood and plasma procurement systems is necessary.

These recommendations are a starting point for benchmarking Ig use on a granular patient level and harmonising the indications for Ig usage within the EU. Collaboration with other EU initiatives with overlapping goals remains vital for optimising implementation and incorporation into actual Ig management strategies and prioritisation plans.

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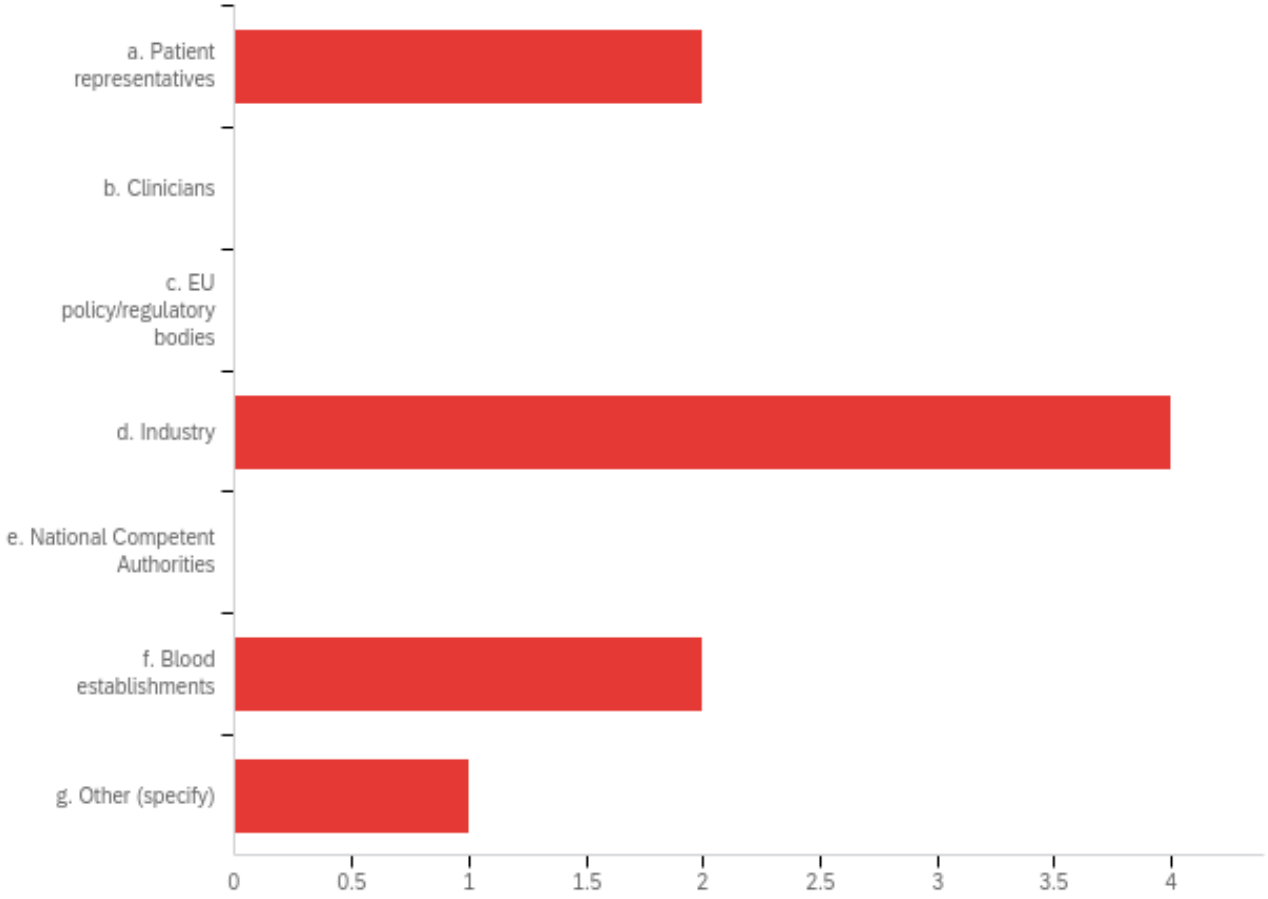
Appendices

Appendix I – Post-workshop survey and results

Below is the exact survey that was sent out and the results received.

