GREEN PAPER

APPROPRIATE USE OF IMMUNOGLOBULINS

VINTURA

COLOPHON

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PREAMBLE

1.1 BACKGROUND

Since its first use to treat primary immunodeficiency (PID) in 1952[1,2,3], human Normal Polyvalent Immunoglobulins (IgGs) have vastly expanded therapeutic options in the previously untreatable and/or fatal diseases and conditions that either require compensation of significant immune deficiency or (*immuno*) modulation of an aberrant immunological homeostasis. The value of these treatments must not be underestimated, as they can prevent premature death, halt disease progression, minimise disabilities, and promote patients' quality of life, thereby having high clinical, societal, and economic impact. A good example of this high impact is the survival rateof patients with common variable immune deficiency (CVID), which was only 22 years in 1979, whilst now the IgGs have increased it significantly and improved overall quality of life[4]. From a socio-economic perspective, in PID, affecting 44,000 patients across Europe, this translates into ~1bnEur/year health gains and almost 1bnEur/year avoidable healthcare costs[5].

However, whilst the therapeutic value of IgGs is evident, the mechanisms involved are not entirely understood, specifically in the case of immunomodulation in autoimmune diseases. This, as well as regulatory and policy issues, has led to differentiation of the indications into those approved by EMA (on-label) and those used off-label. This categorisation varies greatly across European countries[6,7],leading to different care standards and treatment protocols. Additionally, the COVID-19 pandemic has led to disruption in plasma collection and consequently caused focal challenges in access to plasma derived medicinal products (incl. IgGs). In most European countries, limited availability of plasma and plasma derived medicinal products (actual or anticipated) have triggered further restrictions on IgG use via prioritisation of specific patient sub-populations.

These efforts, originally aimed to ensure equitable (also referred to as 'optimal' or 'rational') distribution of the short-supply medicines, have been subject to controversy about the selection criteria.
There is a distinct lack of a holistic method or standard by which to fully assess and appraise the appropriate use of IgGs across indications for which they are currently being effectively used by clinicians. It is against this background that this paper explores possible 'appropriate use' frameworks, supported by evidence of clinical benefits, and expanded through contributions from leading clinical experts from across Europe, representing specialisations involved in IgG treatments.

1.2 WHY A 'GREEN' PAPER?

The format chosen for this paper is that of a Green Paper. As opposed to a White Paper, which strives for a comprehensive review, assessment, and appraisal of all relevant issues, with detailed and actionable recommendations on solutions a Green Paper primarily aims at reviewing the current status of the debate on a specific issue and proposing frameworks, methodologies, and actions to reach recommendations and solutions. The ongoing debate on appropriate use of IgGs is multi-faceted, driven by the complexity and heterogeneity of the therapeutic landscape, and highly dynamic, impacted by the out-of-ordinary COVID-19 circumstances. Whilst the debate has been ongoing for a long time, it has been brought to greater prominence, and even some controversy, due to the COVID-19 pandemic causing a decline in plasma collections and subsequent decline in availability of IgGs in most European countries.

This paper relies on expert knowledge and consensus of the leading clinicians. Whenever incontrovertible evidence is presented, it will be treated as such and included in a set of non-exhaustive proposals and solutions, alongside the agreed frameworks to be used for further assessments of the issue.

1.3 THE APPROACH – EXPERT ADVISORY COMMITTEE

As mentioned above, this Paper is founded not only on a traditional review of existing literature, but primarily on the in-depth knowledge and extensive clinical experience of the panel of experts to serve as Advisory Committee (hereinafter referred to as Advisory). To ensure true patient-centricity, impartiality, and broad multi-stakeholder perspectives, Advisory members represent not only main clinical specialties that use IgGs as therapies in clinical practice but are also collaborating with relevant patient associations and represent leading academic institutions or sit on policy committees at both European and local levels.

This paper is the result of an iterative process with two Advisory plenary meetings where experts shared insights and exchanged opinions, as well as a series of individual interviews, which offered in-depth exploration of each expert's experiences with IgGs, their respective treatment protocols and a broad synthesis of clinical and patient outcomes.

The Advisory was constituted in December 2021 and comprised renowned medical specialty experts: Immunologists- Prof. Isabella Quinti, Prof. Nizar Mahlaoui, Prof. Karina Jahnz-Różyk, Prof. P. Martin van Hagen, Prof. Silvia Sánchez-Ramón; Rheumatologist - Prof. Jacob van Laar; Neurologists - Prof. Mark Stettner, Prof. Guido Cavaletti, Prof. Richard Knight, Dr. Katy Murray; and Dermatologist - Prof. Alexander Enk. For the detailed biographies please refer to the Appendix 1 in this paper.

INTRODUCTION: FRAMING THE DEBATE

2.1 SITUATION ANALYSIS: MEDICAL NEED, MEDICAL DEMAND AND FINITE AVAILABILITY OF PLASMA

Before embarking on the multi-faceted discussion on appropriate use of IgGs, we must further elaborate on the key reasons and the urgency to agree on the framework and definitions of the said 'appropriate use'. The overarching reason has been the growing tension between limited IgG availability and the growing IgG medical need and medical demand, which was further exacerbated by the COVID-19 crisis. Optimal situation obtains when availability, demand and need are all equal to each other. However, if one is lower or higher than the other two, it indicates an imbalance, which can have detrimental effect on patients, society and the healthcare system. This imbalance, most often, takes the form of unmet medical need, whereby there is a deficit of IgGs that is clinically disadvantageous. Need and demand can be the same, but demand may also reflect over- or under-use. For patients, the most suboptimal situation occurs when the demand is lower than the medical need and is additionally coupled with a decline in availability (below the demand level); a situation which some European countries have recently experienced. Universal dictum says that the healthcare needs are infinite, but healthcare resources are finite. For IgGs this is even more accentuated as the medical need is rapidly increasing whilst the raw material for their manufacturing, human plasma, is limited and, recently, donated volumes have decreased and remain lower than pre-COVID levels:

2.2 AVAILABILITY: FRAGILE PLASMA DERIVED MEDICINAL PRODUCTS (PDMPS) ECOSYSTEM AND ITS UNIQUE NATURE

Firstly, IgGs, and Plasma Derived Medicinal Products (PDMPs) in general, are a unique class of biological therapies that unlike chemically synthesised drugs or biological medicines made by recombinant cell lines, are solely produced from human biological material, in particular blood plasma (Figure 1).

