Monographs of the Víctor Grífols i Lucas Foundation 67

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PRESENTATION

In 2017, the Víctor Grífols i Lucas Foundation organised a seminar on the topic of "Ethics and Plasma Donation". The context then was different from today's but there was still a need for considered, in-depth debate on the issues. Owing to its association with the pharmaceutical company Grifols, which collects and processes plasma, there was a risk that the Foundation would not be seen as neutral. However, we believed then and we believe now that it is both necessary and timely to provide a space for this discussion where opinions and perspectives can be presented in the spirit of dialogue and listening that befits bioethics. The Foundation has always enjoyed full independence in its concerns and activities, and issues regarding plasma are no exception. Hence, this new seminar aims to generate reflections on the policies that need to be implemented in this area and which must focus on the health benefits for people, regardless of financial and business considerations.

As a substance of human origin and a component of blood, plasma is an essential element in the manufacture of blood products, many of which are indispensable medicines for numerous chronically ill patients who need these treatments on a lifelong basis. In Europe, some 300,000 people depend on these medicines, and the demand for plasma is forecast to grow, both because more patients will be diagnosed as needing such therapies and due to the identification of new indications for the use of plasma products. Most European countries do not collect enough plasma for their patients, which means that it must be imported from abroad (mostly from the United States).

In our culture, little distinction is made between blood and plasma donation, both of which are placed under the same heading of solidarity and altruistic action, while models that contemplate compensating donors of plasma for use in the manufacture of blood products are viewed with suspicion. However, this confrontation between the compensated model and the so-called "altruistic model" is frequently the result of ignorance rather than of rigorous analysis of what the two terms actually mean.

Aware of this decades-old problem and after the experience of COVID-19, which jeopardised the supply of these treatments to the point that they had to be rationed due to product shortages, Europe is now finalising a regulation that unifies the criteria for all substances of human origin (SoHO). The new legislation introduces "donor compensation" as an element that could help to achieve self-sufficiency in plasma and thus end dependence on imports. It is prompted by the fact that some countries (Germany, Austria, the Czech Republic, and Hungary) already successfully apply this practice and are self-sufficient – – while there is a plasma deficit in other countries that do not compensate donors, with efforts in recent years to recruit more donors through nationwide campaigns yielding poor results

For decades, Europe has defended the notion that "altruism and solidarity" should form the basis of donation in general, and has advocated the principle of non-commercialisation of the human body, portraying commercialisation as a violation of human dignity. This raises several questions. Is compensating donors incompatible with altruism and solidarity? Is compensation the same as commercialisation? Is an altruistic model without compensation workable in terms of responding to patients' needs? Is an uncompensated model fair to donors and patients? Is it acceptable for a country to refuse to compensate donors on the grounds that this is ethically incorrect while, at the same time, importing remunerated donations?

All these questions were discussed in the seminar, the results of which have led to this publication in which we have attempted to analyse all the arguments from an ethical standpoint that encompasses values such as solidarity, responsibility, individual freedom, human dignity, and the principle of fairness, while also describing the current situation in Europe and the need to seek solutions to the scarcity of plasma. As part of the problem, which includes the way society understands these questions, we also discussed the various models that presently coexist, and we reflect the opinions of donors, patients, and their families.

We hope it will be of interest to readers.

Victòria Camps
President of the FVGiL

Plasma Requirements in Europe and the Different Supply Models

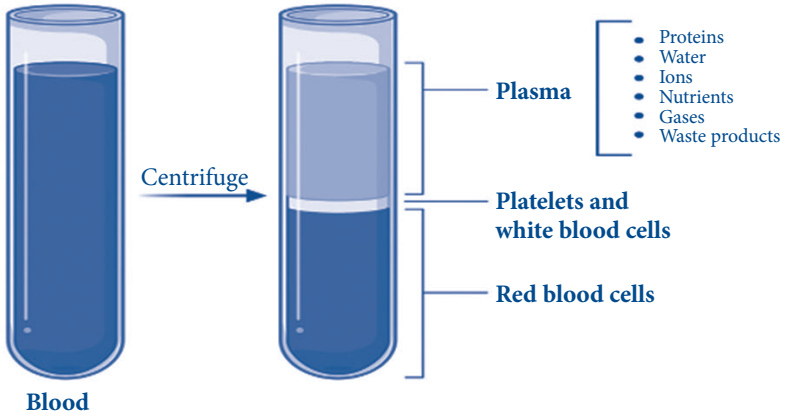
Albert Torelló

Director of Programmes, Ostrom Institute, Catalonia

Plasma and its therapeutic use

Plasma is a component of blood, and consists mainly of water, proteins, mineral salts, and nutrients.

Water constitutes the largest proportion of plasma and provides a transport medium for nutrients, hormones, and metabolic waste. Plasma proteins, including albumin, globulins, fibrinogen, and coagulation factors, play a crucial role in osmoregulation, immune defence, and blood coagulation, among other physiological functions. Plasma also transports gases such as oxygen and carbon dioxide.



Several kinds of therapeutically useful proteins or blood products can be obtained from blood plasma. Among the most important of these blood products are coagulation factor concentrates, which are essential for the treatment of inherited or acquired coagulation disorders. In patients with haemophilia, for example, administration of plasma-derived factor VIII and factor IX concentrates is a primary intervention to restore the organism's clotting capacity and thus to stop potentially life-threatening haemorrhages.

Immunoglobulin, a protein fraction of plasma that contains antibodies, is used to strengthen the immune system in situations where the immune response is compromised. Patients with primary or secondary immunodeficiencies can benefit from administration of immunoglobulin, which provides an additional defence against infection.

Another plasma protein of therapeutic interest is alpha-1 antitrypsin, a deficit of which can cause loss of elasticity of lung tissue leading to respiratory complications like emphysema or chronic obstructive pulmonary disease.

Procuring plasma of human origin

Manufacturing these plasma-derived pharmaceutical products requires supplies of human plasma as the raw material. Obtaining plasma of human origin is a meticulous process governed by strict safety standards. Donation can be made using two main methods: whole blood donation, in which the plasma is separated from cellular components by means of centrifugation; and plasmapheresis, a technique that allows for the selective removal of plasma while the remaining blood components are returned to the donor.

Whole blood donation is a common process in blood banks and donation centres. Once the donation is made, the blood is centrifuged to separate the red blood cells, platelets, and white blood cells from the plasma, which is then stored and submitted to rigorous testing to ensure safety and quality prior to therapeutic use. Using this procedure, donors can give blood between three and six times a year. The process takes approximately thirty minutes and some 250 ml of plasma can be obtained.

Plasmapheresis, on the other hand, allows just the plasma to be extracted. During this procedure, the donor's blood is removed and separated into its components using a special apheresis machine. The plasma is collected, and the other components are returned to the donor. This method yields larger volumes of plasma 750 ml compared to the 250 ml procured via whole blood donation and is frequently used to obtain more significant quantities of blood products. Donations can be made by plasmapheresis between twenty and fifty times a year and the process takes about ninety minutes.

	Extraction	Method	Frequency	Duration	Yield
Whole blood donation	Blood obtained from donation centre	Blood via whole blood donation	3-6 donations a year	30 min.	250 ml of plasma
Plasmapheresis	Plasma obtained from donation centre	Plasma, isolated by apheresis	20-50 donations a year	90 min.	750 ml of plasma

Procuring plasma-derived medical products

The production of blood products from human plasma is a sophisticated process involving several painstaking steps, from the initial donation through to manufacture of the final product.

1. Plasma donation

The process begins with voluntary donation of plasma, either by whole blood donation or using plasmapheresis. Plasma donation is carried out in authorised and regulated facilities, thus guaranteeing the donor's safety and wellbeing.

2. Plasma fractionation

After donation, the plasma obtained is submitted to a process called fractionation. This stage involves separating the different proteins present in plasma, among them immunoglobulins, albumin, and clotting factors. Each of these fractions is essential for different therapeutic applications.

3. Purification and processing

Each fraction is carefully treated to eliminate impurities and ensure the quality of the final product. Advanced technologies such as chromatology and filtration are used to obtain pure and safe plasma products.

4. Pathogen inactivation

Product safety is a priority. Pathogen inactivation techniques are therefore implemented to eliminate any viruses or bacteria which may be present. These methods can include treatment with solvent detergents, heat, and irradiation, depending on the specific nature of the plasma product.

5. Formulation and packaging

After the processes of purification and pathogen inactivation, the fractions are combined in the appropriate proportions to make the plasma product. This is formulated and packaged in accordance with regulatory rules and standards. The stability and integrity of the product are thoroughly checked before distribution.

6. Storage and distribution

Plasma products are stored under specific conditions of temperature and humidity with the aim of preserving their efficacy and safety over time. They are later distributed to medical centres and hospitals where they are available for therapeutic use.

Plasma requirements

Large quantities of plasma are required to provide the raw material for the manufacture of plasma products to treat patients who are often in chronic need of these medicines.

For example, a patient with immunodeficiency requires 130 plasma donations by plasmapheresis per year to receive a sufficient supply of immunoglobulins. A patient with alpha-1 antitrypsin deficiency requires some 900, and one with chronic inflammatory demyelinating polyneuropathy some 465 donations per year.

It is calculated that, in Europe, some 300,000 patients need treatments with plasma-derived medicines. Hence, the quantities of plasma required to treat these patients effectively are very high, as illustrated below.

ANNUAL DONATIONS VIA PLASMAPHERESIS REQUIRED PER PATIENT

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY
465 donations

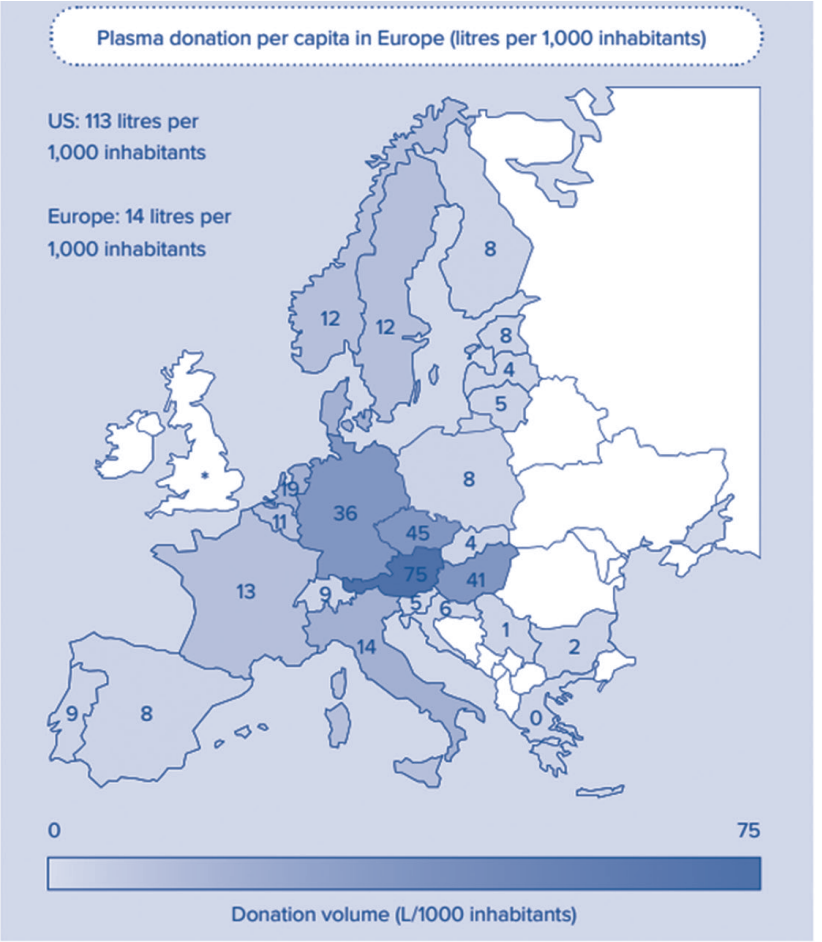
IMMONODEFICIENCIES
130 donations

ALPHA-1 ANTITRYPSIN DEFICIENCY
900 donations

HAEMOPHILIA
1,200 donations

Plasma collected in Spain and in the EU

Plasma collection in the European Union varies widely from one country to another. The volume of plasma donated can vary between 8 litres per 1,000 inhabitants in Spain to 75 litres in Austria. These differences are basically explained by the regulations in force in each of the countries within the overall EU regulatory framework. Countries that permit compensation for plasma donation and the presence of private operators (Germany, Austria, the Czech Republic, and Hungary) are more efficient in their collection, as can be seen in the illustration below. Nevertheless, these figures are still a long way from those of the United States which has an average of 113 litres per 1,000 inhabitants and a model of remunerated plasma donation.



Source: White paper "Key Economic and Value Considerations for Plasma-Derived Medicinal Products (PDMPs) in Europe", PPTA, 2020.

In 2012, more than half (57.2%) of the immunoglobulin administered in Spain was produced using plasma of Spanish origin. The rest came from countries where donation is compensated or remunerated. In 2019 only a

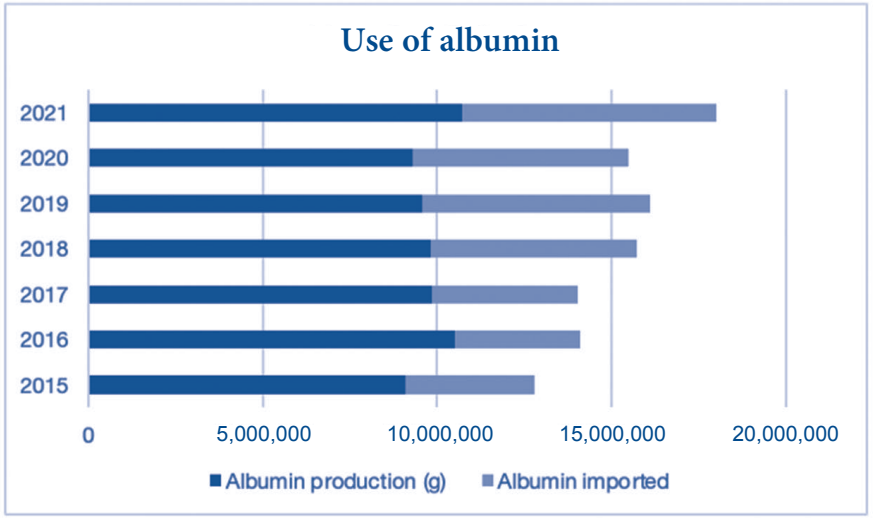
third (33.6%) of the supply came from non-compensated Spanish plasma, while two thirds (66.4%) of the plasma came from remunerated donors in the United States. These variations, which make Spain increasingly dependent on external plasma, are the result of growing demand for these medicinal products, as can be seen in the graphs below, showing the use of albumin and immunoglobulin.

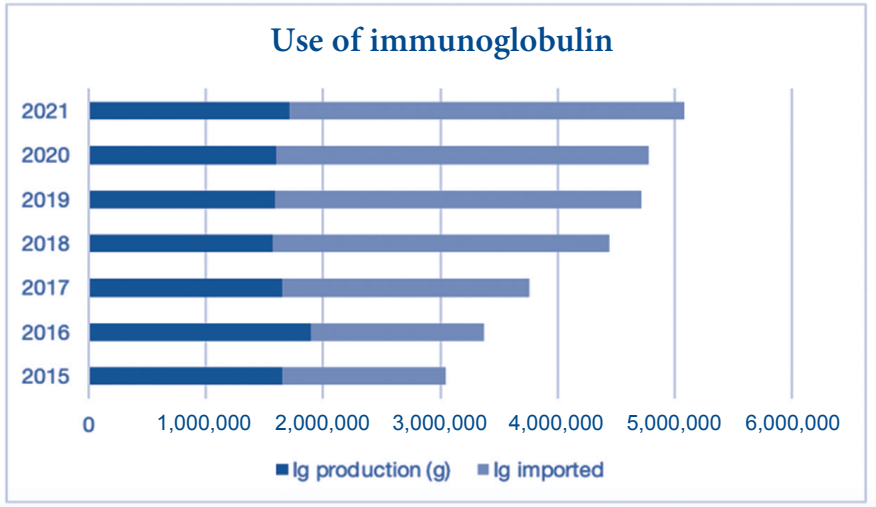
The use of immunoglobulin has increased every year since 2012 when Spain was consuming 2,363,147 grammes of immunoglobulin or a ratio of 51.63 grammes per 1,000 inhabitants. By 2019, this use had doubled to 4,718,967 grammes or 101,78 grammes per 1,000 inhabitants.

In Spain, the proportion of blood products manufactured from material given by uncompensated Spanish donors will continue to decrease in the near future. Rising demand, the prospect of new applications of current therapies, and improvements in the diagnosis of diseases that are treated with plasma derivatives will all contribute to this scenario. The recent SARS-COV-2 pandemic could also be the cause of a significant rise in demand, together with expectations of new applications with more common diseases such as Alzheimer's and dementia. This comes at the very time that the pandemic has revealed the precarious nature of the plasma-derived therapies supply chain, thus exposing a significant risk to the security of supply for patients.

From 1986 until 2014, the compound growth rate of demand for immunoglobulin was 10.7%. It is expected that this demand will keep rising at a rate of between 6 and 10% until at least 2025. In Spain, demand rose by an average of 11.7% per year between 2015 and 2019.

These growth rates have been extended by new discoveries in immunoglobulin applications and also developments in specific diagnostic methods for patients who would benefit from these treatments. For example, immunoglobulin has been proven to be effective in the treatment of Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy. Moreover, a recent publication describes how it may also prevent exacerbation of myasthenia gravis. Although these are rare diseases, they are part of a pattern of new applications for plasma therapy.





Source: Author, using data based on reports on the activity of transfusion centres and services from 2018 to 2021 (Área de Medicina Transfusional, Dirección General de Salud Pública, SG de Promoción de la Salud y Prevención, Ministerio de Sanidad).

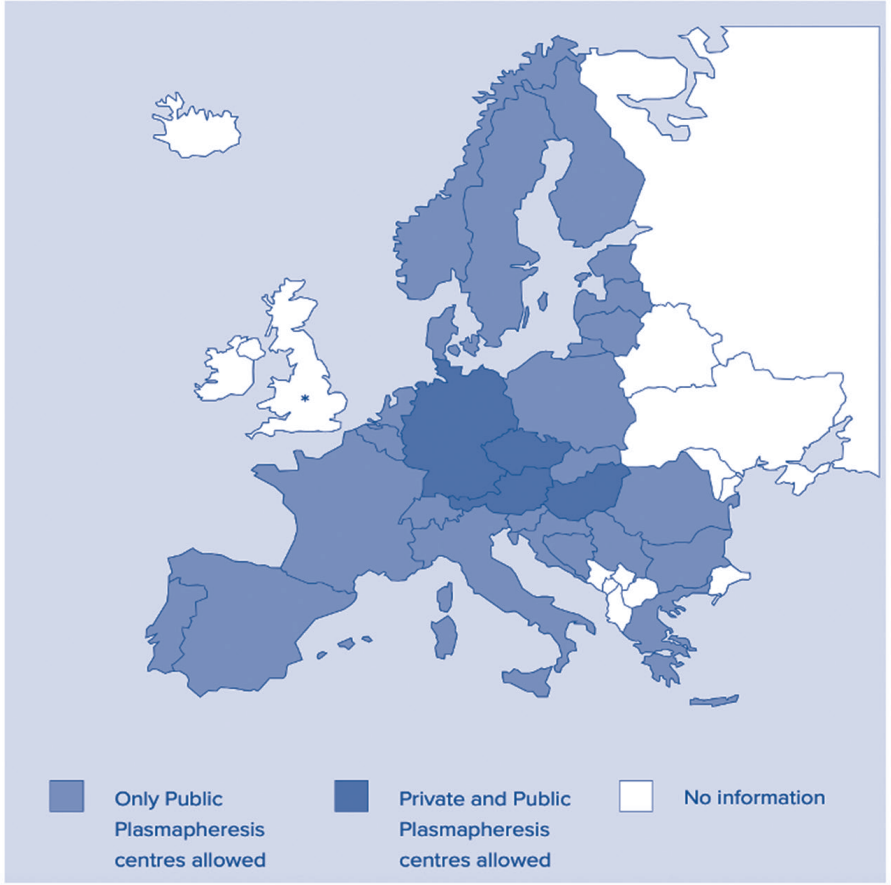
The population of patients who are using immunoglobulin in off-label cases is much smaller than the potential population that could benefit from immunoglobulin but is not currently using it. Considering only primary immunological deficiencies and neurological disorders for which immunoglobulin is either first-line therapy or one of the most recommended treatments, Albert Farrugia et al. estimated a latent therapeutic demand of 250 grammes per 1,000 inhabitants, which is more than double the current use in Spain of 101.78 grammes per 1,000 inhabitants. With one of the strictest regimes for prescribing immunoglobulin, Australia uses 240 grammes per 1,000 inhabitants.