Q1 - Thank you for your participation in our workshop. During this workshop, you were divided into two different breakout rooms where we discussed two main topics: data collection and harmonisation. We would appreciate a few minutes of your time to answer the following questions below. These answers will also be considered in our report. 1. Which group do you represent?



#	Answer	Count
1	a. Patient representatives	2

2	b. Clinicians	0
3	c. EU policy/regulatory bodies	0
4	d. Industry	4
5	e. National Competent Authorities	0
6	f. Blood establishments	2
7	g. Other (specify)	1
	Total	9

Q2 - Please specify which group you are from

Please specify which group you are from

Not-for-profit association

Q3 - 2. The main action points of the Data Collection breakout session were:
Existing data sources on Ig usage by indication need to be identified for each EU member state;
Given the enormity of this task, a short-term pilot to start gathering information on Ig use for some selected indications would be advisable;
Identify of the main actors at the national level who have the local knowledge about current centralised data collection;
Put into place European policy and regulations making it obligatory for a member state to collect data on Ig use and ensure national oversight of the interpretation and implementation of these regulations.
a. Please share below if you have any additional comments or insights

Regarding point on 'need to identify existing data sources': some databases/registries may not be public; the search that had been performed by the WP6 members did not take into consideration such possibility. In order to understand Ig use, data collection should include all indications.

All required, and a worthwhile approach.

Q4 - b. What would be the main challenges to overcome in creating a data collection system following the previously listed main action points?

To obtain the agreement of all involved countries To develop a harmonised system
1) Identifying who has knowledge about current centralised data collection; 2) time needed to put into place European policy and regulations to make data collection and national oversight mandatory for a member state
Privacy regulations.
Identifying individuals who can act as key national champions - both to act as a liaison between national bodies and to advise on local issues (digital maturity of systems, GDPR considerations etc)

Q6 - 3. The main outcome of the breakout session on harmonisation was that a harmonised prioritisation or management plan would need to be a simple framework that includes criteria of: High medical need/unmet need; Added benefit of Ig/consideration of alternative treatments; Quality of evidence;
Quality of life/patient involvement;
The existing EMA list of approved indications.
a. Please share below if you have any additional comments or insights about this topic

Harmonised prioritisation or management plan should be based on scientific society's recommendation and guidelines. There is a difference between Guidelines for EMA IIG core SmPC and guidelines from scientific societies on a particular disease. Firstly, we believe it is important to bear in mind that prioritisation should only be done temporarily in times of crisis, not by default. A harmonised approach for management of patients requiring IGs, would need to consider relevant medical societies' input as part of the core IG indications; for example the European Society for Immunodeficiencies, (ESID) and the European Federation of Neurological Societies (EFNS) and the Peripheral Nerve Society (PNS) amongst others. It is key to understand the patient need, we therefore recommend including patient organisations in the approach, for example the GBS CIDP International Foundation, EPODIN and IPOPI. In addition, a harmonised approach should accommodate for the appropriate use outside these indications despite the off-label-utilisation. We recommend ensuring that learning from similar approaches from the past are incorporated; what can be leveraged in terms of existing databases (e.g., ESID

registry) and account for the continuous maintenance of the database as the true value is built in the long-term and not only launching it.

Again, acknowledging that we start from a position of wishing to avoid the need to activate a prioritisation plan, the above criteria are useful.

Q7 - b. What would be the main challenges to overcome in creating a harmonised prioritisation or management plan?