This makes them highly vulnerable to global crises, such as the COVID-19 pandemic, which reduced donor numbers and collected plasma volumes, breaking up connecting elements of the PDMP ecosystem (Figure 2). Needless to say, supply chains remain in a fragile balance under 'normal' circumstances, due to perennially insufficient plasma volumes and/or restrictive regulatory and policy environments. Additional pressure on the already fragile plasma ecosystem comes from a lengthy (up to 12 months), complex, labour-intensive collection, testing, and manufacturing process that, in majority of cases, remains more costly than for other medicines (Figure 1)[8]. Due to the aforementioned complexity of manufacturing, especially the different and unique technologies for plasma fractionation, individual IgG products are not interchangeable. Furthermore, since the starting material is human plasma, the processes for plasma donation and PDMP manufacturing are separately regulated to ensure patient and donor safety.

"If availability of plasma would not be a challenge, not only more patients in different indications could benefit from IgG treatment, but their clinical and socio-economic impact would be maximised!"

PROF. MARTIN VAN HAGEN

"It is very simple: we must not limit the use of IgGs where they benefit patients; we must urgently increase plasma donations that would make such limitations unnecessary."

PROF. GUIDO CAVALETTI

FIGURE1:

COMPARISON OF PDMP AND SMALL MOLECULES VALUE CHAINS[5]

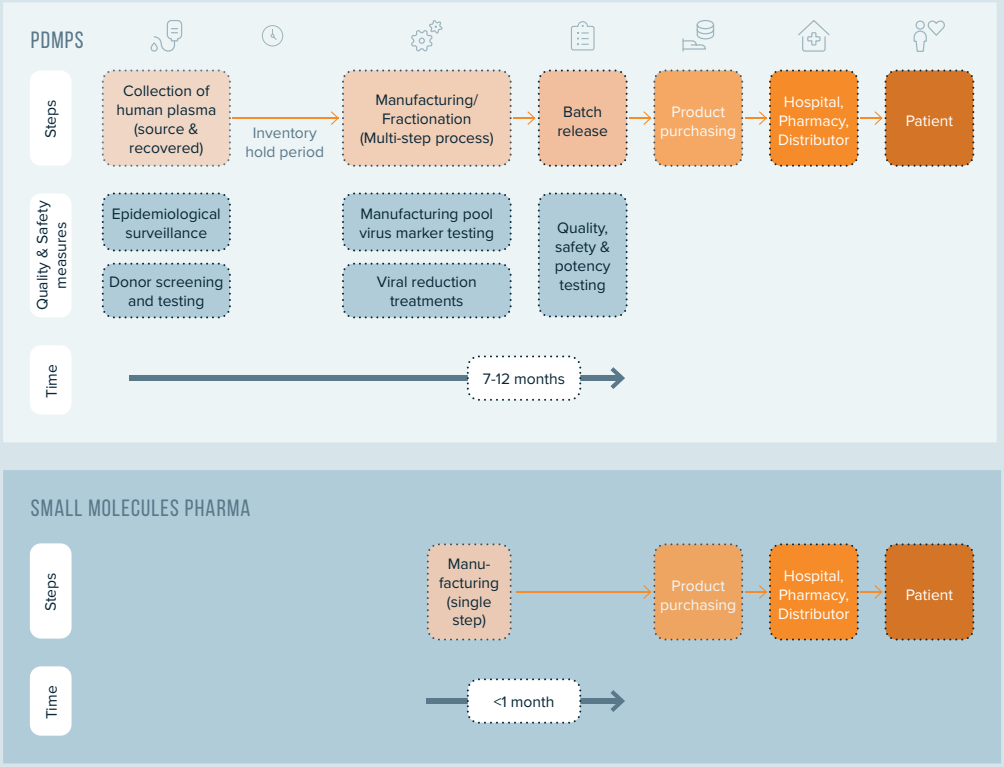
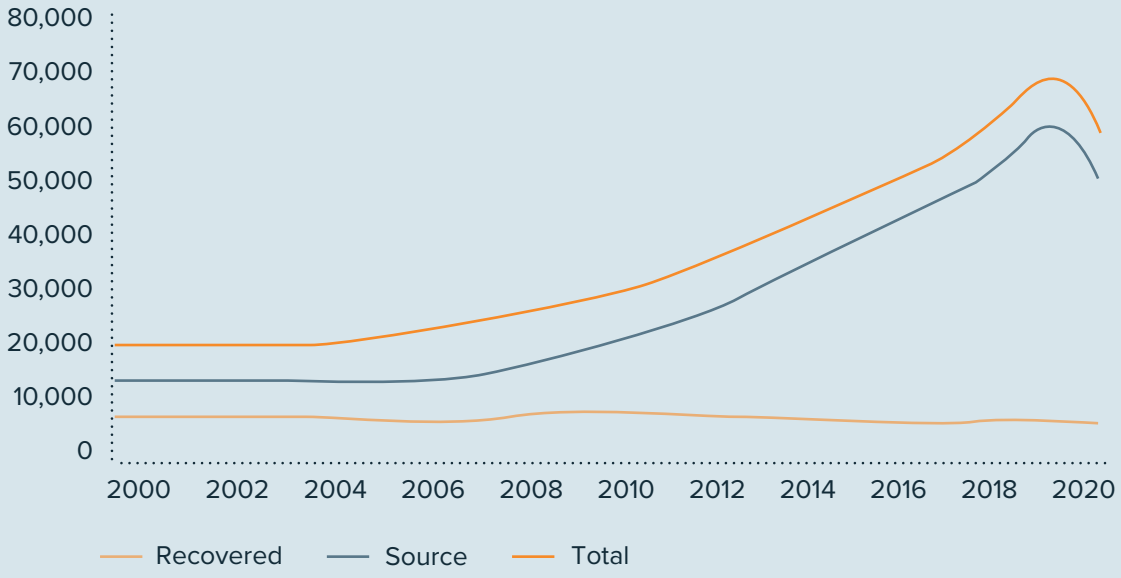


FIGURE 2:

DECREASING GLOBAL PLASMA DONATIONS[9]



2.3 MEDICAL NEED: GROWING MEDICAL NEED AND GROWING USE OF IGGS

Secondly, the medical need for IgGs has been growing rapidly due to demographics (patients on IgG therapy have significantly extended life expectancy), improved diagnosis rates due to education and more accurate diagnostics, and identification of new diseases and indications where patients could benefit from either replacement or immunomodulatory treatment[10]. During the Advisory Committee Prof. Nizar Mahlaoui remarked that the growing medical need for IgG treatments is driven by two key factors – more patients identified as eligible for IgGs due to better functional and genetic diagnostics, and the increasing incidence of secondary immunodeficiencies (SID) as a common side-effect of novel treatments, such as immunotherapy in oncology (B-cell targeted therapies (BCTT)) and immune-mediated neurological and rheumatological diseases together with immunosuppressive therapy in the latter and other medical conditions. These phenomena are also widely acknowledged by a broad clinical expert consensus (e.g., Wildbad Kreuth III)[11], and by data from registries and other healthcare system sources, which indicate that in Europe the use of IgGs over the period of 2003-2018 multiplied by more than 2.5-fold[12] and, if the actual medical demand were to be met, it is estimated to double again by 2025 (Figure 3). This is also reflected globally, with the most recent data from the US, where only in the last 5 years the IgG consumption nearly doubled[13].