Generally speaking, then, any fall in the demand for blood products is highly unlikely, and the growth in the demand for them in recent years is an established fact.

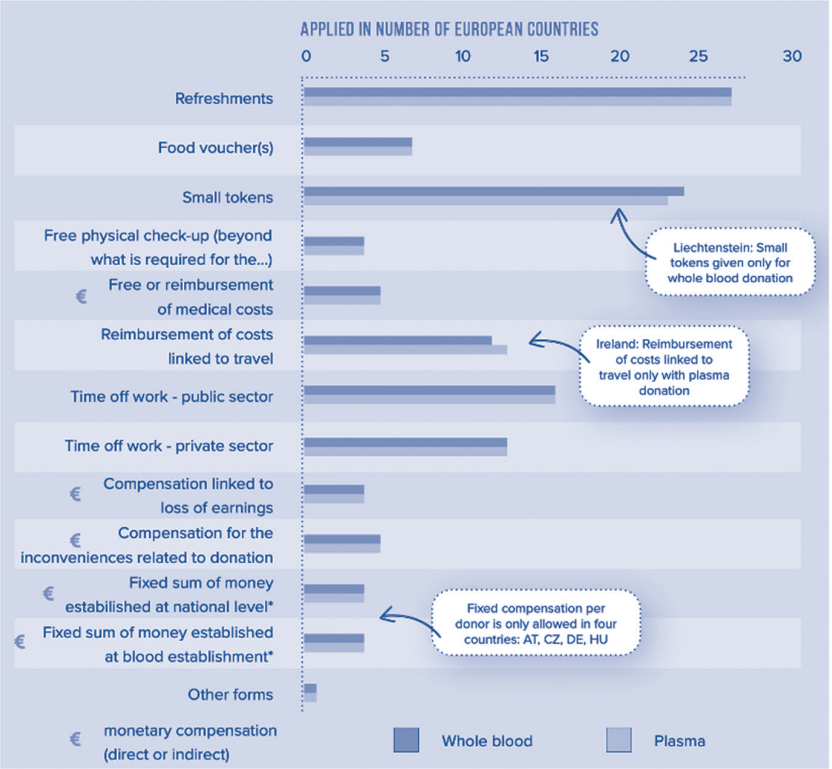
At the same time as demand for human blood plasma was increasing, the pandemic posed threats to supplies, as national blood services had been warning for years. Coronavirus initially provoked a drastic reduction in plasma donations in the United States after March 2020. There has since been some recovery, but it is only partial. Estimates suggest that plasma donations in the United States have fallen by as much as 25%. Since it supplies 75% of the world's plasma requirements for plasma-derived medicinal products, this decline represents a threat not only to patients in the US but to those of the world in general, including Spain.

Plasma supply models

In Europe today, there are different models of plasma provision, which are usually classified as "altruistic" and "compensated", two concepts that are portrayed as being in opposition to one another, although it is debatable whether compensation is really the opposite of altruism. A further distinction is based on whether countries allow only public or both public and private donation centres to operate. At present, only four countries work with private plasma collection centres (see map).



Source: White paper, "Key Economic and Value Considerations for Plasma-Derived Medicinal Products (PDMPs) in Europe", PPTA, 2020.



Source: White paper, "Key Economic and Value Considerations for Plasma-Derived Medicinal Products (PDMPs) in Europe", PPTA, 2020.

To return to the issue of compensation, it should be noted that this can be monetary or in kind. Non-monetary compensation can include a refreshment or snack at the end of the donation, a restaurant voucher, a free medical check-up, paid time off work, and tax deductions. These are forms of compensation that do not involve paying the donor in cash, but they have a clear financial value which may even be greater than that of monetary remuneration. Several countries in Europe, like Italy for example, apply these compensations. As for monetary remuneration, it includes reimbursement of transport or parking costs and can be established as an amount fixed by the state or donation centre, although there are usually ceilings that must be respected. In countries like Germany, the average amount of monetary remuneration is between 25 and 30 euros. The figure shows the different types of compensation and their applications, depending on whether they are for plasma or whole blood donations.

We will now describe the Spanish and Czech models, which represent two very different approaches that coexist in the European Union.

The Spanish model

The Spanish legal framework for plasma donation is based on altruism and voluntarism. The prohibition on receiving financial compensation for plasma extraction was explicitly introduced in its current form in 1985, with the ratification of the National Haemotherapy Plan, which assumes "self-sufficiency in blood and its derivates based on altruistic donations". Royal Decree 1945/1985 expressly prohibited remuneration for the donation of blood or any of its components. Hence, Article 3.1 establishes that:

> Donation of blood or of any of its components is the act of allowing its collection for transfusion or for the purpose of obtaining therapeutic derivates. This will always constitute a voluntary and unpaid act and, accordingly, in no case can there be any financial remuneration for the donor and neither can the recipient be charged any price for the blood that is given. The donation must be carried out under medical supervision and control in compliance with all requisites, minimum conditions, and guarantees set out in this Royal Decree and in the regulations for its implementation.

The text of this article is very similar to that of Article 2 of Royal Decree 1574/1975 which was approved in the final years of the Franco regime and explicitly prohibited financial remuneration for plasma collection.

Then again, Article 4 of Royal Decree 1088/2005 (which replaced Royal Decree 1945/1985 and is still in force) establishes the technical requirements and minimum conditions for blood donation and transfusion centres and services, as well as enshrining the "principle of altruism".

1. Donation of blood and blood components is a voluntary, altruistic act. To this end, voluntary, altruistic donation is defined as that in which a person gives blood, plasma, or cellular components as a matter of free will and without receiving any payment for it, either in cash or in any other form that could be considered a substitute for money. Small contributions such as reimbursement of direct transport costs are compatible with voluntary, non-remunerated donation.
2. The time taken to make a blood donation is considered, to all intents and purposes, as fulfilment of a duty of a public and personal nature.

In addition to the "principle of altruism", it is worth noting two points in Royal Decree 1088/2005. First, this decree establishes in its Preamble that, "altruism and the voluntary nature of blood donation are the best guarantee of quality and safety for both donor and recipient". Second, the aim of the decree is to incorporate into Spanish law two European directives, 2002/98/EC and 2004/33/EC, related to quality standards, safety, and technical requirements when collecting human blood, although neither establishes the principle of altruism as an obligation of Member States. The "principle of altruism" is, therefore, a legislative innovation coming strictly from Spanish lawmakers. It is not an obligation under European legislation in force to date and preceding the approval of future regulation on quality and safety standards for substances of human origin that are intended for use in human beings.

The Czech model

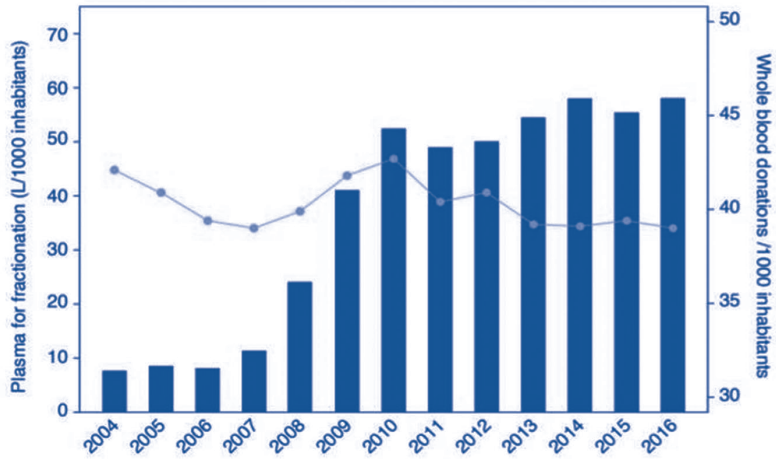
In the Czech Republic, the first private plasma collection centre offering remuneration opened at the end of 2007 and was followed by a significant increase in the presence of similar centres in 2008. Like Spain, in 2007 the Czech Republic depended on imports of blood products made from plasma obtained from remunerated donors in the United States. That year, 116,601 litres of plasma were obtained in the Czech Republic for subsequent processing into blood products. This represented 11.29 litres per 1,000 inhabitants, which represented a significant increase in the volume of plasma sent for fractionation in comparison with the previous year, 2006, when the figure was 82,900 litres or 8.05 litres per 1,000 inhabitants.

The bars on the following graph show the plasma collected, in litres per 1,000 inhabitants, and the line shows whole blood donations per 1,000 inhabitants.

Over the next three years, following the introduction of donor compensation, plasma collection increased fivefold, from 116,601 litres in 2007 to 541,072 in 2010, which is to say from 11,29 litres to 52.38 litres per 1,000 inhabitants. In just three years, the Czech Republic went from importing most of its blood products to obtaining more plasma than it needed for Czech patients and thus joining Germany, Austria, and the United States in ensuring that patients from countries like Spain could obtain the treatments that cover their needs. This is an extraordinary achievement.

In order to compare developments in the Czech Republic with the situation in Spain, and bearing in mind that the Czech population is on quarter that of Spain, some statistics may be helpful. In 2006, Spain sent 302,105 litres of plasma for fractionation, representing a figure of 6.8 litres per 1,000 inhabitants, while the comparable figure for the Czech Republic was 8.05 litres. In 2016, the Czech Republic sent 541,072 litres for fractionation, or 48 litres per 1,000 inhabitants compared with 8 litres per 1,000 inhabitants in Spain.

Total plasma and whole blood donations in the Czech Republic from 2004 to 2016.



These results are even more striking when it is understood that this increase in plasma collection did not come exclusively from the private sector which compensated donors. Plasma donations in the non-profit, uncompensated sector also increased. While the data for 2008 combines private and public sectors (so it is impossible identify the individual contribution of each), the figures for 2009 show that 92,069 litres of plasma came from sources that did not compensate donors, and this figure rose to 103,258 litres of plasma in 2010. The private sector contributed 309,249 litres in 2009 and 408,574 litres in 2010. It should also be noted that the Czech model permits plasma donation with a frequency of every 14 days and a maximum of 33 times per year.

Another question that arises from the issue of compensation is whether this compensated increase in plasma collection will be at the expense of whole blood donations or, in other words, whether compensating plasma donors will result in fewer blood donors. The example of the Czech Republic suggests that this would not be the case. In 2007, 407,993 units of whole blood were obtained from 396,732 donations, In 2008, whole blood donations rose to 419,154 units while, in 2009, 426,824 units of whole blood were obtained from 425,350 donations. In 2010, there was little change, with 421,467 units from 425,234 donations.

These figures suggest that the Czech success with compensated plasma collection did not come at the expense of uncompensated plasma collection or whole blood collection. It would seem that the two sectors complement rather than substitute for each other. Instead of displacing or interfering with uncompensated donations of plasma, whole blood, or platelets, the numbers of the latter increased despite the introduction of the compensated model of plasma donation in 2007.

Conclusions

At present, the supply of blood products in Spain, as in the rest of the EU, is heavily dependent on imports from third countries. This exposes the vulnerability of the supply chain, since external factors can significantly affect the availability of these products which are so essential for the health of many patients.

In contrast, countries whose regulations permit compensated donation and the presence of private donation centres have managed to attain self-sufficiency. They not only satisfy the internal demand for blood products but also become plasma exporters. Being able to compensate for donations has proven to be a key factor in the construction of sustainable and resilient systems for the supply of blood products.

The coming implementation of the SoHO regulation at the European level represents an opportunity to reverse the current situation and strengthen the resilience of the blood products supply chain in Europe. The regulation offers a legal framework that could encourage regional self-sufficiency, bring about compensation for plasma donation, and foster practices that would assure a safe and stable supply of blood products. By seizing this opportunity, the EU could advance towards a more robust and self-sustaining system, reducing dependence on imports, and reinforcing the security of its supplies, to the benefit of patients.

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Europe's Proposed SoHO Legislation

Compensation as a Key Concept: Different Responses to Different Needs

Núria Terribas

Director of the Víctor Grífols i Lucas Foundation Director of the Chair in Bioethics at University of Vic-Central University of Catalonia

The current scenario

As shown in the previous pages, most European countries are not self-sufficient in plasma and on average, imports cover 40% of patient needs, a figure that rises to almost 70% in the case of Spain. The COVID-19 pandemic worsened the situation. In 2020, plasma collection drastically declined so that, in 2021 (the production time for plasma-derived medicines is approximately one year), there were product shortages, which required applying priority criteria for patients and their pathologies, since there was not enough for everyone. This has made it all the more urgent to seek solutions with the aim of achieving self-sufficiency in Europe and reducing dependence on imported plasma.

The aim is to substantially increase plasma donations in general, and particularly by plasmapheresis, a technique that is both more productive and more efficient. In addition to good donor recruitment campaigns and enhanced health structures to reduce the obstacles to donors (donor centers nearby, new instrumentation, trained health professionals etc.), it is also necessary to raise the thorny topic of compensation for donors, as a way of counteracting potential barriers. Donating plasma is not the same as donating blood, because a higher degree of loyalty is required of plasma donors, who are expected to provide more donations per year than whole blood donors. In addition, donors have to sacrifice leisure or working time (one or two hours in total, including travel), and have to travel long distances to donor centers, which are generally concentrated in large hospitals. But any talk of compensation entails grappling with the concept of Voluntary Unpaid Donation (VUD), long-established in European discourse, which portrays blood donation as an altruistic act, a public duty to be performed on an occasional and urgent basis. This principle is still fiercely defended, although its interpretation varies from country to country, both with respect to blood and its components, and with regard to cells and tissues, and this means that donor compensation is viewed as contrary to altruism. And this is reflected in EU regulations on blood and blood components, which restrict the possibility of donor compensation. Maintaining this rigid approach has created the situation described above, and the increasing dependency on imported plasma, given the rising demand for plasma proteins and their clinical applications. In recognition of this, European institutions have been working for some time on a new unified regulation for all substances of human origin (SoHO), and this includes modifying the concept of donor "compensation".

The principle of VUD is formulated in many international texts, such as the European Convention on Human Rights and Biomedicine (1997), Article 21 of which establishes that the human body and its parts may not be used for profit or gain, and the Charter of Fundamental Rights of the European Union (2007) which, in Article 3, prohibits commercialisation of the human body.

However, it is important to ask what "commercialise" actually means, and what we understand by "gain", "profit" and "financial neutrality" because, depending on how these terms are defined, introducing compensation for SoHO need not contravene the general principle.

In this sense, it is necessary to revise the provisions of the two directives so far in force in Europe, Directive 2002/98/EC on human blood and blood components, and the EU Tissue Directive 2004/23/EC, when they refer to this question.

Article 20.1 of the directive on human blood and blood components, referring to voluntary, non-remunerated donation, does not mention compensation: "Member States shall take the necessary measures to encourage voluntary and unpaid blood donations with a view to ensuring that blood and blood components are in so far as possible provided from such donations."

However, the Tissue Directive 2004/23/EC does refer to it in Article 12.1: "Member States shall endeavour to ensure voluntary and unpaid donations of tissues and cells. Donors may receive compensation, which is strictly limited to making good the expenses and inconveniences related to the donation. In that case, Member States define the conditions under which compensation may be granted."

In other words, Europe has already accepted the idea of donor "compensation" in the case of tissues and cells and, although there is no mention of blood and its components, it does not explicitly prohibit it when stating, "Member States shall endeavour to ensure …". The situation in Europe is therefore uneven, with a few countries achieving self-sufficiency in plasma by applying a criterion of compensation with a fixed monetary amount as happens in Germany, Austria, the Czech Republic, and Hungary, while a large majority (although some apply compensatory measures in kind: days off, tax deductions, etc.) – hold to a strict view of altruism which, in my view, is a misunderstanding. In fact, in the self-sufficient countries that offer monetary compensation to donors, it cannot be considered that any norm established in the international agreements – including the principle of prohibition of "financial gain" – has been breached.

Moreover, Article 3 of the European Convention on Human Rights and Biomedicine regarding equal access to health should be highlighted when it states, "Parties, taking into account health needs and available resources, shall take appropriate measures with a view to providing, within their jurisdiction, equitable access to health care of appropriate quality." It can be inferred from this that states are obliged to seek practical solutions to meet these needs, based on the traditional principles of bioethics which are applicable with regard both to patients and to donors:

- Non-maleficence: first and foremost, avoidance of harm to individuals;
- Beneficence: seeking the best benefits among the available options;
- Autonomy: respecting the decisions of those competent to make them;
- Justice: fair treatment and equal and equitable access, according to need.

For the time being, if the necessary blood products are to be supplied for European patients, these solutions entail or require solidarity and donations from citizens without compensation – with scant results – or resort to imported plasma, which is obtained, paradoxically, in accordance with ethical principles that differ from those are in force in the EU. Even so, regular access to plasma-derived medicines is not always guaranteed.

Revisiting the concept of "compensation"

According to the Oxford Dictionary, compensation is "something, typically money, awarded to someone in recognition of loss, suffering, or injury". Its synonyms include terms such as indemnity, recompense, reparation, retribution, counterpart, restitution, balance, equivalence, counterbalance, and equalisation. Its antonyms include penalty, damage, and deprivation..

To compensate someone is to give what is justly due as restitution or reparation for what has been done. In the case of donation, it could be considered that what is being compensated is any suffering incurred, or what has been lost, invested, or no longer received, for example, costs arising from the fact of donation, time spent and not invested in something else, and the inconvenience caused, if any.

From this perspective, compensation would be the practical application of the principle of justice to the donor, as fair treatment in recognition of their effort and solidarity, which also includes essential help in covering the needs of the health system when treating patients.

Compensation may thus include the reimbursement of quantifiable expenses incurred in making the donation (travel and other expenses) but also due consideration of the effort and the time invested, always within parameters of proportionality that would permit transparent justification of such compensation.

The question then is whether the current concept of donor compensation is compatible with the criterion of VUD and the concept of altruism. To judge by the provisions of Directive 2002/98 setting standards of quality and safety

for the collection, testing, processing, storage and distribution of human blood and blood components, it does seem to be compatible since this directive mentions compensation, although without defining it or delimiting the scope of the concept. It follows from this that the legislation currently being prepared at the EU level with a view to unifying the criteria for substances of human origin, including blood and its derivates as well as other tissues and cells, would incorporate the concept of compensation. It should be borne in mind that the directives presently in force are subsequent to the signing of the European Convention on Human Rights and Biomedicine (1997), which stipulates that ,"The human body and its parts shall not, as such, give rise to financial gain." This means that when European legislators drafted Directive 2002/98 and included compensation, they did so in the belief that this did not signify "financial gain". In other words, they did not see compensation as meaning payment. For the sake of consistency, this criterion should be applied to plasma in the same way as it is to other tissues and cells.

I believe this question is fundamental in the light of the aforementioned ethical principles because, in the context of plasma collection, a system of donor compensation would comply with the principle of justice. The current model – based on the assumption that it is the citizen's duty to show solidarity to other human beings without receiving any kind of compensation when this civic effort also covers the needs of the health system which has the obligation to provide patients with medicines – seems totally unfair.

