Deliverable 5.1: Analysis report on the inventory of existing plasma donor protection practices

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1. Introduction

Much is still unknown about the health effects of (frequently) donating plasma. To protect donor health, many plasma collecting organizations have developed their own selection criteria, donation procedures, and systems to prevent and register adverse events. We aimed to take inventory of the range of practices that are used across Europe (and beyond) to protect the health of plasma donors. Therefore, an elaborate online survey was distributed via e-mail and social media to contact persons for blood establishments associated with or connected to the SUPPLY consortium and/or the European Blood Alliance (meaning the survey was also available to organizations outside of Europe). The survey included questions about plasma collection purposes, donor selection criteria, donation procedures, donor vigilance and registration, and studies related to plasma donor protection. The final (optional) part of the survey was dedicated to data (e.g., number of active plasma donors, amount of plasma collected, number of donors deferred). In this report, we summarize the respondents' answers. In the conclusion, we establish a 'modal plasma donation' based on the respondent answers.

2. General information about respondents

In total, the survey was answered by 19 respondents, 1 of whom did not complete the entire survey (but enough to have some reliable info for at least half the survey). 1 organization indicated that they do not collect plasma, so their response is left out. The remaining 18 respondents were from 17 different countries: Norway, Latvia, Canada, England, Denmark (two blood centers), Finland, Germany, USA, Sweden, France, Lithuania, Scotland, Croatia, Estonia, Malta, Luxembourg, and the Netherlands.

Fifteen organizations collect plasma for fractionation, 14 collect for clinical transfusion, 8 for quality control, 7 for research, and 4 for other purposes (such as IgA deficiency, quarantine plasma, diagnostics plasma, or cryoprecipitate). 11 organizations collect for both fractionation and clinical transfusion and 6 of them also combine that with collection for research and quality control purposes.

Fifteen organizations collect plasma via apheresis. Two organizations indicated they only collect plasma by recovering it from whole blood and they use no other methods to collect plasma. Only one organization does not collect recovered plasma (i.e. USA's Life Plasma), while all 17 other organizations do. Finally, 9 organizations also indicated they collect plasma via combined or multicomponent apheresis (all collected plasma during plateletpheresis). We excluded the two organizations who only collected recovered plasma, which means we had 16 responses left that were included in the analyses.

3. Donation frequency/interval

Of the 15 organizations that perform plasmapheresis, the maximum number of plasma donations donors are allowed to give annually ranges from 12 (Luxembourg) to 104 times (USA); the median and mode are 26 (6 organizations use this); the mean is 34.8 times per year. One of the organizations (Croatia) only uses combined apheresis (and not plasmapheresis); they allow combined apheresis 12 times per year max. Three organizations use a lower maximum limit than what is allowed legally (e.g., 52 where 104 is allowed or 26 where 33 is allowed).

When asked what the ideal minimum donation frequency for each donor per year is, the answers from 14 organizations ranged from 3 to 104 donations (average 20.6 times; median and mode 12 times per year).

In the 15 organizations that perform plasmapheresis, the minimum donation interval between two plasmapheresis donations ranges from 2 to 28 days (average 10.8, median and mode 14). One

organization indicated a minimum of 21 days between 2 combined platelet apheresis donations.

4. Selection criteria

Blood banks use selection criteria to make sure donors and patients stay safe. In the survey, we presented the organizations with a list of possible selection criteria and asked them whether they used those criteria, and whether they used additional selection criteria. Furthermore, we asked whether the organization defers donors (temporarily or permanently) if plasma donors do not meet their selection criteria.

All 16 organizations indicated they use most of the selection criteria that we presented to them: weight/height/blood volume, suitability, hemoglobin level (Hb) or hematocrit (hct), use of medication or drugs, cardiovascular events or disease, malignancies, pregnancy, infectious diseases, and auto-immune diseases. Blood pressure is a selection criterium for most organizations as well (14 out of 16). Thirteen organizations indicated they use additional criteria, many of which also apply to whole blood donation (e.g., travel, sexual risk behavior, needle-related risk, transfusion, transplantation, recent/chronic disease, allergies). One organization reported a language proficiency requirement.

4.1 Age

The minimum age for plasmapheresis donation is 16 in one organization, 17 in 5 organizations, and 18 in 10 organizations. The maximum age for donors ranges between 45 and 71, with an average of 59 and a mode and median at 65. For 7 (out of 8) organizations that do combined apheresis, the same age limits are in place for combined and plasma apheresis. For the other organization, the minimum age is 16 for plasmapheresis donors while it is 18 for combined apheresis donors.

4.2 Weight/height

The minimum eligible donor weight ranges from 45 to 60 kilograms; the median and mode are at 50 kg (currently used by 8 organizations). Only 2 organizations apply a minimum height (1.45m and 1.55m). Twelve organizations defer donors temporarily if they are below the minimum weight/height, and donors are permanently deferred in 6 organizations.

4.3 Eligibility

In terms of donors being eligible for apheresis, almost all organizations (13) indicated that they check suitability of the donors' veins. Some also mentioned the importance of blood type (2) and the ability to tolerate the procedure (e.g., no previous adverse events; 3).