The European situation is particularly precarious due to its dependence on US plasma, whereby as much as 40% of plasma for fractionation originates there. Currently Europe uses approximately 25% of global plasma, but only contributes 14% to the global pool. This results in severe deficiencies at a local level that must be compensated with imports (Figure 4).

For instance, until recently, the UK has been particularly vulnerable to fluctuations in plasma collections in Europe and the US as it currently imports the entirety of its plasma for fractionation due to the vCJD regulations. However, where public and private (compensated) plasma collection co-exists in Europe (notably in Austria, Czechia, Germany, and Hungary), the plasma donations are sufficient to cover not only the local medical demand but supply a large portion to the other countries. As the medical demand significantly outpaces the plasma donations volume, a rethink on donors' policies and compensation practices may be necessary, especially within the context of the recent Pharmaceutical Strategy for Europe and revisions to the European Blood Directive[14,5].

The COVID-19 pandemic has also induced a different type of medical or, more accurately, logistic need for certain IgG therapies considering their mode of administration, multiplying pressures on the fragile IgG supply chain. Risk of exposure to SARS-CoV-2 and limited availability of healthcare services affected many patients, especially those with immunodeficiencies. Patients needed to be switched to subcutaneous (injected under the skin) administration of IgGs (SCIG), which can be delivered at home, over intravenous IVIG (infused into the veins), which, in majprity of casaes, requires a hospital or ambulatory setting. In some countries, like in Poland, the proportion of IVIG and SCIG use has fundamentally changed. As Prof. Jahnz-Różyk remarked, in Poland the pre-pandemic use of IVIG constituted 80-90%, whilst now SCIG use is dominant at over 70%. Hence, in a short-term, the growing medical demand will not only be driven by medical need but also by a combination of patient preference and a logistic requirement of a specific mode of administration.

“With advances in molecular or genetic diagnostics, the patient pool with both primary (PID) and secondary (SID) immunodeficiencies eligible for effective and safe IgG treatment will naturally expand by the identification of previously undiagnosed patients but also by the increasing incidence/ prevalence of immunodeficiencies, amongst others, due to common side-effects of novel immunotherapies”

PROF. ISABELLA QUINTI

“The medical need even in the approved indications, like PID, is still not fulfilled outside of the most affluent countries and most advanced healthcare systems. With recent and expected shortages, clinicians may face impossible choices”

PROF. KARINA JAHNZ- RÓŻYK

The need for IVIG or SCIG formulations is not only driven by a crisis, but rather, and primarily, by the best clinical practice and patient tolerability and preference. Prior to the pandemic, there have already been clear guidelines and therapeutic protocols indicating medically most efficacious use of the different IgGs formulations, depending on whether the disease is acute or chronic and whether it requires replacement or immunomodulation. For primary and secondary immunodeficiencies both IVIG and SCIG can be used in low doses, with the former typically administered every 3-4 weeks and the latter every week (or more often in specific cases). By contrast, conditions such as GBS (Guillain-Barre Syndrome - an acute inflammatory disease of the peripheral nerves and spinal roots) require rapid intervention with high doses of IVIG over 3-5 days. Finally, many conditions, which require long-term or lifelong maintenance, are treated with both IVIG and SCIG, depending on many considerations, such as vascular access, tolerability, patient overall mobility and ease of self- administration). These progressive conditions and diseases are typically characterised by a very high patient disease burden and include, amongst others, chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), blistering diseases, and autoimmune encephalitis.

FIGURE 3:

PROJECTED IGG CONSUMPTION IN EUROPE[5]

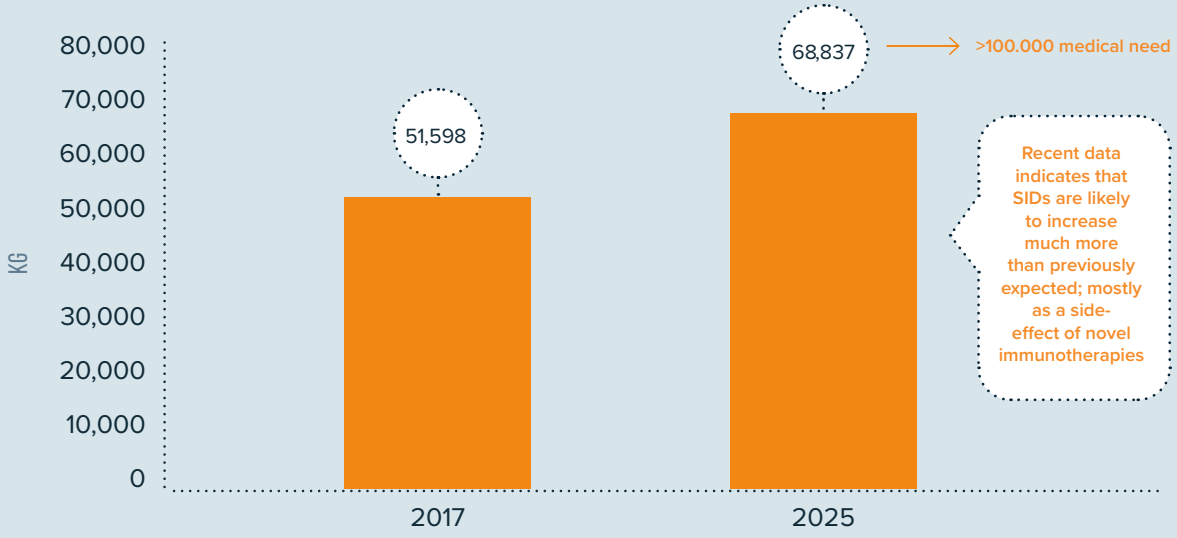
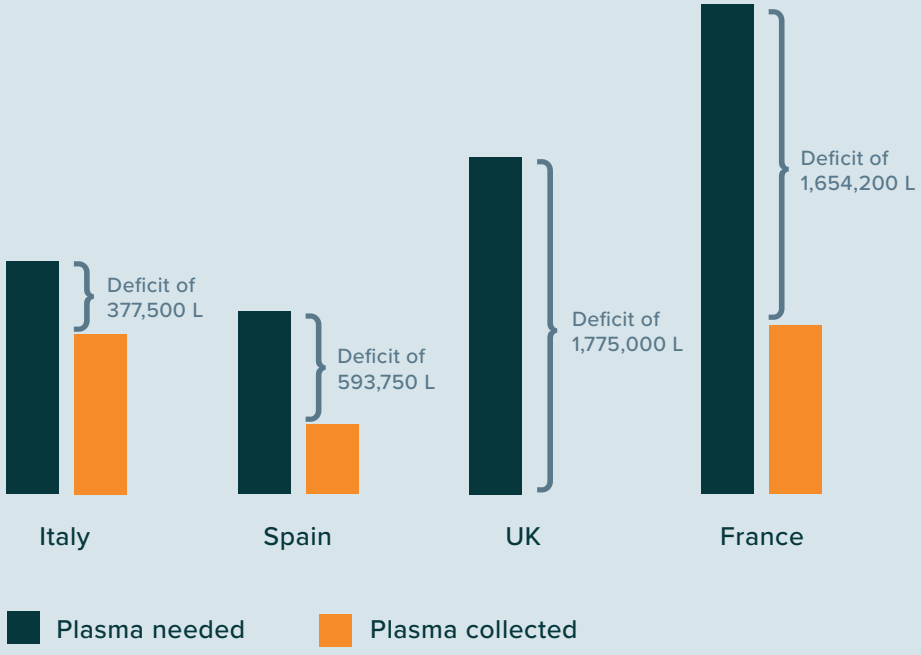