Besides the criterion of justice, a utilitarian argument in favour of compensation is also applicable from an ethical standpoint because when donation is not compensated, there are not enough donors. Although there are dissenting voices on this point, the reality is that European countries that apply a compensation model are self-sufficient in plasma, in contrast to those countries which see compensation as "illicit" and adhere to a rigid principle of altruism. From this perspective, compensation would reflect the criterion of utility: we need plasma and if we do not offer compensation there is not enough, obliging us to import it from countries that do offer compensation. Compensating people for their effort means people will be more willing to donate because some of the disincentives to donation will be neutralised (time, inconvenience, cost).

From the ethical perspective, the utilitarian argument is criticised because it holds that what drives people to donate is not a desire to help out of solidarity, but the wish to receive compensation. From this it is inferred that compensation annuls altruism and solidarity and turns the act of donating into a commercial transaction. Somehow, compensation is equated with "payment" or "purchase" (when, in fact, it is not given in the spirit of either) and, paradoxically, it is then deemed preferable to import compensated plasma than to offer compensation within the country concerned.

This conceptual leap strikes me as neither acceptable nor justifiable and seems to me to be based on a desire to delegitimise anything that departs from the model that has been traditionally applied in this domain, clinging to the idea of donation as a requirement of civic solidarity to which everyone should respond. While such an approach might be valid for blood donated on an *ad hoc* basis, it does not respond to plasma requirements. Accordingly, different needs call for different responses.

Compensation models

There are differences among the countries where some kind of compensation is offered to donors, with the basic distinction being between those that compensate "in kind" or with apparently non-monetary concepts, and those where compensation is a fixed sum, which is the same for everybody. Hence, there are countries like Italy whose compensation formula is based on recognition of time off work, there are models that establish tax breaks or offer gifts like restaurant vouchers, and others. With these models, the fact of not giving monetary remuneration seems to make compensation appear more acceptable since there is no direct form of financial exchange. Nonetheless, each of these measures has an unquestionable associated monetary value, which is often much higher than that of any lump sum in cash.

Monetary compensation is frequently criticised but this does not hold up from an ethical perspective if the reason for compensation is to treat the donor fairly in recognition of the effort they have made. Moreover, monetary compensation makes donation accessible to anyone as a matter of free choice,

and compensation can also be rejected if so wished. By contrast, other forms of compensation such as tax breaks or time off work mean that the donor must comply with certain conditions that would exclude some groups (for example people who are not working), meaning that these would be less equitable models.

However, if this type of compensation is to be truly "just" and if it is not to pervert the desire to donate for reasons of altruism and solidarity, it must be proportionate and not subject to free-market principles that could encourage going to the "highest bidder". Compensation is not payment, as I have said above, and hence the form it takes – in kind or monetary – must be in keeping with objective parameters for understanding what is being compensated: effort made, inconvenience, and time invested.

The concept of "financial neutrality", which is also analysed by the European Committee on Bioethics (DH-BIO) in its document "Guide for the implementation of the principle of prohibition of financial gain with respect to the human body and its parts from living or deceased donors", should be interpreted to mean that what the donor receives for the donation does not constitute financial gain. The aim is to ensure that donation does not become a source of income for some people, especially those who, if they are more socially vulnerable, might see donation as a form of survival. This would violate the dignity of the individual and contravene the principle of non-commercialisation of the human body.

Compensation should not become an incentive that determines a person's willingness to donate, and without which there could be no donation. To judge by models like that of Germany, where the average value of compensation for donation is about 30 euros, even the permitted maximum of 60 donations would only generate an annual income of 1,800 euros, which would not provide a living for anyone. However, it is impractical to assess what compensation would mean for each person according to their individual context and circumstances, and this means that universal parameters must be applied. In this regard, compensation in kind would seem better able to neutralise this potential effect although, as noted, it still has a financial value, and some forms of it may exclude certain groups.

It is therefore important that compensation should not be advertised and that donor recruitment campaigns do not use compensation as a "lure", but rather as just another element in the process. This requirement is already included in several regulations.

The regulatory framework in Spain

In Spain there are, to date, three different regulations on SoHO, one applying to blood and blood products (RD 1088/2005), one referring to cells and tissues (RD 9/2014), and a third relating to gamete donation in the Law on Assisted Human Reproduction (Law 14/2006).

The criteria regarding the principles of altruism and solidarity expressed in these regulations are not exactly the same in the three areas. The differences are described below.

RD 1088/2005 on donation of blood and its components

> Donation of blood and blood and blood components is a voluntary and altruistic action. To this effect, voluntary and altruistic donation is defined as that in which the individual gives blood, plasma, or cellular components of their own free will, *and receives no payment for it, in either cash or kind that may be deemed a substitute for money*. Small contributions like recognition or reimbursement of direct travel costs are compatible with unremunerated voluntary donation.
>
> The *use of time necessary* to make a blood donation is considered to all intents and purposes as being *in keeping with the performance of a public and personal duty*.

RD 9/2014 on donation of cells and tissues

> Promotion and advertising of donation or procurement of human tissues and cells must be carried out in a general manner without seeking benefits for specific individuals, and pointing out its *voluntary, altruistic, and disinterested nature*.
>
> Neither the donor nor any other natural or legal person may receive any financial benefit or remuneration. Living cell and tissue donors *may receive*

> *financial compensation from the institution responsible for cell and tissue retrieval* and this must be strictly limited to covering costs and inconveniences pertaining to the donation in the form of covering specific expenses, reimbursing lost income and the like.

Law 14/2006 on assisted human reproduction with regard to gamete donation

> Donation must never be of a lucrative or commercial nature. *Any financial compensation that may be set* must only be to compensate for physical discomfort and expenses related to travel and work that might arise from the donation but *they may not constitute an economic incentive for the donor*.
>
> Any advertising or promotional activity by authorised centres that encourages donation of human tissues and cells must respect the altruistic nature of the donation and *may not, under any circumstances, incentivise donation by offering financial compensation or benefits.*

Different nuances emerge from the literal wording of these provisions. Hence, in the case of blood and blood products, the text of RD 1088/2005 is strict and rejects all monetary or equivalent compensation while appealing to citizen responsibility to devote time to donate and only contemplating possible reimbursement of travel costs. RD 9/2014 referring to tissues and cells mentions "financial compensation" that includes costs and inconvenience, for example restitution of lost income or similar. This is a broader concept and one that comes closer to the concept of compensation referred to in this text.

This differing criterion for tissues and cells is also confirmed with gamete (ova and sperm) donation where there is also talk of financial compensation to offset physical discomfort, costs, etc. It must be said that, in this area, compensation offered to ova donors is financially substantial (more than a thousand euros) and no one questions its appropriateness or whether it is contrary to VUD or "financial neutrality". In fact, when compensation to egg donors was quantified, among the elements to be taken into account were both objective costs like travel and per diem expenses, and others that were more difficult to calculate such as physical discomfort, inconvenient aspects of treatment, and time spent, which could therefore not be used for other personal pursuits, including work, study, and leisure. Moreover, by way of

justifying a "flat rate" amount, it was argued that individualized compensation to each donor in accordance with a detailed account of direct and indirect expenses could lead not only to bureaucratic and processing costs, but it might also encourage certain kinds of cheating and, in some cases, injustice. It therefore seemed fairer to establish a single maximum amount for all cases.

Evidently, then, Spanish legislation applies one criterion in the case of blood and blood products, which differs from that applied to cells and tissues, where compensation of donors is allowed. This difference of criteria is neither explained nor justified in the regulation, and nor is it discussed in debates on the issue of blood and plasma donation when this clear contradiction appears.

Where the three texts do coincide on the concept of donation is that it must be voluntary, altruistic, and disinterested, and it should not entail incentives for donating or any advertising. However, in the case of gamete donation, the rule against incentivising donation by means of financial compensation is not respected because such compensation is offered in public advertising to recruit donors. In the case of ova donation, which is special and distinct because of its complexity, without this explicit advertising, few women would volunteer for a process which is neither trivial nor harmless for them. Nevertheless, the law technically prohibits it.

Towards a new regulatory framework in Europe

I have described above what the European regulations provide for so far in Directive 2002/98/EC on human blood and blood components, and the EU Tissue Directive 2004/23/EC.

As noted, Europe has become aware of the need to achieve self-sufficiency in plasma and is therefore revising the regulations in this area and bringing together in a single text the quality and safety standards for substances of human origin (SoHO). This will replace the two previous directives with a regulation on standards for SoHO intended for human use. This regulation

will be directly applicable in Member States without the need for it to be incorporated into national law, as is required of directives.

After all the necessary informal interinstitutional negotiations – trialogue – at the level of the three institutions that are responsible for matters of European legislation (the European Parliament, the Council of the European Union, and the European Commission), it is likely that the new regulation will be approved in the coming months.

The wording of the final agreed proposal includes four basic points regarding compensation for SoHO.

- The possibility of compensation to donors not only for expenses incurred in connection with the donation but also for losses related to participation in SoHO donations, including the prospect of establishing a fixed rate and specifying the conditions under which this compensation might be granted, with a maximum limit that would guarantee the principle of financial neutrality.
- Member States must inform the EU – via the SoHO Platform – of the conditions applied for such compensation, as well as reporting any possible modifications.
- Compensation and reimbursement cannot be included as promotional elements when recruiting SoHO donors, and neither may financial incentives or inducements be offered.
- Information for donors must be truthful, understandable, of minimum content, and without bias regarding benefits to recipients of the donation.

The regulation refers to "SoHO providers", which covers both public operators (blood and tissue banks) and private operators (companies). How plasma collection is internally organised in each country, the type of public-private relationship involved, and who will be responsible for managing and compensating donors, are matters the regulation cannot and should not cover, since this should be left to the discretion of the health authorities concerned in accordance with the internal situation in each country. However, it does stipulate that criteria should be established by an independent body and that countries should be accountable to the EU to ensure adequate supervision.

It would therefore seem that Europe, in the light both of existing demand and new demand driven by medical progress and innovation, intends to introduce into its regulations elements that would allow the use of substances of human origin given by live donors in the context of realistic and fair criteria of compensation in recognition of the efforts involved but without violating the basic principle of VUD, while also respecting the norm of "financial neutrality" which is enshrined in the major treaties.

This unified regulation will make it possible to apply different solutions in different countries as there is considerable variation in terms of donation procedures, frequency, and inconvenience. Fair terms could then be established regarding the nature of the compensation deemed most proportionate and equitable in each case.

It remains to be seen what position each country will take, as the proposed regulation does not make compensation compulsory but, rather, permits it under certain conditions. If compensation is based on fair treatment of donors, it should be the same for everyone, and not left to arbitrary criteria established by the states. Since this is a domestic decision when each country has its own procurement policy and plans, time will tell what how things will develop. Some countries may adapt their practices to include compensation, which would lead to increased donations, self-sufficiency (as has happened in countries that allow compensation), and perhaps even a surplus that would enable them to supply other countries that do not wish to implement the new model. If this were so, the need to acquire medicines derived from plasma imported from the United States might be less, but we would continue with a dual reality in Europe with some countries being dependent on imported plasma because they are unable to collect enough themselves, with other countries not only achieving self-sufficiency but also supplying those with shortfalls plasma.

This would not seem to be the most desirable outcome in terms of solidarity and equity. It would prolong, although perhaps only on the European scale, the double-standard model that has predominated so far: "I do not want to compensate my donors because I think it is ethically reprehensible but I will use the compensated plasma of others for my patients."

Final thoughts

In the first place, including "compensation" in the concept of VUD, as contemplated in the new European regulation, in no way ethically discredits the act of donation or annuls its character as an altruistic act of solidarity.

We should take the ethical acceptability of compensated plasma donation as our starting point. This means adopting a criterion of justice towards the donor and also towards patients who are to receive the resulting therapies.

In the European context, the regulation should leave some room for flexibility so that Member States can define their own models (in kind, monetary, or mixed compensation), in accordance with their social and health systems and the general social and cultural situation, but always within limits that guarantee the basic principle of financial neutrality.

Finally, at the European level, the objective should be national self-sufficiency, so that we no longer have a situation where some countries are dependent on others (except in specific situations in which European solidarity should apply) and still less if this dependence is due to rigidity with regard to changing misunderstood, historical notions of altruism and solidarity that do not apply in other areas (for example, gamete donation for reproduction in Spain).

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Voluntary Unpaid Donation: The position of the Council of Europe

Javier Arias

Professor of Surgery and Chair of the Faculty of Medicine, Complutense University of Madrid

I will seek to set out the relevant historical information and basic content of discussions leading to the drafting of the "Guide for the implementation of the principle of prohibition of financial gain with respect to the human body and its parts from living and deceased donors", which is intended to simplify interpretation of the principle of non-commercialisation or prohibition of financial gain in exchange for body parts. This is still considered to be one of the fundamental principles of bioethics.

In May 2014, the Council of Europe, then consisting of 47 countries before Russia's exit, adopted a declaration on the prohibition on any form of commercialisation of body parts. The declaration was jointly drafted by the Committee on Bioethics of the Council of Europe (DH-BIO) and the European Committee on Organ Transplantation (CD-P-TO), and it was subsequently ratified by the corresponding committee of the Parliamentary Assembly of the Council of Europe (PACE) in June 2014, and by the Committee of Ministers in July the same year.

The legal basis is well known. Article 21 of the Oviedo Convention states that, "The human body and its parts shall not, as such, give rise to financial gain". The additional Protocol of 2002, on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin, further elaborated on this principle, while also leaving the door open to compensation for loss of income and other justifiable expenses. This additional protocol was ratified by the Spanish government in 2015 (see Table 1).

Table 1

Article 21 – Prohibition of financial gain

1. The human body and its parts shall not, as such, give rise to financial gain or comparable advantage.

The aforementioned provision shall not prevent payments which do not constitute a financial gain or a comparable advantage, in particular:

- compensation of living donors for loss of earnings and any other justifiable expenses caused by the removal or by the related medical examinations;
- payment of a justifiable fee for legitimate medical or related technical services rendered in connection with transplantation;
- compensation in case of undue damage resulting from the removal of organs or tissues from living persons.

2. Advertising the need for, or availability of, organs or tissues, with a view to offering or seeking financial gain or comparable advantage, shall be prohibited.

The 63rd Assembly of the World Health Organization (WHO, May 2010) again elaborated on the same principles.

Table 2

Guiding principle No. 5:

Cells, tissues and organs should only be donated freely, without any monetary payment or other reward of monetary value. Purchasing, or offering to purchase, cells, tissues or organs for transplantation, or their sale by living persons or by the next of kin for deceased persons, should be banned.

The prohibition on sale or purchase of cells, tissues and organs *does not preclude reimbursing reasonable and verifiable expenses incurred by the donor, including loss of income, or paying the costs of recovering, processing, preserving and supplying human cells, tissues or organs for transplantation.*

In 2016, in order to unify criteria and resolve some ambiguities in the interpretation of this principle, the Council of Europe established an *ad hoc* working group, to which I was privileged to belong as a representative of Spain and member of the DH-BIO Executive Committee. The group consisted of fourteen members. In addition to the representatives of DH-BIO, it included experts from other committees of the Council of Europe, in particular the CD-P-TO and the European Committee on Blood Transfusion (CD-P-TS). The World Health Organization (WHO) and the European Commission also attended the meetings of the *ad hoc* group, which was initially chaired by Doris Wolfslehner (Austria) and subsequently by Ritva Halila (Finland), both of whom are members of the DH-BIO Steering Committee.

The preliminary draft of the resulting guide was prepared by the *ad hoc* group in three meetings that were held in 2016. Then text was then forwarded to the DH-BIO, which carried out an editorial review of the text in 2017, and eventually adopted it on 4 December 2017. The guide was subsequently submitted to the CD-P-TO and the CD-P-TS, and the former adopted it on 11 January 2018.

Three proposals are clearly identified as underlying the principle of no financial gain from donation:

- To safeguard respect for the dignity and human rights of donors and recipients;
- To promote altruistic donation;
- To guarantee the quality and security of donated human body parts, and thereby contribute towards maintaining a donation system that people can trust.

It stresses the importance of respect for the dignity of donors and recipients, and also argues that monetisation of organs and body parts degrades the value attributed to the human being, thus leading down the slippery slope where other forms of exploitation of human beings become possible. If human body parts become merchandise¸ something to buy and sell, this could lead to a purchase of personal choices that would come close to unacceptable limits.

Moreover, altruistic giving itself can be seriously undermined when monetary parameters are introduced. Some authors have expressed this risk very eloquently. In his book *What Money Can't Buy*, Michael Sandel points out that financial incentives subvert the meaning of acts because they transform their ends: "Putting a price on the good things in life can corrupt them. That's because markets don't only allocate goods; they also express and promote certain attitudes toward the goods being exchanged. Paying kids to read books might get them to read more, but also teach them to regard reading as a chore rather than a source of intrinsic satisfaction. […] Hiring foreign mercenaries to fight our wars might spare the lives of our citizens but corrupt the meaning of citizenship."

In his book, *The Gift Relationship: From Human Blood to Social Policy*, Richard M. Titmuss, referring specifically to blood, analyses the decline in altruistic donations that led to the introduction of systems of paid donations and argues that when blood was commercialised. The perception of the moral obligation to donate was lost and the altruistic motivation was "crowded out". In response to the argument that altruism has a limit and could possibly become extinct, he adds, "Altruism, generosity, solidarity, and civic spirit are not like commodities that are depleted with use. They are more like muscles that develop and grow stronger with exercise."

As for the third proposal – guaranteeing the quality and security of donated human body parts – the main arguments are widely known. There is the risk that excessive incentives could influence donors to endanger their own well-being by over-donating. At the same time, the security of the product could vary significantly between altruistic and remunerated donations. Substantial incentives could induce a donor to lie or to conceal circumstances that directly affect the quality of the donated organ or tissue. Moreover, the subjective incentive of any given level of compensation varies widely depending on the socioeconomic situation of the donor, and could have a disproportionate impact on more vulnerable populations.

The current definition of voluntary, non-remunerated donation – the result of consensus among the Council of Europe, the European Commission, and the World Health Organization – is as follows: "Donation is considered vol-

untary and non-remunerated if the person gives blood, plasma […] of his or her own free will and receives no payment for it, either in the form of cash or in kind which could be considered a substitute for money. This would include time off work other than that reasonably needed for the donation and travel. Small tokens, refreshments and reimbursements of direct travel costs are compatible with voluntary, non-remunerated donation."

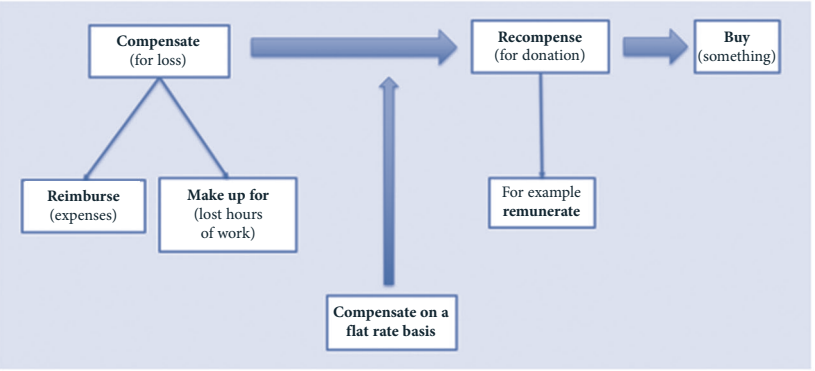
The Nuffield Council on Bioethics proposes an "intervention ladder" in which altruistic approaches are clearly divided from those that entail remuneration, either in cash or in kind (Table 1).

Table 1. "Intervention ladder" for promoting donation (Nuffield Council on Bioethics)

Rung 6 **Financial incentives**	Non-altruist focused
Rung 5 **Payments in kind linked to donation**	
Rung 4 **Interventions as an extra prompt or encouragement**	Altruist focused
Rung 3 **Interventions to remove barriers and disincentives**	
Rung 2 **Recognition of altruistic donation**	
Rung 1 **Information about the need for donation**	

The main debate is still about lump sum or flat rate compensation. A not very edifying example is compensation for egg donation in Spain, for which the current compensation of around €1,000 is equivalent to about three and a half weeks' work at the current minimum wage. This has been associated with reproductive tourism and repeat donations, which are not exactly inspired by altruism. There is nothing reassuring in the logical fact that, whatever the amount, there will always be some sectors of the population for whom it will be an inappropriate incentive.