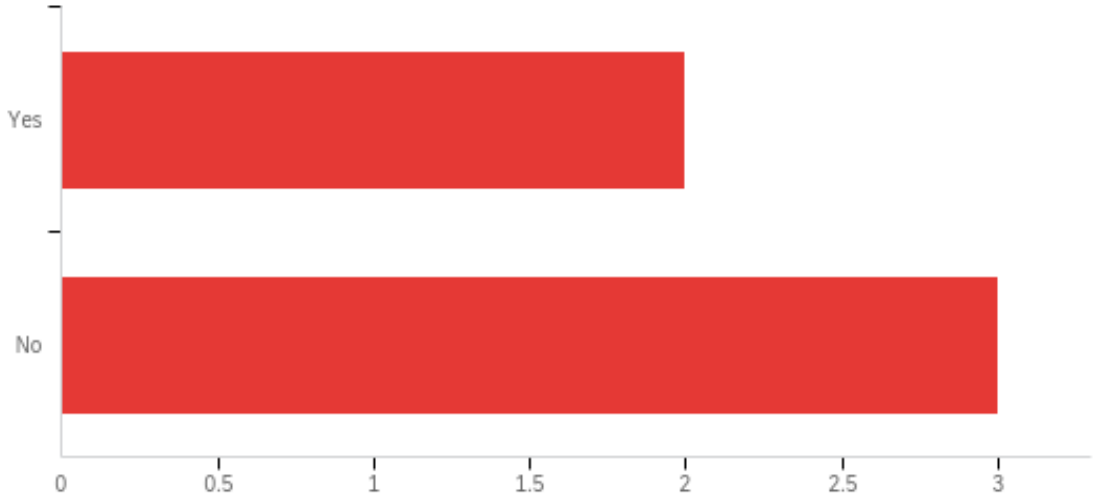
Medical need does not equal the true demand across countries in Europe. Today's use is a function of diagnosis rates and access to IGs. For this reason, it is critical to formally include patient organisations' input in the decision making, for example the GBS CIDP International Foundation, EPODIN and IPOPI. Prioritisation cannot be solely based on the fact that the disease is an EMA indication. This is because Ig is used to treat many rare diseases that may not have a randomised clinical trial in place because of its rarity, and yet there may be clear benefit from Ig treatment.

Involvement of specialists to identify indications that can be added to the existing EMA list of approved ones.

Local Eu members state regulations differ between one another.

Ensuring that terminology and classifications can be applied across the EU; accessing key national stakeholders

Q10 - 4. Do you have any additional comments regarding the workshop?



#	Field	Minimum	Maximum	Mean	Std Deviation	Variance	Count
1	4. Do you have any additional comments regarding the workshop?	1.00	2.00	1.60	0.49	0.24	5

#	Answer	%	Count
1	Yes	40.00%	2
2	No	60.00%	3
	Total	100%	5

Appendix II - Data to be colated and collected to analyse Ig use

Name of the variable	Description	Example
Product level information		
Product identifier	Unique identifying code of the product	UCD7 code in France 9347567 UCD13 code in France 3400893475676 CIP code in France 3400957618964
Product name	Brand name of the product	CLAIRYG
International Non-proprietary Name (INN)		IMMUNOGLOBULINE HUMAINE NORMALE
Description		Substitute treatment in adults, children, and adolescents (0 to 18 years) in the case of PID with abnormalities in antibody production.
Form		Infusion solution at 50 mg/mL
Product dosage		50 mg/mL Solution for Infusion, 1 Vial/100 mL
Package		1 vial of 50 mL
Treatment course		IV, SC
Manufacturer/supplier		LFB BIOMEDIC.
Global supply and demand data - sources manufacturers, distributors, wholesalers		
Product identifier	Unique identifying code of the product	
Unit of time	The time period that corresponds to this quantity of sales/manufacture/export	Annual total 2023, January total 2022. Will depend on how the records are kept.
Quantity sold	For each product, quantities sold by unit of time, by the supplier	
Quantity manufactured	For each product, quantities produced by unit of time, by the supplier	
Quantity exported	For each product, quantities exported by unit of time, by the supplier	
Country of export		
Quantity imported	For each product, quantities imported by unit of time, by the supplier	
Country of import		