FIGURE 4:

MAJOR EU COUNTRIES WITH PLASMA DEFICIT VS MEDICAL NEED



2.4 OPTIMAL USE VS APPROPRIATE USE: CONCEPT VS RECENT RESPONSES

Finally, the limited availability of plasma and the growing medical need and demand, have triggered formal regulatory measures or guidelines to manage the IVIG and SCIG use. Some countries, notably the UK, France and Belgium, have introduced those measures prior to COVID-19 disruption[11], whilst others, like Italy, have formulated their 'demand management' programs as a response to the crisis. Most of these programs have a common set of recommendations based on ranking of indications (highest being invariably: 'the only and life-saving treatment'), definitions of what constitutes limited availability, and contingency plans for such situations. The volatile situation in the past 2 years has also instigated some controversial opinions and publications, calling upon regulators and the clinical community to severely restrict IgGs use to a narrow set of indications[15]. These opinions have been challenged by patient associations, such as IPOPI (International Patient Organisation for Primary Immunodeficiencies)[16], arguing that such practice, especially outwith crisis situations, would deprive many patients of the only or the most effective treatments, thereby risking their lives, negatively impacting disease progression, and consequently affecting their social functioning and general quality of life. This Paper does not strive to provide a definitive guidance on what to do when restricting IgG use to only the 'life-saving treatments' that may be clinically and ethically necessary and would require careful case-by-case consideration by an independent committee. It does, however, attempt to explore systematic ways in which such extraordinary situations could be prevented in the future. The Advisory members unequivocally agreed that the call to permanently narrow IgG indications would be pernicious and unjustified, and may lead to severe deterioration across clinical, social, and humanistic dimensions.

"In particular Neurological diseases, where IgGs have an evident therapeutical value, there is a high level of accuracy in diagnostics and high level of evidence in IgG eligibility for these patients"

PROF. MARK STETTNER

As Prof. Enk elucidated, using licensed and unlicensed categories to stratify 'appropriateness' of IgG use is a partial and often inappropriate solution, especially in the area of rare and ultra-rare diseases, where data required for regulatory approval is often difficult or unethical to obtain. For instance, Pemphigus Vulgaris, a rare dermatological blistering disease, which can be effectively treated with IgGs, is not an approved condition for treatment in Europe (though recent regulatory approval in Japan). This view was further endorsed by Prof. Stettner, who objected to unjustified opinions on overuse of IgG in EMA-approved neurological indications. In the case of an accurate diagnosis IgG have shown efficacy regarding meaningful outcome parameters in acute conditions (e.g. GBS) and halting progression or limiting disability in chronic ones (e.g. CIDP or MMN). Individualization of IgG dosing schemes are a matter of clinical research and due to the complex nature of the conditions some patients may be 'overdosed' while others are 'underdosed'. Current data does not allow a simple generalization on a general overuse of IgG.The Advisory have also indicated the more pertinent issue of underdiagnosis, for instance high risk of CIDP in a very large population of patients with diabetes in whom the diabetes-related neuropathy could be misdiagnosed[17]. This would indicate that the medical need and therefore pressure on IgG availability may be even greater than current estimates.

As outlined above there are multiple compelling reasons and an urgency to propose a consensus-driven framework that would define clear criteria of appropriate IgG use. Such framework must respect patient-centricity, avoid any harm, and maximise the clinical, socio-economic, and humanistic benefits of the effective and safe treatments.

IGGS APPROPRIATE USE: CONSENSUS FRAMEWORK

3.1 CLINICAL PERSPECTIVES: IGG USE IN IMMUNOLOGY, NEUROLOGY AND DERMATOLOGY

The increased therapeutic use of IgGs differs strongly across Europe, driven by regulatory status, clinical protocols and guidelines, procurement practices and even cost containment measures. Advisory members were in agreement that these differences persist not only between different countries, a fact clearly demonstrated in PID by IPOPI[18] but also between clinics and centres of excellence within a single country[12]. Notwithstanding these differences, the largest therapy areas for IgGs are Primary and Secondary Immunodeficiencies (PID and SID respectively), followed by Neurology, with a large number of rare, autoimmune, or immune-mediated diseases (GBS, CIDP, and MMN). Even within the disease areas with wide-spread and long-term IgG use, there are still issues with regulatory approval or adoption of the latest clinical guidelines. For instance, in many European countries, as well as the US, the use of IgGs in SID, GBS, or Autoimmune Encephalitis is a common clinical practice, or evidence-based prescribing, but is still subject to off-label procedure approvals for reimbursement, whereby clinicians must apply for approval of every single patient case. There are many more genetic and rare diseases where the IgG treatments are less common but not less beneficial and a long list of conditions expected to benefit from these treatments (a large number of clinical trials are recently completed or ongoing in rare indications, such as myasthenia gravis or diffuse cutaneous systemic sclerosis.)[1].

3.2 WHO GUIDELINE AND AIFA CTS FRAMEWORK: QUALIFIERS OF CARE, UNMET MEDICAL NEED, ADDED THERAPEUTIC VALUE AND QUALITY OF EVIDENCE

As mentioned throughout this paper, the definition of appropriate use of IgGs is as complex as it is elusive. It is often derived from Health Technology Assessment (HTA) decisions, some from 10-15 years ago, or from the actual frequency of clinical use or through demonstrable therapeutic added value obtained from statistically valid clinical data.