Table 2: What do we mean when we talk about "paying"?



More recently, the *Guide to the quality and safety of tissues and cells for human application* (5th edition, European Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM)) expresses its support for non-remunerated voluntary donation and emphasises the risks for donation of other options entailing monetary or in kind incentives "because they will render living donors more likely to consider repeat donations or to continue donating despite potential risks to their health" and "may lead donors to not disclose all the information necessary for a complete and adequate donor selection".

The Guide concludes that voluntary, non-remunerated compensation should continue to play a central role in the donation of material of human origin. It finds that it is entirely legitimate to compensate donors for expenses and loss of income as long as this is duly justified and does not represent an additional incentive to donation beyond the altruistic desire of the donor. Furthermore, allocation of tissues and cells should be guided by clinical criteria and ethical norms, and never by financial considerations. The rules of allocation must be equitable, based on clinical need, externally justified, and transparent.

A consensus opinion arising from all these considerations is that donation should always remain within the public sphere. Involvement of private enter-

prise brings additional interests into play, and it would be utopian to think that market rules can be applied partially or selectively in any area. The dynamics of financial gain, however legitimate they may be, can lead to inequalities in the allocation of goods and services, and even to shortages as products tend to go to the highest bidder.

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The Proposal of Public Models

Elena Moro

Technical adviser to the sub-directorate of Health Promotion and Public Health Monitoring (Ministry of Health)

The importance of human plasma and Europe's dependence on it

Plasma-derived medicinal products (PDMPs) constitute a group of treatments that are essential for combatting numerous diseases.

The growing worldwide demand for these products in recent years, and for immunoglobulins in particular, is negatively affecting plasma self-sufficiency. The availability of these products is subject both to the ability to obtain plasma and to consumption levels. Technology is enabling better diagnoses, and science is identifying new uses for PDMPs, which means that there is a rising demand for a raw material like human plasma, which cannot be produced synthetically.

All European institutions are clearly concerned about excessive dependence on external supplies (primarily from the United States) of human plasma. All of them point to the need to invest in public systems that aim to increase plasma collection in the EU and to guarantee PDMP supplies.

The sustained increase in plasma use, exacerbated by a worldwide decline in its procurement owing to the COVID-19 pandemic, has drawn attention to the precarious situation of Spain and of Europe in general with regard to medicines that are vital for treating a major group of diseases.

It is estimated that between 35 and 40% of current PDMP needs depend on plasma collected outside the EU.

Main consequences of the COVID-19 pandemic

The most important consequence of the pandemic has been the drastic decline in plasma collection worldwide (between 20 and 25%), which is especially acute in countries where plasma donation is remunerated.

The result has been an imbalance between supply and demand, further exacerbated by the increased price of plasma, which has risen by 30% since the pandemic.

Achieving sufficient plasma autonomy to support the manufacture of medicinal products has become a priority in Europe as this is key to ensuring the supply of these products in the long term. This means that plasma is a strategic element of any public health system, and understanding its derived products is essential.

Current and future plasma needs

Current plasma needs in Europe are estimated to be 20 litres per 1,000 inhabitants per year. However, in Spain, plasma collection is 10 litres per 1,000 inhabitants per year and immunoglobulin use is rising at a rate of 10% per year and is predicted to reach about 200 grammes per 1,000 inhabitants by 2030. These figures indicate that Europe will need to double its plasma collection.

The National Strategic Plan for Plasma Self-Sufficiency (PENAP) and the European SUPPLY Project

It should be recalled that the first objective of the National System for Transfusion Safety (SNST, in the Spanish acronym) is to achieve national self-sufficiency in blood and plasma derivatives by means of voluntary non-remunerated donation (VNRD). Spain has been self-sufficient in labile blood components for transfusion for the last 30 years, plasma collection is insufficient to produce the medicines required to meet the needs of patients.

At present the figure for immunoglobulin coverage from local plasma is 35%. Improving plasma supply is a priority of the Ministry of Health, and one that is shared with the EU.

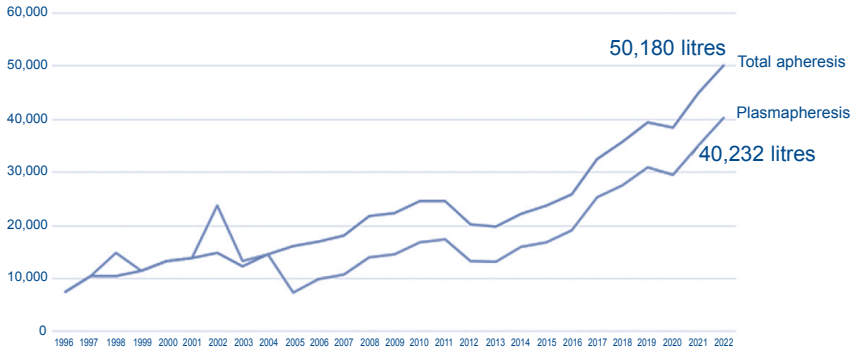
In March 2023, Spain's National Haemotherapy Commission presented the general guidelines set out in the National Strategic Plan for Plasma Self-Sufficiency (PENAP), which aims to alleviate the plasma deficit by strengthening the public plasma collection system based on VNRD. This plan, promoted by Spain's Scientific Committee for Transfusional Safety after prior approval by the directors of transfusion centres, was unanimously endorsed and supported by all the regional authorities and donor associations of the National Haemotherapy Commission.

In this approach, the PENAP is in line with the European Blood Alliance (EBA), the body which leads the SUPPLY Project, which is sponsored by the European Commission and aims to increase European VNRD plasma collection in public health systems, which have proven to be the most resilient in crises, as well as guaranteeing the supply of all products both under current circumstances and in times of crisis. The project focuses on how blood centres can improve and develop non-remunerated plasma collection programmes, while also working to make them more efficient. Emphasis is placed on keeping donors safe but also on obtaining the quality of plasma that is needed for the manufacture of medicines.

The EBA has issued several recommendations in this regard and has called on European countries to increase plasma collection by means of plasmapheresis programmes. Some Member States have already started to do this. Denmark and Italy have reached levels that could be considered self-sufficient. The question of how they managed to do this is easily answered: political will and commitment. Other countries, including Spain, recognise the urgency and the need to invest in public systems and have launched similar programmes. In this regard, it is worth noting that among the measures taken by the Spanish Ministry of Health over the last three years is

the promotion of plasmapheresis programmes through funding allocated to Spain's regions. These measures are starting to bear fruit with an increase in the volume of plasmapheresis-derived plasma destined for industry. The data suggest that we are on the right track, that the Spanish public network of transfusion centres is able to progressively obtain a greater volume of plasma from VNRD, and that this will make it possible to meet the demands of our patients.

Collection of plasma by apheresis (1996-2022)



Voluntary non-remunerated donation (VNRD)

VNRD contributes to respect for human dignity and protection of the most vulnerable people in society as well as achieving high safety standards and, therefore, protecting human health and increasing public confidence in donation systems.

Voluntary non-remunerated donors have been recognised as the mainstay of a safe, sustainable supply of blood and blood products sufficient to meet the needs of the various groups of patients. The scientific evidence and ethical

principles underpinning VNRD have been established and promoted by the Council of Europe, the EU, most of its Member States, and the World Health Organization.

However, despite broad endorsement of these principles, in recent years the activities of "for-profit" companies have been expanding in some EU countries. Violations of these ethical principles led the EBA to review and update the evidence. The main reasons identified by the EBA for giving VNRD priority over paid donations are listed below.

1. Safety for recipients. According to published and subsequently reconfirmed scientific data, paid donors have shown a higher risk of being bearers of blood-borne infectious diseases than non-remunerated voluntary donors. Paid donations entail a greater probability of potentially infectious blood components escaping detection by known routine tests. The preference for VNRD donors is justified as a precautionary measure against future emerging infections.

2. Continuity of blood supply. Recent examples clearly show the risks of competition for donors between non-profit establishments and organisations that pay for donations, with in some cases blood collection being ended due to commercial considerations, with a destabilising impact on the long-term donor base. A safe and stable blood supply is also potentially affected by competition between the public and private sectors

3. Donor safety: A major risk for donors receiving remuneration is that they may submit to an excessively high frequency of donations, which can effect their health, as it can cause alterations of blood components, for example significantly reducing the immunoglobin content, as seen in high-frequency and high-volume plasmapheresis donors.

4. Ethical and legal reasons: Article 3 of the Charter of Fundamental Rights of the European Union prohibits making the human body and its parts a source of financial gain, in accordance with the principles of:

- **Nonmaleficence and beneficence:** The donor must not be subject to unnecessary or unreasonable harm. The act of donation is a medical procedure from which the donor will not derive any direct benefit

(payment and profit encourage high-frequency donations with potentially harmful consequences for donors).

- **Autonomy:** Avoiding any coercion or pressure on the donor (payment makes donation more attractive to members of less privileged socioeconomic groups who feel the need to use this option for income, which could be seen as coercion and undue pressure on their autonomy of decision).
- **Justice:** the burden of donation must not disproportionately affect a particular group or class, especially when the benefits accrue to a different group or class.

The Spanish transfusion network consists of twenty centres in the seventeen Autonomous Communities, and they are responsible for obtaining, processing and distributing blood products and plasma derivatives. Collection of both blood and plasma is always carried out in accordance with VNRD. Taking the WHO definition as a reference, "self-sufficiency" means that the citizens of a continent or region have access to these products whenever they are needed and on an equitable basis. In this context, the principles of respect and non-exploitation of human beings are seen as key elements of social cohesion, in which the safety of donors and patients is paramount.

VNRD reinforces the public system to cope with both stable situations and future crises. It also avoids the risk of wasting plasma from whole blood donations and plasmapheresis in the event of other kinds of plasma collection scenarios. The citizens of Spain do not envisage other donation models.

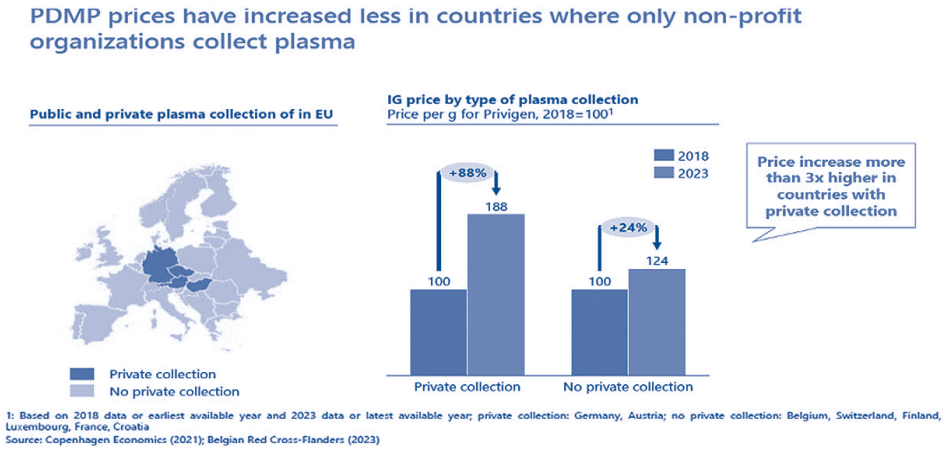
The future Regulation on Substances of Human Origin (SoHO) expressly states that the donation of any SoHO must be by VNRD and based on the principles of altruism and solidarity between donor and receiver. However, it introduces the concept of "compensation", although it does not oblige countries to comply with it. Each Member State must decide, and if it does opt for this, individual establishments can refuse to compensate. In no circumstances is compensation conceived as a solution to the shortfall of plasma donations. It should not be forgotten that turning to financial incentives can have an impact on quality and safety, with health risks for both donors and recipients. The Regulation therefore stipulates that Member States that

choose to consider compensation must comply with the principle of financial neutrality as set out by the Council of Europe Committee on Bioethics. Whatever formula is decided, it cannot lead to competition among the entities, and neither may it be an incentive to donate.

It should also be recalled that the directives in force, on blood as well as tissues and cells, urge Member States to promote donation as a non-remunerated act. Spanish legislation expressly prohibits any type of remuneration, and the Ministry of Health wishes to uphold this principle.

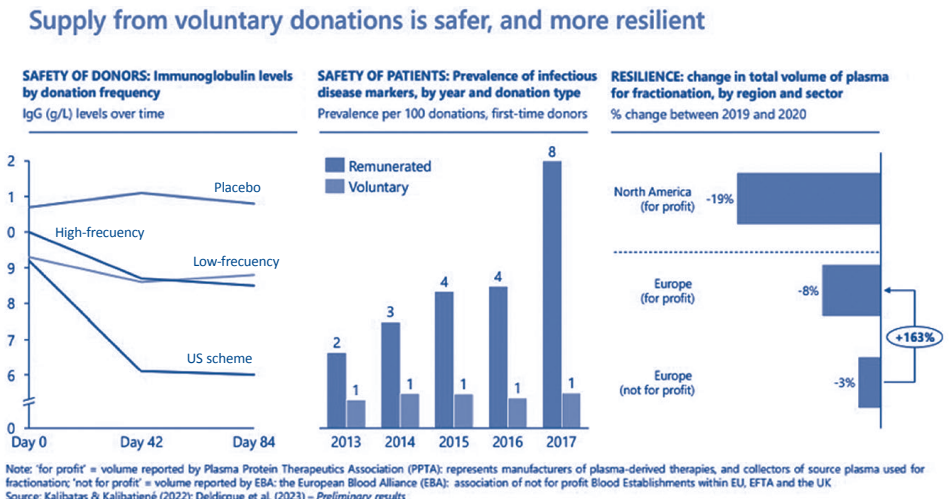
On this point, the presentation in the European Parliament in early 2023 by the Belgian Red Cross of a document titled, "How Europe can ensure sustainable supply of blood components on a voluntary non-remunerated basis", is pertinent. This country is a firm supporter of VNRD, for several compelling reasons, which are described below.

1. Sustainability of the system. A study conducted in Europe between 2018 and 2023 on the evolution of the price of immunoglobulins, comparing countries that remunerate with those that do not, shows that the prices of PDMPs rise less in countries where plasma is obtained only by non-profit organisations. Hence, it was found that the price of immunoglobulins rose by 88% in paying countries (Germany, Austria, Czech Republic, and Hungary),



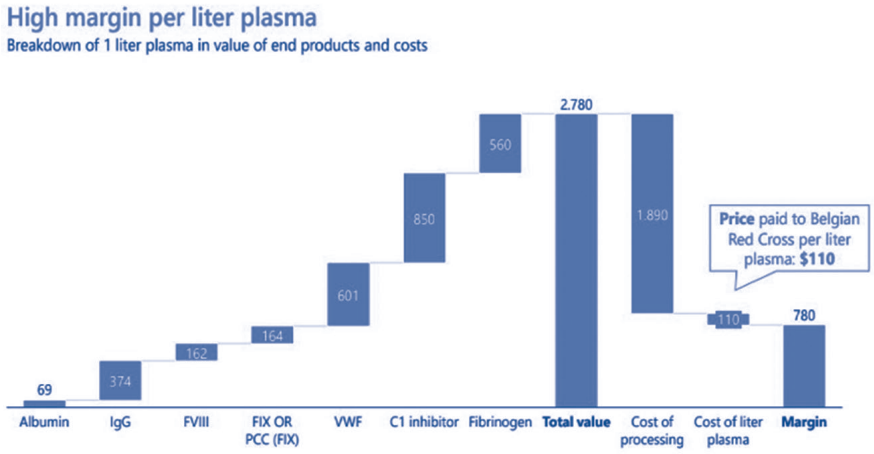
in contrast with 24% in the countries where donation is not paid (and prices rose three times more in private collection). In sum, prices increase less in countries where plasma is only obtained by non-profit organisations.

2. Donor and patient safety. As the graph shows with regard to donors, immunoglobulin levels in plasma over time (gr/l) in high-frequency donations are much lower than the levels in low-frequency donations. The American model, with high frequency donation stands out here because of the very low level of this protein. As for patient safety, it is shown that, in the last year studied, infectious markers were up to eight times higher among paid donors than they were among voluntary donors.



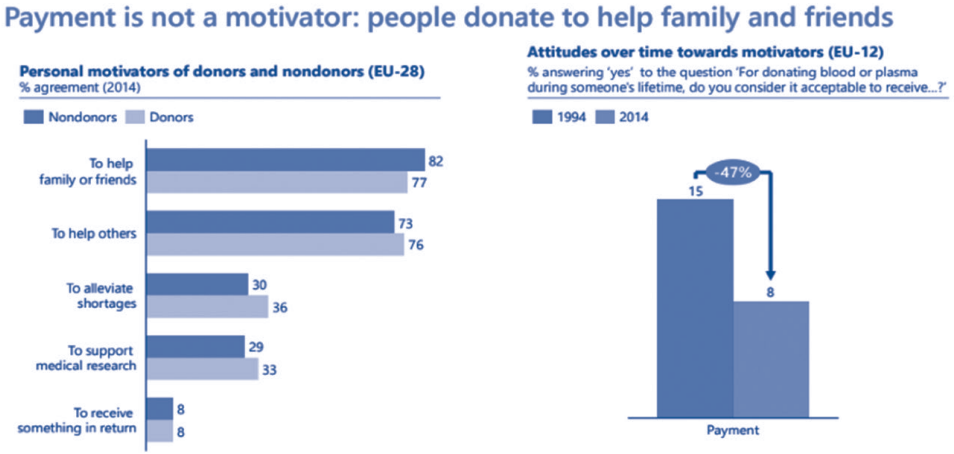
3. Better resistance in crises. The plasma supply models of non-profit organisations proved to be more resistant during the COVID-19 pandemic. Hence, plasma collection in the United States dropped by almost 25%, while in Europe it fell by 8% in countries with remunerated donation, and only by 3% in those with VNRD.

4. On the commercialisation of plasma. One example in this regard is the system in Belgium, which clearly favours VNRD, for reasons that are given below. Here, donation depends on the Red Cross and is not integrated into the country's public health system. The Red Cross collects plasma but sells it to the pharmaceutical industry for €110 per litre. From each litre of plasma, the industry obtains products to the value of €2,780. If production costs, calculated at €1,890, and the €110 initially paid for the plasma are deducted, the profit margin for the industry is remarkably high with a figure of €780 per litre of plasma. It is difficult to justify this plasma profit margin to people who have voluntarily donated.



5. On donor motivation. According to the surveys, payment is not a motivating factor for donors. According to the Eurobarometer, citizens in Spain and Sweden are the most willing to donate without compensation. All donor associations have repeatedly drawn attention to this.

Moreover, a cursory analysis of the European donor base shows considerable room for improvement in all countries. Only 15% of potential donors in Spain donate.



The conclusions presented to the European Parliament were:

1. For the vast majority of the population, payment is not an incentive for plasma donation.
2. A sustainable supply of blood products exclusively by means of VNRD is realistic.
3. The supply of products derived from VNRD donations is safer and more stable.
4. Public investment in collection centres could significantly increase plasma supply and enable the public health system to maintain control over supply and pricing.
5. Remunerated donation does not guarantee the availability of products in hospitals of the countries where this system is operative, despite high levels of plasma donation.

Campaigns: communication and accessibility to plasma donation

One of the aims of the PENAP should be to intensify plasma donation campaigns. The programmes of blood centres include improving communication and accessibility to plasma donation. Communication endeavours should engage European citizens in reflecting on blood, plasma, PDMPs, patient needs and, more generally, healthcare solidarity and sustainability in Europe.

In this regard, the Spanish Ministry of Health launched a campaign in the first half of 2023 with the aims of:

1. Raising awareness among the general population and the donor population about the need to donate plasma, and fostering commitment and solidarity.
2. Providing information about treatments made from plasma.
3. Increasing the number of plasma donors and promoting donor loyalty.

At present, just 3% of the healthy Spanish population gives blood. One plausible objective would be to raise this figure to 4% so that donors could donate less frequently. Management staff in blood collection centres and donors are convinced that it would be possible to attain these goals in a reasonable period of time if the appropriate resources were made available.