Patient-level information: Demographics & health state at first prescription of Ig		
Unique anonymised identifier	The identifier is a unique code that must guarantee a patient correct digital identification, to differentiate a patient from his or her namesake	Social security number or a pseudonymised code
Patient's age	Age at the time of first prescription or date of birth	mm/yy
Patient's sex	male/female/other/unknown	
Patient's weight	Precise weight of the patient since the Ig dosage should be adapted to it	62 kg
Place of residence	The city and the region of residence	Windsor, United Kingdom
Date of diagnosis	Date of the primary diagnosis justifying an Ig infusion	dd/mm/yyyy
Comorbidities_*n*	Variables containing information about the patient's eventual *n* comorbidities	
Patient-level information: Treatment		
Unique anonymised identifier	See above	Social security number or a pseudonymised code
Start date	Date of the Ig infusion	There will be a new record for this patient for each treatment by Lg
Product identifier	Unique identifying code of the product	UCD7 code in France 9347567 UCD13 code in France 3400893475676 CIP code in France 3400957618964
Patient dosage	The dosage is adapted to the diagnosis and to the patient's weight.	50 mg/ml S perf Fl/100ml
Primary diagnosis	Must also specify the precise indication for use: short term/long term, number of infusions, duration of treatment	
Place of treatment	Private clinic/ Public hospital/home/nurses' clinic/Ambulatory Doctor's clinic	
Hospitalisation admission date		NA or dd/mm/yy
Hospitalisation discharge date		NA or dd/mm/yy
Diagnostic Related Group	The DRG is related to a tariff and/or production cost for hospital visits/stays and is weighted by severity of illness/comorbities etc.	08M142 for diagnostic M303: mucocutaneous lymph node syndrome [Kawasaki]
Monitoring	Concentration of Ig, Ig though levels	
Adverse events		Infectious episodes
Annual review of treatment	Yes/No if yes then the date of reviewing	No or dd/mm/yy

Patient-level information: Prescriber		
Profession and specialty	Medical specialty of the Ig prescriber	
Practice/clinic/ work place	Work place of the Ig prescriber: public/private/not for profit hospital as in patient, outpatient, or treated with a specialist in the ambulatory context	
Patient-level information: Pharmacy		
Unique identifier	A unique code associated to the Pharmacy	This may not be possible but it would be interesting to know if the medication was dispensed by a hospital or at a community pharmacy
Type	Hospital or town pharmacy	
Location	City/region where the pharmacy is located	
Patient-level information: Detailed data		
Secondary diagnosis	If applicable, specify the secondary diagnostic associated to the primary diagnosis	
Patients' detailed medical history	Medical history of the patient in relation to the pathology for example grafts, cancer treatments	Would be different variables depending upon the pathology.
Lab results relevant to the disease	Relevant lab result associated to the primary diagnosis	Number of platelets for example

Appendix III – Example of an ideal results table for specific indications

Annual immunoglobulin use Europe & UK - KAWASAKI - Year 2023

		EPI INFO	CLINICAL INFO	Calculation based on EPI and CLINICAL INFO	Supply data (unlikely to be available at pathology level)	Aggregated patient data		
	Country	**Incidence in under five-year-olds per 100 000**	**% Treated by Ig (not all Kawaski patients eligible for Ig)**	**Vol estimated**	**Units sold/available**	**Number of patients treated by Ig**	**Total national vol prescribed (kg)**	**Vol(g)/patient**
0	Europe	10–15						
1	Austria							
2	Belgium							
3	Bulgaria							
4	Croatia							
5	Cyprus							
6	Czech Republic	1.6						
7	Denmark	4.9						
8	Estonia	9.6						
9	Finland	11.4						
10	France	9						
11	Germany	9.6						
12	Greece							
13	Hungary							
14	Ireland	15.2*						

15	Italy	17.6						
16	Latvia							
17	Lithuania							
18	Luxembourg							
19	Malta							
20	Netherlands	5.8						
21	Norway	5.4						
22	Poland							
23	Portugal	6.5						
24	Romania							
25	Slovakia							
26	Slovenia							
27	Spain	11.7						
28	Sweden	7.4						
29	United Kingdom	9.1						

*Ireland hospitalisation data

Sources for incidence data

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