Taken in isolation, these dimensions are partial and may appeal only to specific healthcare stakeholders like payers or regulators. Taken together, they represent a highly unsystematised and heterogenous set of indicators and data points that often remain inconclusive or case-dependent. The Advisory members unanimously admitted the urgent need for what Prof Quinti clearly expressed as: *"transparent and standard methodology or framework to assess and appraise the appropriate use of IgGs {and use} across different geographies and indications".*

In order to find a common ground and reach a consensus on the holistic and effective framework, the Advisory members were asked to consider different dimensions from established and reputable sources: WHO and European HTA bodies. The frameworks that were shortlisted were the WHO principles (Figure 5) and AIFA CTS Innovation Algorithm (Figure 6). The former provides an extensive guidance on patient-centric considerations across three qualifiers of care: Effective (based on valid evidence, unmet need), Consistent (ethical principles, societal impact, etc) and Efficient (cost-effective, value based, avoidable cost, etc). The latter supplies a ready-made and proven matrix with transparent and exhaustive dimensions for appraising a medical technology against level of unmet medical need, added therapeutic value, and quality of evidence. Both WHO and AIFA frameworks were found to be co-extensive and/or mutually complementary. AIFA CTS was chosen due to its granular guidance on specific criteria in each of the three dimensions, which made it most amenable to adaptation. Whilst AIFA CTS was never explicitly intended to define 'appropriate use' and was designed to assess the level of innovativeness of medical technologies, the Advisory members agreed the two are co-extensive and the algorithm is both pragmatic and easily adaptable to IgG use.

The AIFA CTS, as mentioned above, has three assessment dimensions, each one of which has detailed criteria to allocate different ratings, for instance in the case of added therapeutic value and unmet medical need these will range from Highest to Absent and in the case of quality of evidence they will be appraised on a Low to High scale. As this framework is designed to be universally valid for all medical technologies undergoing HTA assessment, it needs to be adapted to the specific and unique nature of IgGs. The most significant adaptation agreed with Advisory Members was to replace the AIFA categories of 'innovativeness' with those of 'appropriateness' (Figure 6). These two concepts are evidently not interchangeable, however their constituent parts, as the next chapter shows, were found to be highly interconnected and meaningful in the search for the definition of 'appropriate use'.

"There is clear Call to Action: we must create a transparent and standard methodology or framework to assess and appraise the appropriate use of IgGs; it must inform a cross-border and cross-indication exchange of best practices, treatment protocols, guidelines, as well as clinical and real-world evidence (RWE) data"
PROF. ISABELLA QUINTI

FIGURE 5:

ADAPTED WHO FRAMEWORK FOR APPROPRIATE MEDICAL USE

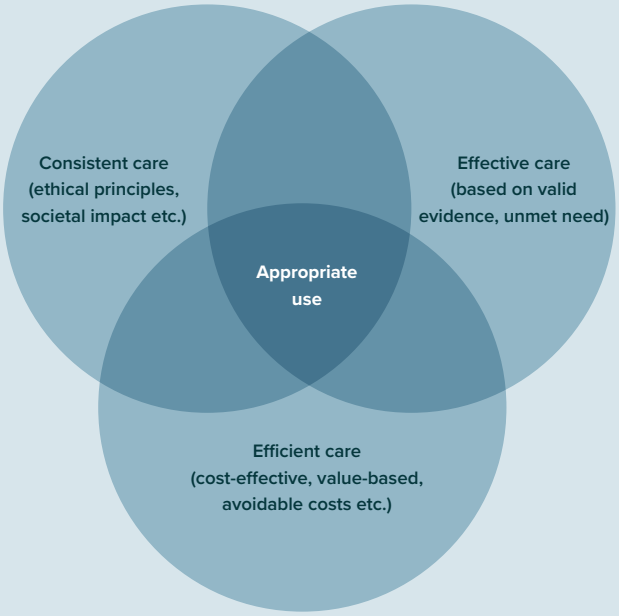
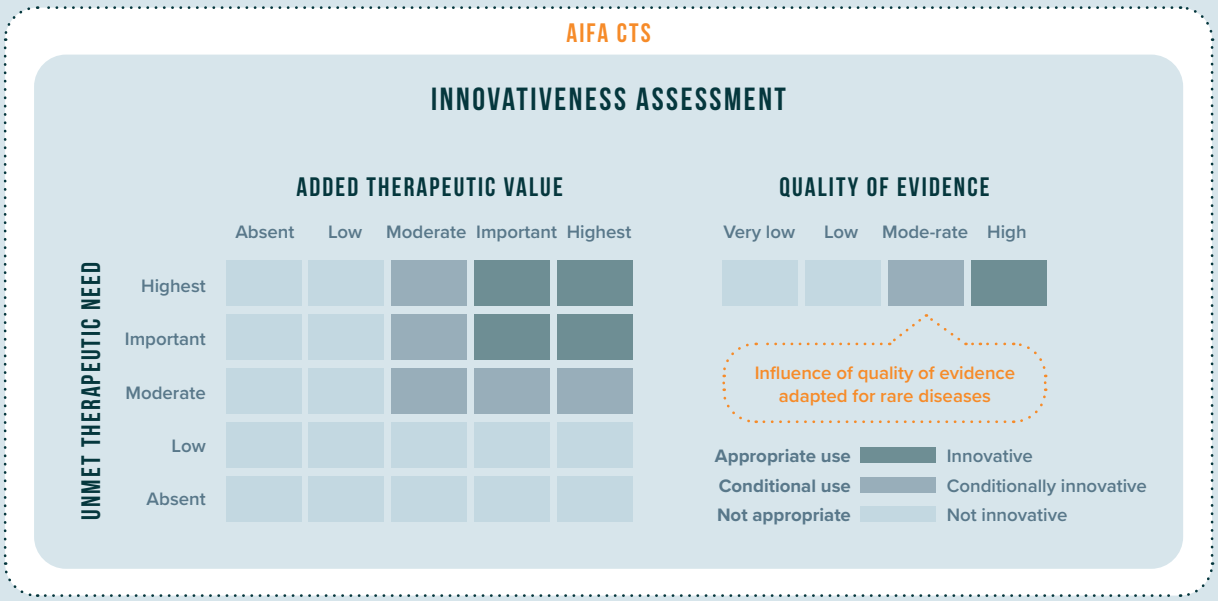


FIGURE 6:

AIFA CTS INNOVATION ALGORITHM ADAPTED TO APPROPRIATE USE



3.3 FRAMEWORK ADAPTATION: ADBOARD CONSENSUS

During a half-day, virtual Advisory meeting on the 18th of February 2022, the discussion centred on adapting the AIFA CTS algorithm to the issue of appropriate use, made specific to IgGs and delineated into detailed assessment dimensions and criteria. Starting with the Added Therapeutic Value, the participants engaged in cross-indication and comparative discussions, reaching a clear agreement on what constitutes different levels of added value. There were three dimensions agreed upon: Efficacy, Safety Profile/Adverse Effects, and Practicality. Whilst the first two are well-established concepts in both clinical and regulatory communities, the third one, namely practicality, is specific to IgGs and concerns frequency, mode of administration and point of care. It also relates, clearly, to patient-centricity and its place in assessing the value of medications or therapeutics; in other words, outcomes and practicalities that are meaningful to patients must also be meaningful for clinicians, regulators and payers. As previously mentioned, the ability to deliver treatment at home or to reduce hospital visits is not only a logistic or avoidable cost issue but also a significant clinical and patient concern. Patients with immunodeficiencies, as part of their treatment regimen, should minimise exposure to infections, especially in situations of heightened risk, such as COVID-19 pandemic. Having an SCIG formulation in addition to IVIG, therefore, can be seen as adding significant therapeutic value. Patients with compromised or difficult vascular access must be treated with SCIG, conversely, where disease is a cutaneous disorder, IVIG might be the only option. Thus, the combination of the three dimensions and their respective criteria allows for assessing the level of added therapeutic value, from *highest* to *absent* (Table 1)

“Whichever framework is applied to define appropriate use, it must be both practical and universally applicable but also specific to IgGs to ensure their unique nature and heterogenous therapeutic landscape are all sufficiently reflected”

PROF. SILVIA SANCHEZ-RAMON

TABLE 1:

DIMENSIONS AND CRITERIA FOR ASSESSING ADDED THERAPEUTIC VALUE

Dimension / Level	Maximum	Importent	Moderate	Poor	Absent
CLINICALLY RELEVANT OUTCOMES	High efficacy and vital	High efficacy	Reasonable efficacy	Low efficacy	Absence of clinical benefit
ADVERSE EFFECTS & SAFETY PROFILE	High safety profile with very low or absent adverse effects	High safety profile with low of absent adverse effects	Reasonable safety profile	Poor safety profile	Poor safety profile
PRACTICALITIES	Practical (easy mode of administration and point of care)	Practical (easy mode of administration and point of care)	Practical (easy mode of administration and point of care)	Less practical (Lack of easy mode of administration and/ or point of care	Less practical (Lack of easy mode of administration and/ or point of care

The second part of the framework, the level of unmet medical need has been subject to significant revision compared to the original AIFA definitions. The Advisory members debated the benefits of considering a counterfactual analysis based on the scenario, where IgG treatments are not available and what unmet medical need would that posit. In the spirit of practicality and universality of the framework, the focus remained on two areas: availability of efficacious alternative treatments and the disease burden in the absence of IgG treatment. (Table 3). The first criterion would assign maximum level of unmet medical need to disease areas or indications where no alternative treatments exist and where disease burden, expressed as DALY, is the highest (e.g., PIDs). Multiple conditions with high disease burden would fall under the category of Important, where alternative treatments, if they exist, show supplementary or of low(er) efficacy. If looked at from this perspective, there are many uses of IgGs that would be addressing maximum or important medical needs (Table 2). This clearly showcases how important it is to rethink what constitutes appropriate use beyond the current regulatory landscape, which remains highly heterogenous across Europe (e.g. uneven number of countries with authorisation in different indications).

TABLE 2:

CONDITIONS FOR WHICH IG HAS BEEN APPROVED (AUTHORISED/LICENSED) AS A THERAPY

CONDITION	EMA[20]	# EU COUNTRIES WITH LICENSED USE	# EU COUNTRIES WITH OFF-LABEL USE
SECONDARY IMMUNODEFICIENCIES IN PATIENTS WHO SUFFER FROM SEVERE OR RECURRENT INFECTIONS, INEFFECTIVE ANTIMICROBIAL TREATMENT AND EITHER PROVEN SPECIFIC ANTIBODY FAILURE[21] OR SERUM IGG LEVEL OF <4 G/L	Yes	All	
ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION	Yes	All	-
AUTOIMMUNE HEMOLYTIC ANEMIA	No	3	16
CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY	Yes	9	14
GUILLAIN-BARRÉ SYNDROME	Yes	All	-
PRIMARY IMMUNE THROMBOCYTOPENIA	Yes	All	-
KAWASAKI DISEASE	Yes	All	-
MYASTHENIA GRAVIS/LAMBERT-EATON MYASTHENIC SYNDROME	No	3	16
MULTIFOCAL MOTOR NEUROPATHY	Yes	6	10
MULTIPLE SCLEROSIS IN PREGNANT WOMEN	No	1	11
PRIMARY IMMUNODEFICIENCY DISEASES WITH IMPAIRED ANTIBODY PRODUCTION	Yes	All	-
SEPTICEMIA/SEPTIC SHOCK	No	7	17
SYSTEMIC VASCULITIS	No	3	14

European Medicines Agency. Core summary of product characteristics for human normal immunoglobulin for intravenous administration (IVIG) rev. 6, 16 December 2021. Available online: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-human-normal-immunoglobulin-intravenous-administration-ivig-rev-4_en.pdf (Accessed June 7, 2022);

TABLE 3:

DIMENSIONS AND CRITERIA FOR ASSESSING UNMET MEDICAL NEED

DIMENSION / LEVEL	MAXIMUM	IMPORTANT	MODERATE	POOR	ABSENT
ALTERNATIVE TREATMENTS (VS IGG)	No alternative treatments available	Alternative treatments exist with inferior results (e.g. worse outcomes, lower efficacy, worse safety profile and higher complexity)	Alternative treatments exist with similar results (e.g. similar outcomes, efficacy, safety profile and complexity)	Alternative treatments exist with better results (e.g. better outcomes, higher efficacy, better safety profile and lower complexity)	Alternative treatments exist with much better results (e.g. better outcomes, higher efficacy, better safety profile and lower complexity)
DISEASE BURDEN	Very High DALY (severe disability and premature death)	High DALY (severe disability or high risk of premature death)	Moderate DALY (disability and risk of premature death)	Moderate to Low DALY (risk of disability)	Low DALY (minimal impact on Quality of Life)
PRACTICALITIES	Practical (easy mode of administration and point of care)	Practical (easy mode of administration and point of care)	Practical (easy mode of administration and point of care)	Less practical (lack of easy mode of administration and/ or point of care)	Less practical (lack of easy mode of administration and/ or point of care)