Monitoring immunoglobulins consumption. One important aspect to consider is control of PDMP use, especially immunoglobulins as a blood product which is a crucial determinant when calculating current plasma needs. It is necessary to adjust its use to the clinical evidence (which is to be one of the PENAP areas of work). Proper usage would reduce plasma needs.

Resilience and global competitiveness: The Granada Declaration. In September 2023, under the Spanish presidency of the EU, the report *Resilient EU2030* was published, in which the concept of "the EU's open strategic autonomy" was presented and ways of strengthening it were proposed. The document analyses the economy as a whole, including the health sector. It draws attention to areas where supply problems could arise while empha-

sising that Europe should not try to produce everything it currently imports but that efforts should be focused on high-value sectors as well as those that are "crucial for survival". In doing so, it identifies strategic goods, services, and raw materials for which the EU should increase its productive capacity by 2030.

After debating the future of Strategic Autonomy, the 27 heads of state and government approved a joint declaration of commitment (the Granada Declaration), setting out the EU's strategic priorities. Among other matters, it states the following: "We will … reduce external dependencies in other key areas where the EU needs to build a sufficient level of capacity to guarantee its economic and social welfare, such as digital and net-zero technologies, critical medicines and raw materials." In this regard, human plasma would, as raw material, have the status of a critical material if the importance of the repeated allusions to Europe's independence in plasma is taken into account. The Granada Declaration would then recognise the high strategic value of plasma in the general interest of public health.

To sum up:

- Improving plasma self-sufficiency is a priority for our public health system, as several other countries in our region have also decided and as is recognised as a shared EU objective.
- Plasma must be considered as a strategic public service. This designation would guarantee PDMP supplies.
- Spain and the EU should promote the implementation of plasmapheresis programmes in public health systems, which have proven to be more resilient to crises.

Transfusion centres should have sufficient capacity to obtain, by means of VNRD, a progressively larger volume of plasma, which would make it possible to meet the demand of all Spanish patients without damaging or interfering with the public health system, which is well known for its excellent performance over the years. This model would best guarantee donor protection, and also long-term maintenance of product supply.

- It is essential that VNRD should continue to be the indispensable condition for blood and plasma collection for several well-founded reasons.

  a) It has been shown that, with investment in adequate programmes within the public system, the required self-sufficiency can be achieved and more cost effectively.
  b) The pandemic has shown that a system of remunerated donation is more vulnerable to supply shortages.
  c) If left in private hands, there is a risk of becoming dependent on private industry for the supply of crucial blood products and of vulnerability to the imposition of prices by the private sector.
  d) It is essential to ensure access to treatment for all citizens (guaranteeing equity) and also to offer better guarantees of donor and receiver safety.
  e) Ethical principles.

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The German Model and a Note on Hungary

Svenja Tatjana Barckhausen

Member of the Board of Directors of Haema AG, Germany and director of Haema Plasma Kft in Hungary

Plasma is essential for the manufacture of blood products and, in particular, immunoglobulins. It is the only raw material from which this kind of product can be obtained, and immunoglobulins are not only a cure but also a treatment. Plasma contains proteins that are vital for many patients for whom no other alternative exists, so this blood component is essential for treating people with congenital diseases such as haemophilia and various immunodeficiencies. Furthermore, it is vital for the production of many essential medicines for treating, for example, patients with primary immunodeficiency who have a lifelong dependency on these products if they are to survive.

Plasma collection has several facets. The concepts and models vary widely both globally and within the EU. In particular, there are differences in the following aspects:

a) The sector that contributes: public, private or both;
b) Compensation: for plasma and blood, only for plasma, or for neither;
c) Frequency of annual donations permitted.

In this text, I shall present the main characteristics of the German model and, using this case study, I will examine the relationship between blood donation and plasma donation. In particular, I will seek to understand the functioning of a system that is open to several participants in blood and plasma collection and, using the example of Hungary, discuss what alternative is available.

History of the German System

Since the Second World War, blood donation by means of private organisations has been permitted and encouraged in Germany. Blood, administered as blood products, is a vital element in many areas of healthcare, for example surgery, oncology, and transplants. This means that the availability of blood is part of a country's vital infrastructure. It is so essential that, after the Second World War, no state organisation was allowed to have a monopoly on blood because of its strategic importance associated with times of crisis. The legislation introduced at the time and still in force today allows private organisations to collect blood, which makes this a unique model in Europe. Many private operators were established in the domain of blood and plasma donation and coexist with semi-public institutions such as university donation centres and clinics. The German Red Cross, a non-profit organisation that does not belong to the public sector, also plays a prominent role. And there are several organisations that manage installations for blood and plasma donations. The German model, with all its different agents, is very unusual when compared to other countries and has been very successful for many decades.

Agents in blood and plasma collection

In Germany, there is no centralised system of either blood or plasma donation. There are private companies that collect only plasma but also others such as Haema AG that collect both plasma and blood. In addition, many hospitals have collection centres for both, and numerous cities have a range of agents all operating at the same time. In Leipzig, for example, Haema AG has three donation centres, and these coexist with the Red Cross, and a blood bank at the University of Leipzig.

The government does not own the blood banks, although some are supported by public funding.

But how is blood supply managed and access for hospitals secured in Germany?

Article 2 of the Transfusion Act (*Versorgungsauftrag*) establishes a requirement for supply and an obligation to cooperate. To this effect, it stipulates a cooperation agreement according to which all blood centres should work together, accept the duty of protecting blood supplies in the country, allocate them fairly, and manage any delays in delivery.

Donation centres in Germany

The aim of this section is not to give a detailed description of the process of donation in German centres but, rather, to highlight some of its special characteristics.

There are three kinds of plasma donation centres.

- *Donation centres with a freezing chamber*. In this type of centre, the plasma is frozen in the donation centre and the fractionator takes the frozen plasma.
- *"Satellite" centres with centralised freezing*. These centres do not have a freezing chamber, so the plasma must be taken to a centralised freezing chamber where it is collected by the fractionator.
- *"Satellite" centres with central freezing in another centre*. In this case, the larger centre freezes the plasma for these satellites. The fractionator only collects at the centre where the freezing is done.

As for the centres themselves and their operation, they must offer a degree of comfort and an agreeable appearance because attracting donors is the most difficult part. It should be borne in mind that the most highly valued donors are the frequent ones as they already know the process, and take care of their nutrition and lifestyle so that they can donate again. Each centre has a manager who is responsible for the centre's functioning and operation, and there is always a doctor present who is responsible for taking care of the donors.

The donor is never left alone in the donation room and their security and wellbeing are ensured at all times. Finding a well-functioning team is another challenge and centre managers must oversee a multidisciplinary staff of receptionists, doctors, phlebotomists, and medical assistants.

Although, as described here, the German model of blood and plasma donation may seem very open, it must also be said that it is strictly regulated. While blood and plasma donors can be compensated (with maximum amounts for plasma and an average of 25 to 30 euros per donation), it should be noted that compensation cannot be mentioned or even alluded to in any advertising or marketing activity seeking to recruit donors. Promotional campaigns aimed at potential blood and plasma donors must be based on altruistic donation. This is appropriately called "altruistic marketing".

As for frequency of donations, according to the Haemotherapy Act (*Richtlinie Haemotherapie*) plasma may be donated up to 60 times per year. The intervals permitted between donations are as follows:

Plasma → Plasma: interval of 3 days.
Plasma → Blood: interval of 3 days.
Blood → Plasma: interval of 4 days.
Blood → Blood: men (8 weeks), woman (12 weeks).

Every fifth donation, the donor's IgG and total protein values are checked and if the results are close to an IgG threshold of 6g, the doctors at the centre set longer donation intervals (for example, 7 or 14 days).

With people making non-consecutive donations, a criterion of caution and safety is applied according to which such donations are postponed or suspended, temporarily or permanently, if the donor's IgG value is below the 6-gram threshold three times, regardless of the person's age.

These measures always aim to prioritise the donor's safety and protection.

The German plasma market

In Germany, there are no restrictions on the import and export of plasma. This means that the plasma collected is available to all fractionators and there are no limits applied to the purchase of plasma by other countries. Hence, German plasma is used for patients throughout Europe and is not subject to tender or competition but is supplied in a free market system. The price of plasma is determined by the market. For hospitals and blood banks, plasma sales to fractionators are a source of income for running their medical services.

Advantage of blood and plasma symbiosis

The physical examination and criteria for excluding donors are the same for plasma and blood donors. Nevertheless, in order to give plasma, the donor must undergo checks before the first donation with laboratory tests to determine their suitability. To this end, a blood sample is taken and analysed, or the person makes a blood donation, which is analysed without the need for taking another sample. This check can only be done in mixed centres where plasma and blood donations are offered.

The plasma donor base is much larger than that of blood donors because more plasma donations can be made per year. Hence, a combined centre benefits from the large number of plasma donors in having enough available donors of a certain blood group when needed. Plasma donors can be channelled into blood donation if blood bank reserves are low, and a specific shortfall needs to be covered.

Plasma and blood can be given in the same donation room. A blood donation takes about 30 minutes and a plasma donation about 50 minutes, except in the case of first donations. As we know, plasma is obtained from whole blood but is not sufficient for producing derivates in the quantities that are needed. A blood donation yields only 250 ml of plasma by comparison with a plasma donation by plasmapheresis in which up to a litre of plasma can be obtained (the quantity allowed varies between 750 ml and 1,000 ml in countries where plasmapheresis is permitted). Furthermore, the frequency of blood donation can vary between four and six times per year, depending on the gender of the donor, while plasma donation, in the various models around the world, can vary between 16 and 104 times per year, in line with the different legal requirements. The average donor gives much less than the permitted maximum. Frequent donors are the ones who contribute the volume that is necessary for fractionation. In this case, a fortnightly donation is deemed to be frequent.

The demand for whole blood donation is driven by the demand for red blood cells in hospitals, while that for plasma is determined by patients' needs for plasma derivatives, which are in short supply in many countries. Many patients who depend on these plasma products suffer the consequences of this deficit and sometimes require longer treatment periods, a situation that can be detrimental to their quality of life.

Models: public and/or private

In most countries, blood collection is a task of the health authorities. The state blood bank collects and supplies the blood to hospitals. In the search for an appropriate model, many countries rely on an inherited system that only envisages collection of whole blood but not of plasma and, frequently, there is no culture of plasma donation. The development of the technique of plasmapheresis allows the possibility of much more efficient direct plasma collection for the ultimate purposes of its subsequent processing and production of the medicines that are derived from it.

One basic question that arises is whether plasma collection from donations for subsequent fractionation to produce plasma derivates can be exported in case of a surplus, and who the agents involved should be.

An overview of the various models reveals different combinations, depending on the country:

- Public blood collection and public plasma collection: Spain.
- Public blood collection and private plasma collection: Hungary.
- Public and private blood collection and private plasma collection: Germany.

In this regard, it is essential to check whether there are resources to carry out such an activity and if the public sector can manage it or if the private sector needs to be involved.

The use of red blood cells – requiring whole blood – can be managed to a degree, although immunodeficiency patients are reliant on a constant supply of blood products. The donation volume required for fractionation is enormous. A PID (primary immunodeficiency disorder) patient requires plasma derivates that are equivalent to 130 donations per year. This is a theoretical figure because, in order to start an industrial fractionation process, a minimum of 1,000 litres is needed, which means that the quantities collected must be much greater.

Given this reality, a public-private balance should not be difficult to achieve. Indeed, this would benefit the development of a blood and plasma collection programme by enabling the investments necessary to ensure the establishment of a plasma centre in the right conditions, and thus to do the marketing necessary to attract donors. It is easier for the private sector to finance such centres. Competition favours development and, accordingly, progress. The world does not stand still, and patient and product needs are constantly growing. The donor base is changing and so is the world. We have an informed donor who knows that plasma is a raw material needed by the pharmaceutical industry to produce immunoglobulins and other plasma derivates.

Apart from what I have mentioned above, the models differ regarding question of whether compensation is permitted for blood or plasma donation. The prevailing model in many countries is that blood donation should not be compensated. However, in some places, in-kind compensation is offered, in the form of a day off work, a snack, and suchlike. While I do not intend here to explore the question of whether this kind of compensation is or is not equivalent to monetary remuneration, I would note that a day off work for blood donation clearly has a financial value.

The data clearly shows that, in countries where plasma donors receive some kind of compensation, there are enough donations not only to supply the country itself but also other countries.

Conversely, a model based solely on non-remunerated blood and plasma donations is empirically unsustainable as it does not provide the required quantities of plasma, and neither is it economically viable. The countries that have opted for it will keep depending on compensated donations and a small number of donors and hence on other countries, or they must cover their needs with imports of plasma derivatives obtained by means of compensated

donations. This is the situation Spain where, without compensated donations from the United States, Germany, Austria, the Czech Republic and Hungary, there would be an even more serious shortfall. For more than 30 years Spain has been self-sufficient in blood products for transfusion, but not in terms of plasma donations, where it is a long way short of its targets.

Paradoxically, however, Spain is the birthplace of plasmapheresis, a technique that was developed and patented in Barcelona by Dr Josep Antoni Grífols i Lucas. Until the late 1980s, there were no plasmapheresis centres in Spain. Since then, the donation situation has changed but the volume of only 50,000 litres per year, which is the total amount of plasma collected in Spain, is only equivalent to the quantity obtained by a single large German centre.

Despite years of effort to improve this figure, Spain continues to import more than 300,000 litres of plasma. This creates a gloomy prospect for Spain's self-sufficiency and those who suffer most will be patients, because the intervals of IgG treatments are lengthening and supplies are not guaranteed. If Spain could collect at least the quantity to cover the national demand for plasma derivatives, patients would benefit greatly from the increased availability of plasma products.

The Hungarian model, another alternative

In Hungary, blood collection is managed only by the public sector while the private sector is responsible for plasma collection. However, each plasma donation centre must sign an agreement with the National Blood Institute so that all plasma donors will be previously vetted or deemed suitable, after which they must make one donation of blood per year to the public blood banks and thus obtain the plasma donor's certificate. If the centres do not sign the agreement, they cannot obtain permission to operate. Hence, the Ministry of Health monitors the number of authorised plasma donation centres and guarantees blood donations from all donors once a year. There is also a programme where the blood bank sends a team to the plasma centres so that donors can be vetted when giving their first blood donation in the plasma centre of their choice so that there is no need to travel too far.

The Hungarian model, which makes the country self-sufficient, has the advantage of securing the supply of blood products with plasma donations while also ensuring continuity of a high level of blood donations.

Summary

1. Donating blood in the public sector and plasma in the private sector, as happens in Hungary, is workable. Keeping both kinds of donation in the private sector alone also works if the various agents jointly manage the blood supply in their country. The private sector has more resources for managing plasma donation centres and attracting donors on a regular basis, since this requires investment in marketing. Compensation for donation is helpful but it is not the only reason why people donate.
2. Blood donation is different from plasma donation and, accordingly, the donor base is different. Analysis of the data shows that plasma donors are willing to give blood but blood donors are less willing to give plasma. Only 50% of blood donors consider giving plasma.
3. In the German market, the agents involved are not in competition as balance and symbiosis prevail among them. In some German cities, there are blood and plasma donation centres of different agents in the same locality. This has the advantage of raising the public's interest in plasma donation and therefore attracting new donors.
4. Likewise, in Germany there is no distinction made between blood and plasma donors in the physical examination, the questionnaire, and the criteria for exclusion.
5. If there are doubts about competition, the Hungarian model would be the solution. The donors who go most frequently to the centres are the most highly valued as they know the requirements, lead healthy lives, and there is no risk of their being blocked as unfit for donation.
6. The public-private balance is not difficult. Neither is it necessary, but it does facilitate the investment in marketing that is needed to attract donors and to motivate them to donate frequently. The public-private concept is also beneficial as both sectors take advantage of the synergies and generate awareness of blood and plasma donation.

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Altruism, Solidarity, and Responsibility in the Context of Plasma Donation

Begoña Román

Faculty of Philosophy, University of Barcelona

1. Words, nuances, and contexts

Sometimes it is good to remember the contexts in which words first appear, are used, and are transformed. When we disregard the layers with which words are covered in the course of their history, their meanings become impoverished. Like "smooth pebbles" (Nietzsche, 1990), words are worn down and polished, but they are also enriched with polysemes and can create confusion. If the words concerned are moral categories, transformation and confusion are almost guaranteed. Discussions about these words, which are important issues concerning things or matters, end up becoming ideological defences of certain positions. This happens with terms like "altruism", "solidarity", and "responsibility" which, moreover, are relatively new words dating from the end of the eighteenth or early nineteenth century.

Auguste Comte is credited with coining the term *altruism*, which is defined in the Oxford Dictionary as "disinterested and selfless concern for the well-being of others". Near synonyms include abnegation, generosity, liberality, detachment, selflessness, charity, philanthropy, and humanity. This proliferation of synonyms alludes to the many nuances the word altruism entails, which contributes to the confusion I mentioned above. To give just a couple of examples, charity is considered humiliating and even anchored in Catholic morality, while it would also seem that only those who practise liberality are altruistic.

The main point to be highlighted in this definition is that the altruist prioritises others. However, we do not know why this is so, and still less whether

this altruism is disinterested. Internal, intimate motivations are not always easy to elucidate. Neither would it seem to be a good idea to ask, beyond the altruistic act, about its whys and wherefores if there is no exact way of ascertaining this. As Kant stressed, it is impossible to know the real reasons why one does one's duty (Kant, 2000).

Indeed, when people speak of donation, and in this case of plasma, they tend to use three adjectives that qualify or disqualify the act of donating: voluntary, altruistic and disinterested. Donating assumes 1) someone who offers something voluntarily; 2) the thing that is donated; and 3) someone who receives it. These three conditions are necessary in a donation. If a donation is not *voluntary* it is not a donation, even if something given and a receiving person exist. From an ethical standpoint, autonomous willingness matters as a key aspect, at least in contemporary ethics and bioethics. Likewise, the donation is altruistic because something is given, not because it is surplus but simply and precisely because the other person needs it, especially when this is a vital need.

The word that gives rise to most doubt is the adjective disinterested since it seems to establish a "pure" altruism as if adding other motives to the act of giving would contaminate the altruism. I have already mentioned the difficulty of delimiting this purity or disinterestedness because altruism entails advantages, namely personal satisfaction, confidence in the world we are helping to create or sustain with our action, social prestige, and so on. Sometimes, disinterested means free of charge, or receiving nothing material in return because, in that case, it would be an exchange and not, strictly speaking, an altruistic donation. There is a difference, however, when the thing donated is not sold but, rather, something is received in return as a token of gratitude.

However, some definitions of altruism go further, emphasising the possibility that it may involve an almost supererogatory donation, an act of great generosity, frequently portrayed as a heroic act in campaigns to raise public awareness of blood and plasma donation. This transformation of something that we need to be ordinary, routine even, into something extraordinary and heroic does not help to attain the goal of national self-sufficiency in altruistic, disinterested, and voluntary donation.

Solidarity is defined by the Oxford Dictionary as "unity or agreement of feeling or action, especially among individuals with a common interest; mutual support within a group". This requires identification with the other, in sharing their enterprise or cause. Solidarity implies altruism inasmuch as there is a cause or endeavour of *an other*, but the fact that the adherence to this case is circumstantial is a reminder that the other is in a condition of vulnerability, and that this is the motive or reason for the solidarity. It is assumed that the action of solidarity will remedy or alleviate the vulnerability, which would then signal the end of the duty of adhesion to the cause or endeavour.

Solidarity aims to strengthen social cohesion, especially in the light of the triumph of France's revolutionary liberty, equality, and fraternity. French sociology appealed to a sense of community, of mutuality, in which if a member of a collective was weak or in need of help, the other members responded. At the core of solidarity is the idea of fragility, and the duty to offer support, help, protection, a network to the other, who is one of us. Nevertheless, the core focus now tends to be on cohesion of the group which protects its own, any one of its members.