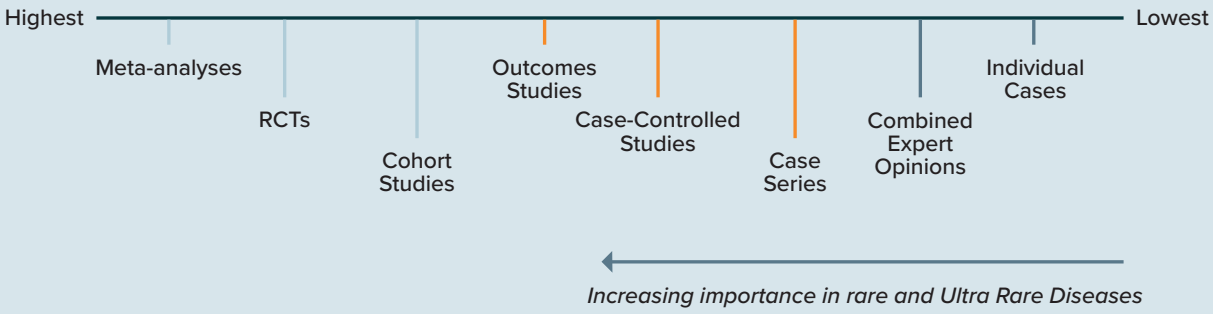
“Dermatological disorders are often overlooked and commonly believed to be ‘minor ailments’ or ‘aesthetic issues’; nothing is further from the truth when you look at life-threatening conditions like blistering diseases or scleroderma. It is extremely important to acknowledge the high disease burden of these conditions in assessing whether IgG use is appropriate”,

PROF. ALEXANDER ENK

The use of unmet medical need and therapeutic value as primary dimensions for assessing IgG therapeutic use is invariably conditional on the ability to provide compelling data to support any such claims. As the majority of IgG indications are rare or ultra-rare, they share a challenge of data availability, data quality and comparability, and, finally, the feasibility or ethicality of data generation. The AIFA algorithm uses data quality as a filter of the other two dimensions; a claim that a therapy efficaciously addresses high unmet medical need must be sufficiently demonstrable using acceptable methodologies and analytics. However, this framework makes specific allowances for orphan diseases, where a flexible interpretation of data quality can be applied. This flexibility stretches into both the method of generating data (trials, studies, case reports, opinions from clinicians, patient group surveys) but also the contents or inputs (primary endpoints, novel endpoints, functional endpoints, patient reported outcomes (PROs)). The Advisory members agreed that, as a departure point, one should adopt an accepted categorisation of evidence quality, such as the Centre for Evidence Based Medicine (CEBM) scale (Figure 7)[22]. However, the IgG situation is unique in that there are many indications with little or no clinical trial data or where such data would be unethical to generate. Until higher quality data or real world data is gathered, the regulatory authorities and clinical community may wish to consider greater flexibility in accepting case studies and expert opinions. At the same time, the members agreed on a call to action to maximise efforts to create pan-European registries and studies, to elevate the quality of evidence from cases to, where possible, in-depth outcomes studies. Equally, there is a need for further exploration of various endpoints across IgG-treated conditions, to ensure the ones being used are clinically relevant and meaningful to the patients.

FIGURE 7:

QUALITY OF EVIDENCE SCALE, ADAPTED FROM OXFORD CENTRE FOR EVIDENCE BASED MEDICINE



"For any assessment framework to work indata-poor diseases, it needs to be flexible enough to allow for alternative or novel endpoints; surrogate, functional or patient-reported! The challenge remains in choosing endpoints that are simultaneously clinically relevant and also meaningful to the patients and physicians!,

PROF. RICHARD KNIGHT

IGGS APPROPRIATE USE: OUTSTANDING QUESTIONS AND PRELIMINARY RECOMMENDATIONS

As mentioned in the Preamble, this paper does not intend to provide categorical recommendations or definitive answers. However, based on the proposed IgG appropriate use framework, certain conditions must be met for it to become truly effective. These conditions enumerated below can be treated on the one hand as preliminary recommendations and on the other as an indication of areas for further exploration or potential challenges.

It is clear that 'appropriate use', as defined by the Advisory Committee, does not solve the tension between the availability of IgGs and the growing medical need and/or medical demand. In fact, should all indications with immune deficiency or aberrant immune homeostasis be re-assessed using the above framework, it is likely that the medical need for IgGs would be discovered to be even greater than previously estimated based on growing consumption. This re-assessment, however, is critically important to ensure appropriate treatment for all patients in all indications where IgGs have a high or very high therapeutic value. For all patients to have unrestricted access to IgG treatments, a fundamental issue of plasma donations volume must be addressed in parallel. The Advisory Committee have therefore identified two sets of Preliminary Recommendations:

4.1 ADDRESS THE ROOT-CAUSE OF IGGS' AND PLASMA'S LIMITED AVAILABILITY

1. **RESILIENCE**: explore key conditions and actions necessary to ensure resilience of European healthcare systems, both in terms of increasing plasma collection volumes and ensuring IgGs' availability for appropriate therapeutic use.
2. **EDUCATION**: build awareness through local and pan-European public health education, tailored to all ages, promoting regular plasma donation initiatives.

3. **INFRASTRUCTURE**: invest in modern infrastructure and expertise for efficient plasmapheresis delivery, alongside all effective measures for boosting source plasma donations, including coexistence of private and public systems.

4.2 RE-ASSESS AND ENABLE ACCESS TO APPROPRIATE IGG USE

4. **RE-ASSESSMENT**: systematically reassess and acknowledge growing medical need for IgGs to ensure equitable access for all patients who will benefit in line with the appropriate use framework.
5. **ACCESS**: review regulatory requirements to authorise appropriate IgG use in line with the proposed framework criteria and evidence scale.
6. **EVIDENCE**: intensify efforts to generate and analyse high quality clinical trial and real-world data across rare immune-mediated diseases and secondary immune deficiencies
7. **COLLABORATION**: stimulate pan-European collaboration to exchange best clinical practices and data and foster joint initiatives, studies, and registries, at both the single indication level and cross-indication level.
8. **PATIENT VOICE**: ensure patients and patient advocacy groups are educated and meaningfully involved in the discussion on IgG therapeutic value and the future of the IgG therapeutic use in Europe.

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APPENDIX 1: DETAILED BIOGRAPHIES OF EXPERT ADVISORY COMMITTEE MEMBERS

Immunologists

- Prof. Isabella Quinti (Italy) is a Professor in Internal Medicine, Clinical Immunology at Sapienza University of Rome and Head of Primary Immunodeficiencies Unit at Azienda Policlinico Umberto I, Sapienza University of Rome. Her major research areas are Primary Immunodeficiencies, vaccines, B-cell lymphoproliferative disorders, chronic obstructive pulmonary disease, as well as health-related quality of life assessment and outcome measures. Prof. Quinti is also responsible for the Italian Network on CVID (IPINET: Italian Primary Immunodeficiency Network) since 2001.

- Prof. Nizar Mahlaoui (France) is a pediatrician specialized in immuno-hematology at Necker-Enfants Malades University Hospital in Paris (France). He manages the French National Reference Center for Primary Immune Deficiencies (CEREDIH, chaired by Prof. Alain Fischer) and serves as a member of the Scientific Advisory Board of the French National PID Patients Association (IRIS) and of the Ataxia-Telangiectasia patients association AT-Europe. He is a member of the European Society for Immunodeficiencies (ESID) since 2008 and has served on the ESID Board as the Registry Working Party Chair Elect (2014-2018, Vice-Chair 2018-2020). He also serves on the International Patient Organization for Primary Immunodeficiencies (IPOPI) Board as Chair of the Medical Advisory Panel (Vice Chair: 2013-2017, Chair: 2017—, www.Ipopi.org).

- Prof. Karina Jahnz-Różyk (Poland) is the head of the Department of Pneumonology, Allergology and Clinical Immunology, Military Institute of Medicine – National Research Institute, Warsaw and was appointed by the Minister of Health to act as a national consultant in the field of allergology. Prof. Jahnz-Różyk is a specialist in internal diseases, lung diseases, allergology and clinical immunology.

- Prof. P. Martin Van Hagen (The Netherlands) is a Professor of Clinical Immunology and the head of the section ‘Clinical Immunology’ of the Department of Internal Medicine at Erasmus Medical Center. Prof. Van Hagen is also a staff member of the Eye Hospital in Rotterdam, and a visiting Professor Immunology of Chulalongkorn University in Bangkok, Thailand. His expertise lies in treating patients with immune-mediated diseases including PID and sarcoidosis.

- Dr. Silvia Sánchez-Ramón (Spain) is the President of the Society of Immunology of the Community of Madrid (SICAM), a clinical immunologist and the Head of the Immunology Department at Hospital Clínico San Carlos, and a researcher and an Associate Professor of Immunology at Complutense University of Madrid. Her clinical research focus is on Neuroimmunology, Immunoregulation and immunodeficiency. Dr. Sánchez-Ramón is also part of the Medical Advisory Panel at IPOPI. Sha is an Associate Editor of Frontiers in Cellular Neuroscience. Dr. Sánchez-Ramón, has received several national and international awards and has participated as jury of the Salud 2000 and Aspire scientific awards

Rheumatologist

- Prof. Jacob M. Van Laar (The Netherlands) is a Professor at the Department of Rheumatology and Clinical Immunology at UMC Utrecht. His main research interests involve clinical and pathogenetic aspects of systemic sclerosis and rheumatoid arthritis, aimed at improving the outcome of patients with rheumatic diseases by innovative clinical-translational research. He is also the Founding Member Stichting ARCH, a member of the Scientific Advisory Board at the Edith Busch Stiftung, and a member of the EUSTAR (EULAR Scleroderma Trials and Research).

Neurologists

- Prof. Mark Stettner (Germany) is a senior consultant neurologist, and Associate Professor at the Department of Neurology and the Head of the outpatient department at the University of Essen (Germany). His research and his clinical focus are immune-mediated neuropathies, the mechanisms leading to damage and identification of target antigens. In addition, he works on clinical surrogate parameters to better monitor patients with peripheral nervous system inflammatory diseases.

- Prof. Guido Cavaletti (Italy) is a senior consultant neurologist and the Head of the Neuroimmunology Center, at the S. Gerardo Hospital, Monza. Prof. Cavaletti is also the Head of the Experimental Neurology Unit at the School of Medicine and Surgery and former Director of the PhD program in Neuroscience, University of Milano-Bicocca, Monza. He is a Member of the Board of Directors of the Peripheral Nerve Society as Chair of the Toxic Neuropathy Consortium, the Vice Rector for Research at the University of Milano-Bicocca and the Coordinator of the steering committee of the international CI-PeriNoms group on the investigation of chemotherapy-induced peripheral neurotoxicity.

- Prof. Richard Knight (The United Kingdom) is an academic clinical neurologist in the National CJD Research & Surveillance Unit (of which he is a past Director), in the Centre for Clinical Brain Sciences, University of Edinburgh. He is Chair of the UK Creutzfeldt-Jakob Disease (CJD) Support Network and an Expert Advisor to the International CJD Support Alliance.

- Dr Katy Murray (The United Kingdom) is a consultant neurologist with a special interest in multiple sclerosis (MS) and neuromyelitis optica (NMO). She leads the Scottish Neuromyelitis Optica Clinic, in addition to holding weekly MS clinics at the Anne Rowling Clinic and general neurology clinics in Forth Valley. She recruits to MS and NMO research trials and collaborates with the National NMO team from Liverpool.

Dermatologist

- Prof. Alexander Enk (Germany) is the Head of the Department of Dermatology at the Ruprecht Karls Universität Heidelberg. He specialized in immunodermatology and was an elected member of the German Academy of Sciences “Leopoldina”. He is a former president of the ESDR and a Board member of the ISID. Prof. Enk is an honorary member of the Society for Investigative Dermatology, the French Society for Dermatology, the Austrian Society of Dermatology and Venereology (ÖGDV), the Japanese Society for Investigative Dermatology (JSID), and of the Hungarian Austrian Dermatology Society.

APPENDIX 2: LIST OF ACRONYMS

AIFA CTS	Italian Medicine Agency Technical Scientific Commission
AIFA	Italian Medicine Agency
ARCH	Arthritis Research and Collaboration Hub
BCTT	B-cell Targeted Therapies
CEBM	Centre for Evidence Based Medicine
CEREDIH	French National Reference Center for Primary Immune Deficiencies
CIDP	Chronic Inflammatory Demyelinating Neuropathy
CJD	Creutzfeldt-Jakob Disease
COVID-19	Coronavirus Disease 2019
CVID	Common Variable Immune Deficiency
DALY	Disability-Adjusted Life Year
EMA	European Medicines Agency
ESDR	European Society for Dermatological Research
ESID	European Society for Immunodeficiencies
EU	European Union
EUSTAR	EULAR Scleroderma Trials and Research
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
HEOR	Health Economics and Outcomes Research
HTA	Health Technology Assessment
IgG	Immunoglobulin G
IPINET	Italian Primary Immunodeficiency Network
IPOPI	International Patient Organisation for Primary Immunodeficiencies
I.R.I.S.	Association de Patients Deficits Immunitairies Primitifs
ISBT	International Society of Blood Transfusion
ISID	International Society for Investigative Dermatology
IVIG	Intravenous Immunoglobulin
JSID	Japanese Society for Investigative Dermatology

MMN	Multifocal Motor Neuropathy
MRB	Marketing Research Bureau
MS	Multiple Sclerosis
NMO	Neuromyelitis Optica
ÖGDV	Austrian Society of Dermatology and Venereology
PDMP	Plasma Derived Medicinal Products
PID	Primary Immunodeficiency
PNS	Peripheral Nervous System
PROs	Patient Reported Outcomes
RCTs	Randomized Control Trials
RWE	Real World Evidence
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCIG	Subcutaneous Immunoglobulin
SICAM	Society of Immunology of the Community of Madrid
SID	Secondary Immunodeficiencies
UK	United Kingdom
UMC	University Medical Center
USA	United States of America
vCJD	Variant Creutzfeldt-Jakob Disease
WHO	World Health Organization