If solidarity entails a degree of altruism, it also involves self-interest. We are interdependent and faced with the vicissitudes of life, and it is therefore in our interest to trust in the group and to rely on the mutuality principle of "you today, me tomorrow". The great enemy of solidarity, when not accompanied by altruism and a sense of belonging, is the free rider, the scrounger, the freeloader, who benefits from the solidarity of others without participating in it. While altruism points to a personal diligence focused on a decision to give, solidarity focuses on the group and the need to count on it.

Solidarity calls for a kind of social bonding, especially since one cannot always manage alone and there may be times when one needs others. Solidarity entails a certain trust in the collective and avoidance of possessive individualism (which can be philanthropic) and of totalitarianism (which annihilates autonomy). Since human beings are by nature social and vulnerable, in general we are interested in a society of solidarity, of trust in institutions and in the group we live with.

Responsibility entails being liable for the – usually bad – consequences of free actions. Its numerous synonyms include maturity, reasonableness, formality, judgement, seriousness, obligation, duty, debt, commitment, competence, remit, undertaking, and even guilt and culpability.

From an ethical point of view, responsibility alludes to being liable for the consequences of one's actions for another, typically someone who is more fragile and vulnerable. This is why it is logical to associate responsibility with power and care. In the case that concerns us here, responsibility refers to the duty to respond to the vital requirements of people who need plasma. Failure to respond when we can do so constitutes a moral failure. In the words of Jonas (1955), the fragile and vulnerable are not given what they need when it is in our power to give.

We see how altruism, solidarity, and responsibility come together in the case of plasma donation when national health systems attend to the vital needs of some citizens.

It is worth considering some of the characteristics of plasma donation today. We start from a position of experience, one in which we are able to draw on evaluations of different models, and have a broad understanding of the scale of the problem. We cannot simply treat all the parts of the human body as if they were the same, flatly stating that they should not be treated as merchandise. Plasma donation is not a question of solid organs. What concerns us here is the problem of the lack of self-sufficiency of national health systems when they cling to altruistic, voluntary, and free donation, even if this means they must buy plasma at market prices, elsewhere, in places where this is legal.

We resist turning to the market as a solution to the problem of self-sufficiency both because the premise of not commodifying the human body aligns with our moral intuition regarding the concept of the dignity of physical integrity, and in light of the duty to protect more vulnerable people, who would be more prone to having to sell body parts, fluids, tissues, etc.

The aim is to achieve national self-sufficiency in plasma so that patients can be treated with the blood products they need without turning to the market

or being subjected to the inconsistencies of double standards. Neither profit nor business is the aim.

It strikes me as irresponsible to deny the possibility of compensation and to ask for more time, as most European countries have done so far, and as Spain also continues to do. Compensation should not be an incentive or remuneration at market prices. The concept of proportionality is also crucial. This is a matter of compensating efforts. It is determined not by market prices but by inconvenience, trouble taken, time, and even the expenditure (travelling and parking costs) the donor must incur because of the donation.

It is important to stress the specific nature of plasma donation. Blood and plasma donations are not comparable in terms of fairness to the donor, especially as the frequency of plasma donation is greater (24 to 33 times per year by comparison with two to four times per year in the case of whole blood, depending on the regulations). Plasma donation takes longer (about one and a half hours) and the effort and personal costs are greater (travelling time, transport, other "inconveniences" and so on). Apart from all these particularities, which also vary from person to person and time to time, I believe that donation should not entail financial costs for donors, or at least that such costs should not be an obstacle to donation.

Both incentives and compensation are intended to increase the supply of plasma. The objective is the same, but the meaning and the message are not. To compensate means to make up for some kind of damage or harm that has been caused. With an incentive, however, the donor's only or main motive is the reward. Without this, there would be no donation because willingness to donate depends on this. Compensation is not a euphemism for payment but a gesture of gratitude for the expenses and inconvenience incurred. It is also a gesture in recognition of the donor's altruism and solidarity towards the community.

The point is that compensation should not be the main reason for donating. Hence, consciousness-raising campaigns should emphasise the fact that people donate because this is a need and because, given life's unpredictability, any one of us might need plasma someday, or because it is soothing to know that one belongs to a caring society where altruism and responsibility

are encouraged as everyday attitudes (and not just the actions of self-sacrificing heroes).

It is true that, in real life, it is difficult to appreciate the difference, to evaluate the donor's inner willingness, and altruistic motivations, and the point at which compensation acts as the sole motivation. Theoretically, two differences can be established:

1. Neutral financial compensation aims to bring out the difference with incentive, and hence the importance of the amount being proportional to rather than exceeding the donor's efforts (expenses and inconvenience).
2. In public awareness campaigns encouraging plasma donation, information about the amount of compensation must not be the focus because it should not be the main reason for donation. First, information should be given about patients' needs together with encouraging altruism, solidarity, and responsibility towards the community. Society's recognition of the donor's efforts and compensation for it should be left for the end.

2. Plasma donation: a reading from applied ethics

Applied ethics deals with the level of risk people are willing to accept when they make a decision. A typical aspect of applied ethics is having to deal with complex problems which require answers that are open to revision after a time, precisely because the problems are complex, because they can be managed one way or another, and because the conflicting parties have good reasons for defending their position, thus creating a thesis and antithesis. In the search for a synthesis, the best answer available at the time is chosen. Sometimes these are tragic problems, as there are many pros and cons involved in each of the possible solutions.

Applied ethics therefore has a pragmatic side. It addresses problems in the context of morally plural societies where "reflective equilibrium" (Rawls, 2010) and trade-offs are required if the response is to be effective, where we

seek to identify the most legitimate solution and where, if circumstances change, we have to rethink our decisions. Examples include choosing between voluntary and compulsory vaccination, or the depenalisation of practices such as prostitution or drug consumption.

This reflective equilibrium reminds us of the duty to opt for consensuses that maintain a certain consistency between moral intuitions and the basic principles and values with which we wish to characterise our response. In the case of plasma donation, the principles and values are dignity and physical integrity, access to treatment for patients, and protection of economically more vulnerable people. If only the first option of "'pure' altruism were enough. That would surely be ideal. But it is not realistic and the reasons for donating must therefore be expanded (but not replaced).

Spain prohibits compensation for plasma donation but buys what it needs from abroad. At the same time, it is not adverse to compensating participation in clinical trials or egg and sperm donation. These are major contradictions that can be understood not only as a legal paradox but also as moral hypocrisy (Camps, 2018),

We need to think about why the plasma donation model currently operative in Spain needs to be reviewed. This is not the same country that launched the national health system, and nor is the system the same. The mentality of the Spanish people is not the same; their trust in society and its institutions is not the same; we can no longer sustain the simplistic view that public provision is always best, and that the market and profit are the devil's work.

From the standpoint of applied ethics then, this is a matter of choosing middle ways of action that do not simply hope for time to resolve the problem of self-sufficiency by means of a national plan, without changing any of the factors that are creating the problem today (and even aggravating it by prolonging the double standard applied when dealing with the needs for blood products).

This optionality does not mean that all alternatives are equally valid. Applied ethics requires us to explain the reasons for continuing to choose a system of free, altruistic donation but also, if one freely wishes (as this is not obligato-

ry), of accepting compensation. If this system can be saved by means of proportional compensation coexisting with altruism and solidarity, there is no reason not to propose it as a complement that would broaden the donor base. This option entails neither relativism nor arbitrariness.

In search of an effective middle path, it is necessary to shun both the idealist extreme which believes that the inefficiency of altruistic voluntary donation without compensation can be resolved by asking for more time, and the other extreme that succumbs to crass pragmatism and buys plasma at market prices.

However, there can also be extremes in the sphere of moral convictions. At one extreme there is 'pure' altruism, which is not only inefficient as noted above, but also supererogatory and naïve with regard to the basic reasons why individuals donate. At the other extreme are proposals for compulsory 'donation' because vital needs are at stake (Puyol, 2019). In this latter case, there can be no comparison with paying taxes or obeying traffic regulations. Whereas the collection of taxes or restrictions on the freedom of movement do not threaten physical integrity, the forced collection of plasma would entail just such a threat with, presumably, inspectors and police obliging people to submit to plasmapheresis.

Not covering plasma needs and simply depending on the market means a loss of altruism, solidarity, and responsibility, values we want to protect as a society. Efficiency does not justify any means. The imposition of donating would also mean a loss of ethical values. Ethics is about what we want to do, not just about what we actually do. The various reasons for doing should be respected except for two: doing something out of compulsion, and doing something only if one is paid to do so in accordance with the laws of supply and demand.

What matters in applied ethics is mitigating or resolving a problem within certain limits. In a morally plural society, we should not impose intentions or judge the reasons why people decide to donate. Moral pluralism reminds us that we are not all going to be of one mind in these intimate motives. The reasons for donating can vary from one individual to another and during an individual's lifetime, and they also depend on trust in the institutions, and coherence and transparency in the way they function.

There will be citizens who donate purely out of altruism simply because they feel it is a moral obligation they impose on themselves. Others will do it for the satisfaction of knowing they are being generous. There will even be some who do it for the compensation even when the amount is small. Yet others will do it because of the health report they are given when they make the donation, while there will be some who trust and expect that after contributing with their efforts, they will also receive plasma if they should ever need it. Some people hope they will never need it but prefer to live in a world where people, including themselves, give plasma. All these reasons for donating depend on personal contexts and moral positions.

In applied ethics, we must present deontological, consequentialist, and procedural arguments. In the first case, one must recall the right to healthcare and treatment, and society's duty to provide these and to protect economically vulnerable people in cases where remuneration is offered at market prices. As for consequentialist arguments, it is about managing to be efficient in obtaining the amount of plasma we need. However, in processes and procedures about how to respect rights and comply with duties while trying to attain goals, the stakes are also very high. Besides being effective, the process must be aligned with the values being promoted.

Complementing the disinterested altruistic model with the possibility of proportional compensation does not mean buying (Sandel, 2013) since we continue to opt for people's freedom even while facilitating the choice so that, at least, it will not be so burdensome. Cash allows us to simplify and to avoid the heterogeneity of in-kind compensation and the bureaucratisation of a monitoring system that requires proof in the form of metro or parking tickets. Money is the simplest way to settle compensation and it allows donors to decide what to do with it.

In-kind compensation, which seems to be less controversial, is still a euphemism. From the ethical point of view, in-kind compensation is equally acceptable since, after all, a remunerated day off work, or a tax reduction, still translates into money. However, financial compensation may be fairer since it would be the same for everyone, while tax breaks and a paid day off work will vary according to income. Moreover, unemployed people or students cannot be compensated in this way.

It is only fair that people in need of blood product treatment should not be abandoned to their fate, and it is also fair that we should be aware of the particular situations that influence the decision of each and every citizen to donate. Equality of opportunity should be guaranteed not only when receiving plasma but also when donating. Compensation mitigates the inconvenience, discomfort and costs that people have to accept. This way, we are not always burdening the same altruists but broadening the donor base, without taking intentions into account but setting limits to the amount and the number of times they can donate. Financial compensation would certainly not be a prime motivation for those people who already donate, but it could prompt them to go more frequently and also attract more donors.

The notion of the slippery slope is an expression of mistrust with respect to managing and delimiting risks. The solution is to implement constraints where they are needed and to allow for moral pluralism in terms of intentions. What is not acceptable is the double standard that ends up validating something we do not want. We want to preserve altruism but not to demand it or to practise it as it something pure. We want to encourage solidarity, which suggests that the donation should be voluntary, and we want to foster responsibility so that each person, whatever their circumstances, can decide once the donation has been made, whether to accept compensation that is proportional to the effort made and do with it whatever they wish, or not to accept it.

Conclusions

Altruism and solidarity are desirable, and governments should encourage them. Nevertheless, the evidence shows that it is not possible to obtain sufficient plasma donations without some kind of compensation. Offering compensation for this effort would not annul the "goodness and solidarity" of the donation. The idea is to promote a system of proportional monetary compensation to cover the donor's expenses and inconvenience when giving the donation (time, frequency, travelling, effort). Compensation can also be understood as a gesture of courtesy in gratitude for the donor's commitment to their fellow citizens.

When advocating that plasma donation should be complemented with a system of proportional compensation (which would not be a key point in awareness-raising campaigns) we stand for altruism and solidarity, but in a way that allows for nuance because altruism and solidarity admit degrees and reasons, and there is room for more or less. Responsibility also requires time and resources, offering facilities so that the act of altruism is not so burdensome and draining. This is why it is necessary to set limits on prices and frequency, among other aspects, to make sure that the economically vulnerable are not exploited.

Compensation does not mean buying. Nuances make the qualitative difference. With proportional monetary compensation of the same amount for those who opt for compensation, and not used as the main incentive when addressing the need to donate plasma:

a) citizens would be allowed to decide their own reasons for donating and these will depend not only on their wishes, but also their personal circumstances;
b) setting the same financial and optional amount avoids bureaucratisation and the comparative disadvantages that appear when the donor is a student or unemployed, and when days off work are compensated at different rates;
c) work could proceed, meanwhile, on a national plan to achieve self-sufficiency without resorting to the double standard of doing outside the country what we do not want to do within it, namely buying and selling.

The collection, processing and distribution of donated plasma requires more complex professional and technological support (structures and installations) than are required for whole blood collection. Location and accessibility also influence donation. A certain degree of public-private collaboration is probably the best way to achieve the desired national self-sufficiency. Since trust is a key factor, this would require government monitoring. Naturally, evaluation of the model would demand transparency, and checking to identify whether and, if so, why altruism is being harmed.

It is the role of the authorities to promote cooperation and solidarity. However, if these efforts fail, we cannot ignore the reality of a therapeutic

demand that the authorities must also strive to satisfy. Proportional, neutral, and legally recognised compensation could achieve this, as has been demonstrated in other European countries such as the Czech Republic, Austria, Hungary, and Germany. The United States and Canada have different systems and are plasma exporters. However, comparing these systems is beyond the scope of this article.

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What Do Citizens Think?

The Donor's Experience

Sabin Urcelay

Head of Section, Basque Centre for Transfusion and Human Tissues, Gipuzkoa (FCVTTH.G)

In all areas of the world, in every discussion, in every exchange of opinions, Campoamor's law applies. This was first formulated by Ramón de Campoamor (1817-1901) in his poem "Las dos linternas" (Two Lanterns):

> And in this treacherous world,
> nothing is truth or lie:
> it all depends on the colour
> of the glass held up to the eye.

Perhaps it would be more precise to say that nothing is as each one of us sees it. The image that comes to us is greatly influenced by the glass through which we look, and I would add that, with time, we gradually equip ourselves more or less consciously with glasses that make us see reality in the way that best suits our desires or convenience.

In this text, my glass will be the one that most befits me for considering this problem from the standpoint of donor organisations and my experience as president of Blood Donors of Gipuzkoa these last twenty-five years.

To introduce this subject, I would like to present the sculpture "Squaring the Circle" created by the UK-based artist group Troika and designed to demonstrate subjectivity in perception of reality. Depending on where the person observing the sculpture is situated, they will clearly see that its form is a perfect circle (1), but another person looking from elsewhere will be sure of seeing a perfect square (2), while a third person looking from a different viewpoint will see a complex, three-dimensional figure (3).

Certainly, no one will have the absolute true view but as soon as we move, we realise that figures 1 and 2 are further from reality, even though this fact will

Figure 1 Figure 2 Figure 3

not change the perception of people who see the perfect square and the perfect circle.

With regard to the problem I wish to discuss here, there are three well-defined points of view:

a) The fractionation industry, which aims to receive raw material to obtain the greatest possible quantity of medicines with which to supply the market.
b) Patients who aim to obtain a complete supply of the medicines they believe necessary to treat:
    I. pathologies that have been shown to improve only with plasma-derived products;
    II. pathologies that may improve with other treatments but where these have a lower degree of efficacy and comfort;
    III. pathologies that can be tested to see if they improve with these plasma-derived medicines.
c) Donor associations and transfusion centres that aim for strategic independence, which means achieving 100% self-sufficiency in medicines needed for those pathologies that have been shown to improve only with plasma-derived products and, if possible, to achieve 75% coverage of all necessary medicines.

Starting from these premises, I shall review the concepts of donation and altruism. Donation (from the Latin *donationem*, giving) has been with humanity since the earliest civilisations, as demonstrated by the potlatch practised by the Indigenous people of the Pacific Northwest Coast of Canada and the United States and comparable rituals of many societies in other parts of the world, where donations are intrinsic. Such donation frequently encompassed an obligation both of acceptance and of reciprocation, and they were generally a sign of power and status in relations established between communities, tribes, and families.

Nowadays, when we talk about donation, we are basically referring to a personal, unidirectional action, and generally from the perception that the person who donates does so in the belief that they have something the recipient lacks or needs. We also make donations to organisations that represent people or groups, with whom we empathise and see as being in need.

These donations are intended to solve a problem that is experienced in these groups but, generally speaking, we rarely think about it as we do not imagine that, at some point, we could be in this situation. Donations may result from feelings of charity, a commitment to social justice, or simply reflect effective marketing campaigns. With these donations it is possible to distinguish between people who donate on a continuous basis because their convictions make them believe this is the right thing to do, and others who do so in response to appeals on the street, or to news items, or to public awareness campaigns that appear in the various media outlets.

As for altruism, this is a term that has been used as a counterpoint to family or paid donations, which were quite common until the 1960s. However, this is not a concept that very clearly defines the motivation that leads a person to donate blood or plasma.

In his book *Give and Take: Why Helping Others Drives Our Success*, Adam Grant presents a simple classification of people in terms of the concern they show for others and for themselves:

- People with little concern for others or for themselves: apathetic.
- People who are very much concerned about themselves but care little about others: selfish.
- People who are very much concerned for others and with a low concern for themselves: altruistic. These people – with rare exceptions – tend to burn out and abandon their philanthropic work and actions.
- People with high levels of concern for others and for themselves are what Grant calls "otherists". They are people who feel gratified by their actions in which they try to help others. This would be the case of blood and plasma donors who become loyal donors because of the gratification they feel when helping others.

		Concern for the interests of others	
		LOW	**HIGH**
Concern for one's own interests	**LOW**	Apathetic	**Altruistic** Self-sacrificing
	HIGH	Selfish	**Otherists** Feel compensated

In our promotional campaigns to attract donors, we try to appeal to a sense of solidarity. We seek caring people who are happy to participate in the construction of a caring society where people help each other. The difference with other kinds of donations is that we know that any one of us, at any time, might need a transfusion or some kind of plasma-derived medication.

In Gipuzkoa we have spent some years sending out the message that, "If transfusion is everyone's right, then blood donation should be a shared responsibility".

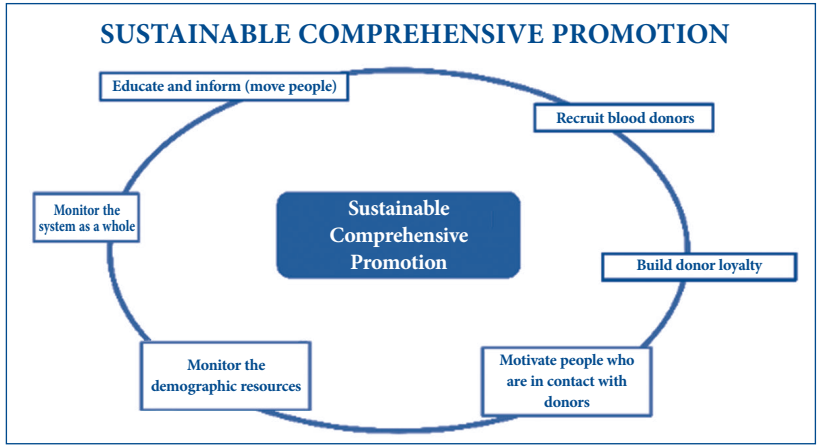
Fortunately, just 4% of the population need to donate to cover the needs for treatment with blood and blood products.

However, when we state that blood donation should be a shared responsibility, we are saying that the whole of society should shoulder this responsibility so that the whole society would be assured the right to transfusion.

In 2004, the Spanish Ministry of Health published a document titled *Promoción Integral Sostenible* (Sustainable Comprehensive Promotion) which

described six primary and 19 secondary actions when addressing promotion of blood donation in a comprehensive way (and not only thinking about obtaining blood donations), with the idea of building donor loyalty in a sustainable process. Every member of society should, to the best of their ability, contribute to the success of this sustainable comprehensive promotion. The six primary actions would be:

1. Educate and inform (move people).
2. Recruit blood donors.
3. Build donor loyalty.
4. Motivate people who are in contact with donors.
5. Monitor the demographic resources of donors and the general population.
6. Monitor the system as a whole.



1. **Educate and inform (move people).** It is essential that the general population should be informed about the need for blood and plasma donors but donors' associations believe there is a lack of statements from patients' associations expressing gratitude for treatments received thanks

to blood donations. With such recognition, two crucial things would be achieved. First, blood and plasma donations would be properly valued and, second, donor loyalty would be increased if the results of this solidarity were made visible. It would also be appreciated if the administration were to mention the surgical operations that are done thanks to blood donations, or if they spoke about them when praising organ and bone marrow transplants because, without blood donation, none of this would be possible. It is striking that the vast majority of news items about bone marrow and organ donations are very positive but, in general, blood donation tends to become newsworthy only when reserves have dropped to alarming levels. Patients and the administration should reinforce positive news about blood and blood product treatments as well as drawing attention to the generosity of people who give blood for this purpose. In this regard, it would seem that, at present, transfusion is a gift that elicits no emotion or gratitude.

2. **Recruiting donors.** Fortunately, the intake of new donors in Spain is continuous. The culture of blood donation is well-established in this society and thus provides fertile ground for the success of other donations such as bone marrow or organs. We speak about recruiting donors but not about achieving donations because the important thing is to attain a donor base that is sufficient to ensure that we obtain the necessary donations. We must think like cultivators and not like nomadic foragers.
3. **Build donor loyalty.** Much of the process of building loyalty is in recruitment, and the motivation that makes a person come to donate for the first time. Hence, incentives to donate must aim to convey feelings of solidarity, of shared responsibility, and of belonging to a caring society. If we manage to ensure that the first time people come to donate blood they bring with them some of these feelings, our job will be limited to consolidating their commitment during the first four or five donations which, according to studies on the matter, is when the point of loyalty is reached, this being when donors have acquired sufficient inner motivation to keep donating blood with almost no external stimuli (which does not exempt us from trying to reinforce these motivations in subsequent donations).

If we made the effort to develop these three points together, with complementary help from transfusion centres and donor associations with the three remaining points, we would have enough donors to ensure the donations we need to achieve the strategic independence we have set as our goal.

There is currently much talk about the danger of shortages of plasma-derived medicines, a fear that has been exacerbated in the wake of the COVID-19 pandemic. We are in a situation that is not unlike the one regarding blood translations in Spain in the mid-twentieth century, when Dr Carlos Elosegui wrote in his *Manual de Hemoterapia* (Manual of Haemotherapy, 1942), "The day must come when the practice of Haemotherapy, always subject to official control, must be limited to those cases in which it is deemed indispensable." Continuing with his predictions, he added, "The supply difficulties will increase. The numbers of voluntary occasional donors will fall, paid donors are asking and will ask for more payment, and eventually it will be the state that will have to regulate this pressing aspect of the matter, even making blood donation compulsory, at least in certain cases and circumstances."

At the time, donors were paid five pesetas for 9cc of blood. In 1972, in my university days, I knew of remuneration of 800 pesetas for a blood donation to meet the haemotherapy needs that were not covered by family or replacement donations. Happily, 50 years later, we have a network of transfusion centres which, thanks to voluntary, solidary, and responsible blood donors, achieved 1,371,537 blood donations in 2022.

Although it is only very recently that blood donation campaigns have been organised, in all the autonomous communities of Spain, it is clear that the problem of not achieving the necessary plasma donations is not due to the number of donors but, rather, lack of the necessary infrastructure to be able to attend to potential donors. In Gipuzkoa – in the sampling we have carried out among donors (by way of small informative sessions) we have achieved more plasma donors than we can attend to.

One example I could mention is the case of the town of Azkoitia where, after speaking with the head of the local blood donors' association, we gave them some very simple leaflets explaining what plasmapheresis is and why it is necessary to increase this type of donation. The leaflet was presented in three sessions of whole blood donation. In less than two months more than 110 donors, 1% of the population, had registered. This figure is much higher than what we would need to obtain the plasmapheresis needed for Gizpuzkoa if we applied an average of four plasmaphereses per donor per year. This experience suggests that with more information and more intensive campaigns these results could be reproduced in the other towns of Gipuzkoa.

Blood donors are eager to take things further: to become plasma donors and help to fix a problem which, in the very near future, might affect any one of us. Moreover, plasma donation and its current indications and implications may attract people who believed that this problem had been resolved and had focused their solidarity on other causes.

In Spain, there have been successful experiences like that of the Hermandad de Toledo which, with the resources and motivations of 30 years ago, managed to achieve an annual average of 2,500 plasmapheresis interventions in its mobile units. This represented 15% of total donations.

After the pandemic, and especially in the last two years, plasma donation programmes have been implemented in almost all Spain's autonomous communities, with a notable increase in donations in all of them.

To paraphrase Archimedes' hyperbole – "Give me a place to stand, and I shall move the world" – we would say from the donor associations, give us machines and staff and we will flood the transfusion centres with plasma.

To conclude, it is understandable that – from the ethics of conviction and with a focus only on obtaining plasma – the fractionation industry believes that if offered a financial incentive people would come forward to give the necessary plasma and that patients would think that, with this plasma, they will have the medicines they need. However – from the ethics of responsibility – those of us working in donor associations and transfusion centres, knowing that we need donors, remembering that the financial incentive for blood donations was a failure, aware that we know of no country which, through financial incentives, has achieved self-sufficiency in blood products, and believing that introducing a system of compensation to get people to come and donate plasma will destabilise the presently existing model of donation, are committed to promoting plasma donation campaigns based on voluntary, solidary, and responsible donors, thus avoiding future repercussions that we can neither predict nor deal with.

Patients' Thoughts on Solidarity and Altruism

Carlos Jiménez

President of AEDIP patients' association (Spanish Association for Primary Immunodeficiencies)

First of all, I think it would be useful to define what primary immunodeficiencies are. Primary immunodeficiencies comprise a broad group of diseases that appear when some components of the immune response system (especially blood cells and proteins) do not work properly. A normal immune system helps the organism to eliminate infections caused by such microorganisms as bacteria, viruses, and fungi. People with immunodeficiencies are more prone to infections than other people.

Immunodeficiencies derive from defects in genes (in other words, parts of DNA) that are involved in the development and functioning of the immune system. There are many known genetic defects that cause immunodeficiencies such as Severe Combined Immunodeficiency (SCID), Chronic Granulomatous Disease (CGD), and hyper IgE syndrome. Most of these defects are inherited from parents, but others can result from genetic mutations that occur in pregnancy.

The only treatment once the disease is diagnosed is immunoglobulin replacement therapy. The immunoglobulin is obtained by fractionating human plasma from healthy donors. Immunoglobulin treatments are carefully selected and have an excellent safety record. Although immunoglobulins do not prevent all infections, they do reduce the frequency and gravity of many of them in patients with primary immunodeficiency. This is the only treatment for these diseases. In other words, there is no therapeutic alternative.

In Spain, most plasma is obtained by processing donated whole blood, with the plasma then being sent to the fractionation industry for use in the manu-

facture of medicines. In Spain, whole blood donations account for 91% of plasma collected, against an average of 40% for the European Union as a whole.

Direct donation of plasma in Spain is far below the European average at only 0.7 litres per 1,000 inhabitants compared with 8 litres per 1,000 in the EU in 2019, which means that Spain collects one tenth of the volume of plasma collected in leading collector countries such as Austria.

This places Spain in a situation of greater vulnerability than that of its neighbours since the amount of plasma obtained by separation of whole blood is much lower than that obtained from each direct plasma donation, and this directly affects the number of treatments that can be obtained.

It should also be noted that blood donations have declined in recent years, in part because of a reduced need for red blood cells due to improvement in indications and therefore better use. This decrease in blood donations inevitably results in a smaller collection of plasma and, accordingly, a fall in the

Situation in Spain	2015	2016	2017	2018	2019
No. total donations whole blood and apheresis)	1,706,973	1,698,759	1,686,463	1,682,579	1,684,501
No. whole blood donations	1,651,074	1,639,606	1,615,665	1,605,752	1,602,368
No. plasma donations	28,045	31,724	42,387	48,134	52,258
Plasma from Plasmapheresis (L)	16,790	19,053	25,365	25,500	30,999
L per 1,000 inhab. Spanish average	0.4	0.4	0.55	0.6	0.7
L per 1,000 inhab. EU average	5.9	6.25	6.3	8	8

Source: Author, using data published by the Ministry of Health

production of treatments and this is even more marked when most fractionated plasma in Spain depends on whole blood donations.

Plasma collected in Europe accounts for only about 65% of the amount needed to manufacture the treatments in demand. The rest is mostly purchased from the United States. In Spain, this dependence is much greater, as we purchase more than 65% of the plasma we need. All these shortcomings create a situation of high vulnerability with potential problems in the supply chain, as well as posing challenges of coping with the estimated mounting demand arising from new indications. Moreover, there is considerable inequality among the countries in terms of donation volume. Just four countries – Austria, the Czech Republic, Germany and Hungary – collect more than 55% of total plasma in Europe for use in manufacturing derivative treatments. It should be borne in mind that Spain, France and Italy use their collections exclusively to attend to internal needs, which diminishes the amount of plasma available for the EU as a whole.

The verb 'to compensate' refers to giving something by way of redress for an injury or to equalise, in the opposite sense, the effect of one element by means of the effect of another different element.

In Spain, the applicable legislation establishes that "donations of blood and blood components are voluntary and altruistic acts", which are defined as those in which "a person gives blood, plasma, or cellular components of their own free will without receiving any payment, either in cash or in kind, that could be deemed a substitute for money". It also expressly states that "small gifts such as recognition or reimbursement of direct expenses to cover travel costs are compatible with non-remunerated voluntary donation." Accordingly, Spanish legislation, essentially altruistic, establishes a broad framework that contemplates the possibility of solutions for compensating time and expenses associated with donation, for example hours off work allowed by public and private employers, or reimbursement of travelling costs, and even compensating for the time spent when donating. Hence, one can say that compensation is contemplated in Spanish law. Moreover, it does not exclude the concession of tokens or prizes as a way of recognising those who donate, for example in the form of coupons, discounts in restaurants, trips, experiences, keepsakes, mentions in social media, tickets for football matches, etc.

Another possible form of compensation would be the application of income tax incentives by cross-checking with registers of donors. Finally, local cultural factors should be considered. If in a totally altruistic system in which donors receive no kind of compensation, Spain is self-sufficient in blood donations and a leader in organ donations yet highly dependent in the case of plasma donation, it would be logical to accept the reality and recognise that the current model needs to be changed. The current model does not work and, despite the improvement we have certainly achieved in the last two years, Spain does not seem likely to achieve the strategic sufficiency it needs in the near future.

Voluntary describes an act of born of volition and not as a result of force or extraneous necessity. It also refers to something that is done out of spontaneous willingness and not because of obligation or duty. We could therefore conclude that every donation in Spain is voluntary since nobody is obliged to donate. We also understand that altruism is the stance of people who seek or procure the good of others, even to their own disadvantage. To be very specific, in the domain of plasma donation, one might add that an altruist is a person who gives without expecting any benefit in return. These principles enshrined in Spanish law coincide with European legislation and the principles of the AEDIP (Spanish Association for Primary Immunodeficiencies). We are all in agreement about the general principles.

However, compensation is not remuneration, and this nuance is what the new European SoHO legislation clarifies and presents, and it coincides with what we advocate at AEDIP.

As long as it does not go beyond the threshold of financial neutrality or, in other words, provided that compensation does not exceed the costs of the act of donating, the donor is being compensated but not paid. Paying is what we are doing indirectly right now when we buy plasma from the United States, which is remunerated. Hence, if the aim is to have plasma obtained voluntarily and altruistically, then we must change the present model, since the system by which Spain currently obtains plasma is evidently not altruistic. If we were to compensate donations in a general and systematic way, the plasma thus obtained would meet the requirements of being voluntary and altruistic.

It should be borne in mind that, generally speaking, for the donor (although there are blood banks that compensate in one way or another by covering parking or taxi costs, etc), the fact of giving is not only not neutral in financial terms but showing solidarity also costs money since they must bear the expenses involved when going to make the donation. This is a constraint, especially for young people who might be willing to donate but are put off by the costs they might incur if they donate.

If something in a country is not working – and our plasma collection model is not working – then the country must make changes to make sure that it will work. If we keep doing what we have done in the past, we will have the same result, which is not in the interests of patients or the health system.

I cannot assert that, if compensation were unapologetically included across the board, the problem of strategic dependence on plasma would be resolved. But I can point out that the four countries that collect more than 55% of total plasma collected in the EU – Austria, the Czech Republic, Germany, and Hungary – have compensation models. The evidence is overwhelming. It is also true that importation of a model does not have to be all-inclusive. Models should be adapted to conditions in Spain.

Consequently, sufficiency is necessary to:

- guarantee gamma globulin replacement therapy for the patients who need it, with particular attention to those who have no other treatment alternative, in which case this is an absolute priority;
- strengthen the health system, because with plasma obtained by unpaid donation (with or without compensation because compensation is not payment) we would save millions of euros in health resources as we would not have to buy the gamma globulin that we are not capable of producing by means of domestic donation, which is what we should be doing now;
- counter the moral inconsistency of being "purist" on the theoretical level and then buying plasma from countries that obtain it by payment. If Spain is so opposed to remunerated plasma (a model that we reject), the best option is to guarantee self-sufficiency using the means currently allowed by the law and applying the mechanism of compensation in keeping with the principle of financial neutrality.

In order to attain strategic sufficiency, which requires persuading thousands of citizens to accept the challenge of becoming blood and plasma donors, it is necessary to clear away the obstacles standing in the way of making the most of the solidarity that already exists in our society, as is demonstrated by organ donation, which is compensated by offsetting the associated expenses that are currently borne by donors. Naturally, we do not know if this measure alone would be sufficient to achieve the goal, but one thing we can be sure of is that it would not subtract but would only add.

This is an extremely important moment as a major debate is occurring at the European level:

- The European Commission opted to introduce compensation (14 July 2022);
- The European Parliament opted for compensation (quantifiable losses, reimbursement of expenses, 18 July 2023);
- The Council of Europe opted for compensation on the same terms as the European Commission (26 October 2023).

Taking advantage of this important European debate and coinciding with the Spanish National Plasma Plan that the Ministry of Health presented in 2022, and given the problem of plasma dependence, it is urgent that measures should be taken in the short and medium term that will lead to achieving the goal of sufficiency. We all agree on the aim and Europe is paving the way to achieving it (in keeping with our principles of voluntariness and altruism). Article 54 proposed by the European Commission states that, "Member States may allow for the compensation or reimbursement from the SoHO entities to donors for losses related to their participation in donations through fixed rate allowances. In such case, Member States shall establish the conditions for such allowances in national legislation, including the setting of an upper limit that ensures that allowances are financially neutral and consistent with the standards laid down in this Article. They may delegate the setting of conditions for such allowances to independent bodies that are established in accordance with national legislation."

The Strength of Patients' Associations

Teresa Lluch

PhD in Biochemistry and CIDP vice-president of GBS/CIDP Immune-Mediated Polyneuropathies (Spain)

Our association

Our association consists of a heterogeneous group of patients and family members affected by immune-mediated polyneuropathies (or acquired autoimmune inflammatory neuropathies) with members based all over Spain. In order to overcome the barriers of physical distance and to accommodate the challenges posed by functional divergence, we exist as a digital association. We have not held any in-person meetings but, thanks to mobile phones and videoconferencing, we have built a "great little family", which we hope will grow stronger over time. The establishment of an association as a way of addressing our pathologies was supported by the GBS/CIDP Foundation International in the United States and by EPODIN (European Patient Organisation for Dysimmune and Inflammatory Neuropathies). We received confirmation of registration in April 2020, with the COVID-19 pandemic at its height, but we did not allow this situation to prevent us from achieving our objectives of raising the visibility of our community, in order to foster research and improve the standards of care both at the individual level and in collaboration with other entities.

The pathologies we represent

Acquired autoimmune (or dysimmune) inflammatory neuropathies, also known as immune-mediated polyneuropathies, are a set of neuromuscular syndromes that come under the heading of "rare diseases". Guillain-Barré syndrome (GBS) has an incidence of between one and two cases in every 100,000 people, while chronic inflammatory demyelinating polyneuropathy

(CIDP) has a lower incidence rate but, as a chronic condition, is the neuropathy with the highest prevalence rate, at around eight cases per 100,000.

These neuropathies affect the peripheral (long fibre) nervous system and involve demyelination and thus affect all nerves except, in principle, the central nervous system, the brain, and the medulla. They can be acute, like GBS, or chronic, like CIDP and multifocal motor neuropathy (MMN). They are triggered by a dysimmune reaction (malfunctioning of the autoimmune system) but the specific mechanisms are still unknown except for some more recently identified antibodies.

Table 1. Classification of inflammatory neuropathies

	ANTIBODIES DESCRIBED
Guillain-Barré syndrome and variants	
Acute inflammatory demyelinating polyneuropathy (AIDP)	
Acute axonal motor neuropathy (AMAN)	GM1, GD1a
Acute axonal sensory-motor neuropathy (AMSAN)	GM1, GD1a
Sensory GBS	GD1b
Acute sensory ataxic neuropathy (ASAN)	Disialosyl
Miller-Fisher syndrome	NeuNAcNeuNAcGal
Ataxic GBS	GQ1b
Local-regional variants	
Pharyngo cervical brachial palsy	GT1a
Acute pandysautonomy	
Chronic inflammatory demyelinating polyradiculopathy (CIDP)	
Typical CIDP	P0,PMP22,P2
Atypical CIDP	LM1
Pure sensory CIDP	CAMs, Contactin-1,
Pure motor CIDP	Neurofascin 155,
Distal acquired demyelinating symmetric neuropathy (DADS)	NrCAM, gliomedin,
Asymmetric (Lewis Summer variant)	Neurofascin
Multifocal Motor Neuropathy (MMN)	
MMN with conduction blocks	GM1 IgM
MMN without conduction blocks	
Polyneuropathy associated with monoclonal gammopathy of uncertain significance (IgM-MGUS)	
MGUS associated with anti-MAG antibodies	MAG
MGUS with IgM monoclonal gammopathy without anti-MAG	

These are very incapacitating diseases which can cause total paralysis in a few days (as happens with GBS, which is acute) or may be slower and more gradual, taking anything between four weeks and two years (as happens with CIDP, which is a chronic condition). In short, autoimmune neuropathies constitute a very heterogeneous set of neuromuscular diseases with different clinical and pathological particularities, as shown in the classification[1, 2] of Table 1.

Immunoglobulins as first line treatment

Despite advances in research, standard treatments date back to the 1980s with immunoglobulins[3] as the main treatment and, in the case of multifocal motor neuropathy (MMN), the only treatment. Immunoglobulins – antibodies found in plasma which act by neutralising our own antibodies, thus preventing attacks on the myelin sheath – are not a cure but they do hold back the advance of the disease, giving our body time to regenerate the myelin sheath which has been stripped from the nerves like the plastic casing on an electricity cables. Since the percentage of immunoglobulin in blood is low (0.006% of total blood volume), thousands of donations are needed for plasma fractionation in a process that takes between seven and twelve months. Immunoglobulins therefore determine the requirements for plasma donations. Around 380 to 420 plasma donations are needed for the annual treatment of a single patient with CIDP. Immunoglobulins are in short supply in the European Union, and the main reason for this is insufficient plasma as Europe collects only 60% of the plasma it needs and depends on imports from the United States for the other 40%.

The pandemic and immunoglobulin shortages: current situation

Blood and plasma donations dropped considerably during the pandemic, which led to a shortage of blood products, especially immunoglobulins, which were also used to treat COVID-19, with everything that implied for people who depended on them for their survival. In Spain, the problem was exacerbated by the fact that more than 70% of plasma derivatives are imported. In

fact, Spain is Europe's third largest importer of these products, a situation that contrasts starkly with the levels of blood and organ donations.

The result of this shortage was a major cutback in immunoglobulin treatment of autoimmune neuromuscular diseases such as ours, with serious consequences in terms of loss of health, deterioration in quality of life, and psychological suffering. At present, this situation has not yet been remedied because, although donations have increased, we are still importing large amounts of plasma and the price of immunoglobulins has risen steeply, all of which makes it difficult to continue with this treatment, and also creates uncertainty and anxiety among those of us who need it.

This situation coincides with the introduction of the SoHO regulations, which are the focus of this conference, in which we have participated through our federation EPODIN.

Unity is strength: working together for plasma sufficiency

As noted, one of the collateral effects of the pandemic was a shortage of immunoglobulins. However, thanks to the existence of our association at the time (and although it was still very new), we were able to gather strength and start a campaign to raise awareness of what was happening to us. We created an online petition, speaking as people who were affected by the shortage of immunoglobulins, addressing the Ministry of Health and the Spanish Agency of Medicines and Health Products (AEMPS), and asking for plasma and blood donations. We also wrote press notes that were published in a range of local and national outlets as well as in health magazines. We sent letters to the Ministry of Health and to the health ministries of the various autonomous communities requesting responses to our situation, and we made contact with other associations of people for whom treatment with blood products is essential, adding our voice to calls for plasma sufficiency and contributing to the document "Spanish Consensus for Sufficiency of Plasma and Its Derivative Treatments". All this demonstrates the power of associations, which is even greater when they unite for a common cause.

Conclusions

To sum up, patients' associations are essential in performing an important social role, as the Spanish health system does not cover all the needs of people with rare chronic diseases.

In addition to the typical functions of patients' associations in seeking to ensure that patients, their families, and nearest and dearest can cope with an illness in the best possible way, with the support of people with first-hand experience of the problems, I would also mention here the figure of the "expert patient". Patients' associations are increasingly acquiring new skills in their relations with health services and professionals, and with other members of these systems. Our aim is to foster the effective participation of patients in the healthcare and social systems of our country, as in the case that has now brought us together.

If this is to happen, a commitment to greater patient involvement in the design and implementation of health policies is required, to build a future in which a new culture of dialogue and collaboration is established and, on this basis, to design and implement policies and management models that are better suited to addressing current and future challenges and the needs of patients and other members of the health system.

Notes

1. Meyer zu Horste G, Hartung HP, Kieseier BC. From bench to bedside: experimental rationale for immune-specific therapies in the inflamed peripheral nerve. *Nature Clinical Practice Neurology*. 2007; 3: 198-211.

2. See: https://www.tesisenred.net/handle/10803/125868#page=1 [Internet] [accessed 10 November 2023]. Online at: http://hdl.handle.net/10803/125868

3. Allen J. A., Berger M., Querol L., Kuitwaard K., Hadden R. D. Individualized immunoglobulin therapy in chronic immune-mediated peripheral neuropathies. *Journal of the Peripheral Nervous System*. 2018; 23(2): 78-87.

Perspective of the Blood and Tissue Bank

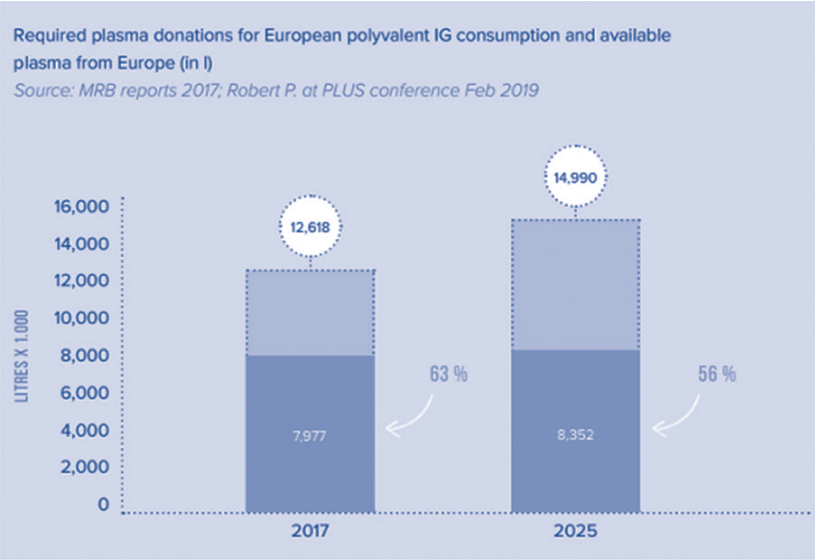
Altruistic Donation: Backing a Successful Model

Anna Millán

Managing director of the Blood and Tissue Bank of Catalonia (BST)

In recent years, human plasma has come to be regarded as a strategic resource on a global scale, as has been the case with water, energy and, at some points in history, blood. The European Union has recently made this clear with its recommendation that each Member State should ensure that its own needs are met. Dependence on plasma imported from the United States is a scenario that could become dangerous in a global crisis.

At present, Catalonia only produces enough plasma to cover 39% of the immunoglobulins required by patients affected by primary immunodeficiencies, autoimmune diseases and coagulopathies. This is the main use for the plasma that we are unable to supply, and this need increased by an annual average of 6.7% between 2010 and 2021, according to a study by the Market Research Bureau (MRB). Another study by the Plasma Protein Therapeutics Association (PPTA) warns about Europe's plasma needs if this imbalance between growing demand and lack of donations continues. By 2025, Europe's self-sufficiency could fall to historically low levels, and it would obtain no more than 56% of the immunoglobulins it needs.



At the same time, the figures show that, in countries that allow financial compensation to donors, among them the United States, Germany and Austria, the quantity of immunoglobulins consumed is much greater than in some of the countries where plasma is obtained altruistically. In this respect, it is essential to apply the principle of rationalisation to the use of blood products and adjust prescriptions to approved clinical needs with evidence of efficacy. The constantly increasing use of immunoglobulins is largely explained by an excessive application of inappropriate or unjustified indications. Plasma is a scarce and highly valuable commodity, and it is the responsibility of the public health system to ensure that there is no possibility of wasteful practice.

IMMUNOGLOBULIN CONSUMPTION PER CAPITA IN SELECTED COUNTRIES (Kg. per Million Inhabitants)

	2014	2017	2020
Austria	107	119	152
Belgium	108	174	218
France	130	167	174
Germany	93	103	126
Hungary	13	26	42
Italy	73	89	111
Spain	77	93	116
Sweden	126	150	177
E.U. Average	57	71	81
USA	200	248	334

This pattern of coexistence among the different models of donor retribution means that the amount of plasma obtained in each country per 1,000 inhabitants varies greatly from one country to another. The highest figures appear in countries where pharmaceutical companies reimburse plasma donors, and the lowest coincide with those where donation is altruistic. As can be seen in the map on p.17, Germany currently collects 36 litres of plasma per 1,000 inhabitants and Austria collects 75 litres per 1,000 inhabitants, but figure falls to 13 litres in France, while Spain has the lowest rate of all, at 8

litres per 1,000 inhabitants. However, in one sense this is good news for the challenge that faces us because it is clear that plasma collection figures could be improved without modifying the principle of altruistic donations.

Leaving aside blood products, if we analyse plasma transfusions, these are covered by fractionation of blood donations (although they represent a much lower use by comparison with the need for blood products). In fact, according to the 2019 "Epidemiological Study of Blood Transfusion in Catalonia" (https://www.bancsang.net/professionals/sang/epidemiological-study/), plasma transfusion fell by 56.1% from 2007 to 2019, while 3.4 units were transfused per patient in 2019, compared to 4.3 in 2007. More careful treatment, improved programmes for blood saving and transfusion alternatives, new medicines, and increased efficiency in surgical and medical specialties are reducing the overall need for this component, a factor that contributes to improving the volume allocated to the manufacture of immunoglobulins.

The possibilities of an untapped model

In Spain, the European recommendation to move towards self-sufficiency in plasma took the form of a resolution adopted on 2 November 2022 by the Interterritorial Council of the National Health System. The agreement provided money to the autonomous regions over a two-year period with the dual aim of progressively increasing the plasma donor base and establishing permanent plasmapheresis programmes. Catalonia received €385,538.19 in 2022 and €328,849.22 in 2023.

This directive meant that, in the current year, the focus of action of the Blood and Tissue Bank of Catalonia has decisively shifted towards promoting and publicising the need for plasma donation from the population. The figures obtained indicate that the plasma shortage could largely be alleviated by raising awareness of the need to donate plasma. The intensification of awareness campaigns aiming to inform about and promote donation led to a significant rise in donation via plasmapheresis in 2023. Achieving the proposed goal – 50,000 donations in 2025 – is feasible. At present, self-sufficiency would be achieved with 65,000 donations per year in an estimated period of four years.

	2019	2020	2021	2022	2023	2024	2025
Total donations	18,890	19,039	25,634	21,692	(Nov.: 26,419) **31,262**	**40,000**	**50,000**

Source: Blood and Tissue Bank.

Debate on the suitability of compensation for plasma donation has not been officially contemplated in the Catalan public health system until now. However, it has become a matter for discussion since Europe presented its first regulatory proposal with a view to encouraging self-sufficiency and thus paving the way for minimum compensation of donors for their voluntary effort.

Spain has a welfare state based on a public ethos that is very different from systems in other countries such as the United States. Here we share a deeply rooted public health system and a historical conception of altruistic donation that is based on collective solidarity. We can affirm that this is a successful model in Catalonia. The Blood and Tissue Bank (BST) has been self-sufficient in blood since 1985, when state legislation regulated blood donation as a voluntary altruistic act. People give blood on a voluntary and unpaid basis, and receive blood gratis. The right to receive medical care is implicit in tax policy, which covers the costs of public healthcare. The only recompense offered to donors is payment for travel costs (for example, parking) when they come to donation points.

Plasma donation: the great unknown

The available figures highlight the findings of studies like the one conducted in 2022 by the Spanish Association for Primary Immunodeficiencies (AEDIP) titled "Consenso español por la suficiencia de plasma y sus tratamientos derivados" (Spanish Consensus for Sufficiency of Plasma and Derived treat-

ments).[1] State planning is not yet responding adequately to present and future plasma needs, and nor is there any ambitious regulation to promote plasmapheresis and further the work done by blood banks, transfusion centres and donor associations. This lack of knowledge and scant awareness among both authorities and society in general must be addressed.

The challenge of achieving strategic self-sufficiency in plasma requires a nationwide effort that cuts across all sectors and goes far beyond the planning led by the Blood and Tissue Bank and its partners in the donation, transfusion and blood products manufacturing networks. Public health campaigns in the media, awareness-raising at the various stages of education, and across-the-board involvement of the different public bodies are essential conditions for achieving an objective that is both necessary and strategic.

The present situation is that, in Catalonia, as in other EU countries (and a good part of the world), the plasma obtained by fractionation of donated whole blood or directly by means of plasmapheresis remains insufficient to cover the needs of the blood products required by patients. In the last ten years, blood donations have fallen by about 20,000 units because there is less need for red cell concentrates. According to the 2019 "Epidemiological study of blood component transfusion in Catalonia",[2] red blood cell transfusion is decreasing, with a decline of more than 13% in twelve years.

This downward trend – which is repeated in developed countries owing to improvements in medical techniques and health systems in general – has meant a reduction in the amount of plasma obtained by fractionation, primarily for transfusion: however, considering that the plasma needed to manufacture blood products comes from donation by plasmapheresis, this might be an additional opportunity for shifting the emphasis of appeals to the blood donating population towards plasma donation and intensifying the focus of public campaigns in this regard. We should not forget that plasmapheresis, even if it is more burdensome and less familiar to donors, yields an average 650ml per donation compared to just 250ml being obtained through blood fractionation.

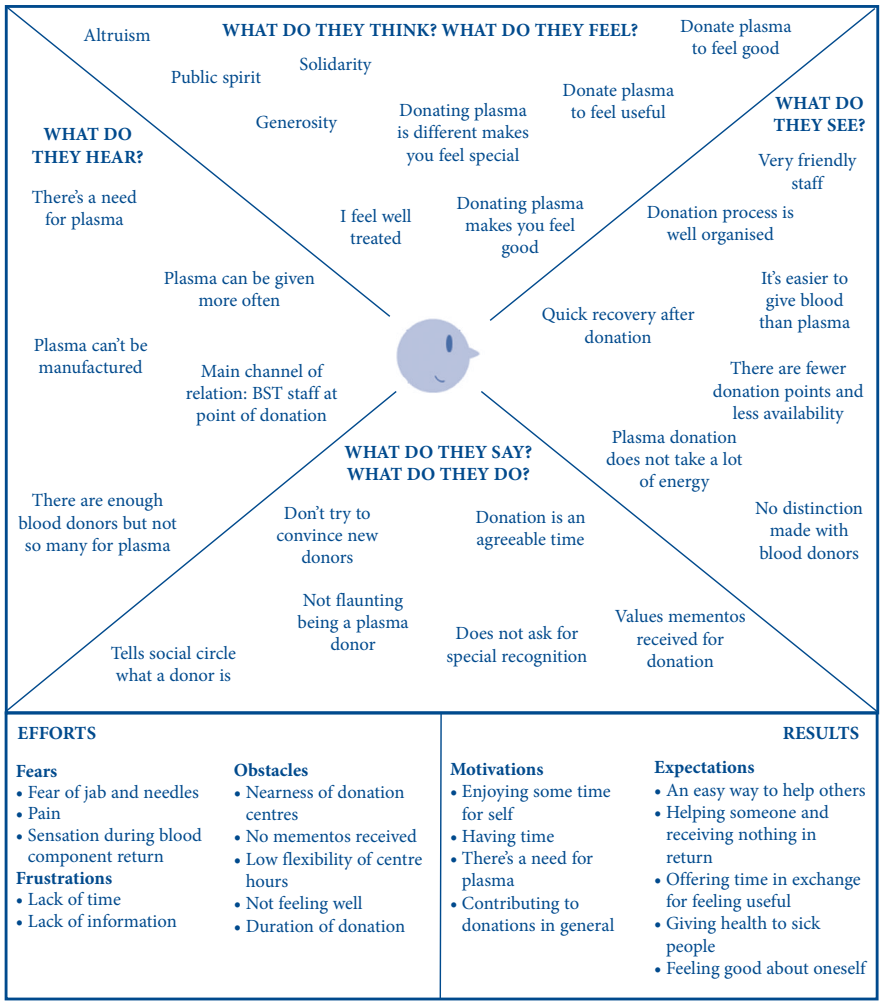
A donor who can give much more

Of the 14,500 plasma donors now in Catalonia, 55% make only one donation per year and 45% make two or more. If these donors gave blood three or four times per year, the result would be self-sufficiency. It should be noted that plasma donors can donate up to 24 times per year since plasma can be given every two weeks. This means that a donor could give 15 litres of plasma per year, a figure that is low considering that, in Germany, it can be as high as 38 litres and, in the United States, 83 litres. Evidently, together with boosting donor loyalty, it is important to increase the number of new donors, as every year there are people who, for health reasons, travelling, or other causes, are unable to keep donating.

Some of the few sociological studies that exist on donation have shown that the motivations of plasma donors resemble those of blood donors: altruism, perceived usefulness, satisfaction, personal pride and appeals. This is made clear by the Social Lab de l'Établissement Français du Sang[3] but people also report more barriers to donation, identifying among other obstacles, distance to place of donation, lack of time, fear of fainting, anxiety about the return of red blood cells and also about pain and, more generally, a set of mistaken ideas about plasma donation, for example: that two needles, or bigger needles are used; that it takes four hours; that it is done by bone puncture, and so on.

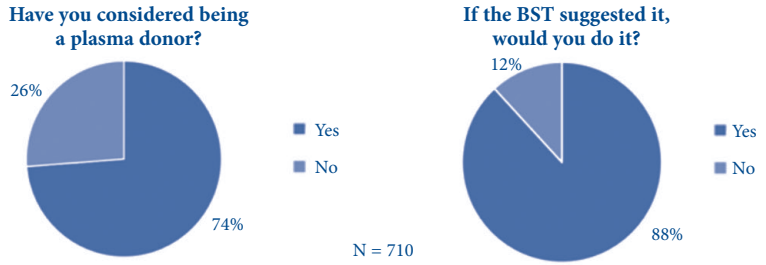
According to a qualitative study the BSC commissioned from GOC Health Consulting[4] in 2023, to better understand the behaviour of plasma donors, the latter spontaneously stated that they did not need compensation and that they did not feel comfortable about being recognised or treated in any way that was different from the treatment of blood donors. Nevertheless, when offered a range of tokens in recognition of their effort, they opted for time off work, cinema or theatre tickets, access to video platforms, some small item they could choose, or tickets to visit landmark places. It is curious that they did not specifically identify themselves as plasma donors. They did not hide this but neither did they show off or try to convince anyone. For the time being, it is hoped that these results will help to deepen the potential of the present system of altruistic donation.

Empathy map of the plasma donor



Questionnaire for blood donors

A group favourable to plasma donation



28% say they are not donors because no one has suggested it

The present challenge for the BST is to achieve and consolidate self-sufficiency in plasma, along the same lines as the model for blood. In Catalonia, opting for remuneration as Germany and the United States have done, could have a double boomerang effect as it could, of course, undermine altruistic blood donation. It is no accident that Catalonia has, for many years, been a leading country in terms of organ donation. The BST model is based on a society that has made solidarity an active, collective policy and we must now be able to transfer this legacy to plasma donation.

Blood banks that advocate altruistic donation are aware that we must activate mechanisms and incentives to generate more altruism in the population and find ways to motivate the public authorities. These are keys to self-sufficiency. The need for plasma is a public health issue that affects everybody, so informing about it, making it known, and appealing for support must be transversal. Without going so far as introducing compulsory donation – a provocative alternative proposed by Àngel Puyol, lecturer in Ethics at the Autonomous University of Barcelona in his article "Ética, solidaridad y donación de sangre, Cuatro perspectivas a debate" (Ethics, Solidarity, and Blood Donation: Four Perspectives under Debate),[5] comparing plasma donation with other obligatory health policies such as compulsory vaccination, food inspection, and required medical tests in certain professions – it is true that it is necessary to raise public awareness of the fact that plasma donation,

like all donations, requires little personal effort (comparable with blood donation) while, in contrast, it contributes to social altruism that brings enormous benefits.

Notes

1. https://aedip.com/pdf/consenso-medicamentos-derivados-de-plasma.pdf
2. https://www.bancsang.net/professionals/sang/estudiepidemiologic/
3. https://www.efs.sante.fr/lefs-les-publications/les-cahiers-de-lefs-social-lab
4. https://www.gocnetworking.com
5. https://doi.org/10.1344/rbd2019.0.27786

List of Authors

- Javier Arias, Professor of Surgery and Chair of the Faculty of Medicine, Complutense University of Madrid
- Svenja Tatjana Barckhausen, member of the Board of Directors of Haema AG, Germany and director of Haema Plasma Kft in Hungary
- Carlos Jiménez, president of the patients' association AEDIP (Spanish Association for Primary Immunodeficiencies)
- Teresa Lluch, PhD in Biochemistry and CIDP vice-president of GBS/CIDP Immune-Mediated Polyneuropathies (Spain)
- Elena Moro, technical adviser to the sub-directorate of Health Promotion and Public Health Monitoring (Ministry of Health)
- Begoña Román, Faculty of Philosophy, University of Barcelona
- Núria Terribas, director of the Víctor Grífols i Lucas Foundation and of the Chair in Bioethics at University of Vic-Central University of Catalonia
- Albert Torelló, director of Programmes, Ostrom Institute, Catalonia
- Sabin Urcelay, head of Section, Basque Centre for Transfusion and Human Tissues, Gipuzkoa (FCVTTH.G)

With the collaboration of:

- Anna Millán, managing director of the Blood and Tissue Bank of Catalonia (BST)

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