4.4 Hemoglobin/hematocrit

Hemoglobin levels or hematocrit are closely monitored in most organizations: 11 organizations assess Hb or hct prior to every donation, while 3 organizations assess Hb or hct prior to donation but not at every donation. Only 2 organizations indicated not to assess Hb or Hct prior to donation at all. Of the 3 organizations that did not assess Hb or hct at every donation, 2 indicated they assess it for new donors and donors returning after more than 2 years and 1 organization tests it once per year.

To acquire the samples for Hb or hct measurement, 9 organizations take capillary samples (e.g., via finger prick), 4 take venous samples, and 1 organization indicated they do not test it prior to donation, but within 15 minutes of the start of the donation. Samples are tested most often using a photometer (10 organizations), but also using a copper sulphate test (1 organization), a hematology analyzer (2

organizations) or a microhematocrit centrifuge system (HamataStat; 1 organization).

The required levels for Hb or hct are often different for men and women (11 organizations); only 2 organizations use the same levels for men and women (both located outside of Europe). For women, the lower limit ranges between 115 and 200 grams per liter (g/l); most often 120 or 125 g/l is applied for the lower limit for women (9 organizations). For men, the lower limit ranges between 125-200 g/l; 130 and 135 g/l are most often used as lower limit for men (9 organizations). Only 4 organizations mentioned upper limits for Hb/hct. For women, all these organizations used 165 g/l as upper limit. For men, the upper limit ranged between 175 and 187 g/l.

Donors whose Hb or hct levels were below the lower limit (or above the upper limit in some organizations) were temporarily deferred in 14 organizations. In addition, 6 organizations indicated that (in certain cases) permanent deferral was also possible if Hb or hct levels were outside of the acceptable range.

5. Donation procedure

Several factors in the donation procedure can influence the occurrence of adverse events during and after the donation. In the survey, we therefore explored what machines were used in the different organizations, how much volume is collected during donation, what anticoagulants and replacement fluids are used at which ratio, and whether standard settings were in place for the flow rates.

5.1 Apheresis machines

Many different apheresis machines are used in the organizations that have responded to the survey. In the 16 organizations that shared information about the machines used, we found that at least 10 different machines were used. Fresenius Kabi is the brand most often used; 8 organizations use their Aurora model, 3 use their Amicus model, 1 uses their Autopheresis-C model, and 1 uses their AmiCORE model. Haemonetics is also used relatively often; their models NexSys PCS, PCS2, and MCS+ are used in 2, 2, and 3 organizations, respectively. Other brands and models used are Medica's AFERsmart (1 organization), Stradis Med's Nigale Digipla 80 (3 organizations) and Scinomed's SPC6+ (1 organization).

5.2 Volume

Out of 16 organizations, 7 have a threshold for the maximum volume donated per year. This maximum ranges between 9.5 (Luxembourg) and 47 liters (Canada), with the mode and median being 15 liters per year.

Even though not all organizations use an annual threshold for the maximum volume donated, all 16 organizations have restrictions on the maximum volume donated per donation. These maximums range between 400 and 896 ml per donation (average: 747 ml per donation; often including anticoagulant or replacement fluids).

Of the 16 organizations, 12 used personalized volume calculations to determine how much plasma to draw per donation. The 4 organizations that did not use personalized volume calculations had a standard donation volume between 400 and 720 ml per donation. All of the 12 organizations that used personalized volume calculations used weight and/or height information to determine the volume to be collected. They used several methods to determine the volume to be collect from the donor, such as the organizations' weight/height rules (sometimes calculated by the machine; 6 organizations), the Nadler Allen formula for estimating blood volume (with 16% extracorporeal volume; 4 organizations), the ISCH formula to estimate blood volume (1 organization), or the FDA '92 nomogram (1

organization). In addition, 5 organizations differed between men and women and 3 organizations used factors such as women's age and hct to determine the volume that could be collected.

5.3 Anticoagulants and replacement fluids

Of the 16 organizations, 10 did not use replacement fluids after donation. The 6 organizations that did use replacement fluids all indicated they use a saline infusion.

Anticoagulants are used in all organizations to prevent the blood from clotting during the apheresis procedure. All 16 organizations use citrate-based anticoagulants, yet with different percentages of citrate. Six organizations use trisodium citrate (TSC, 4% citrate), 5 organizations use acid citrate dextrose-A 3% (ACD-A, 3% citrate), 4 organizations use sodium citrate (4% citrate), 2 organizations use citrasol (4% citrate), and 1 uses ACD-A 8% citrate.

The amount of anticoagulants relative to the amount of whole blood outside the body ranged between 6 and 11%, or 1 unit of anticoagulant to 9-16 units of whole blood. In 11 organizations, this ratio is restricted, while this is not the case in 3 organizations.

5.4 Flow rate settings

How fast the blood flows from the donors to the machine and at what pace the red cells are returned to the donor may impact adverse events for the donor. Therefore, we also asked if standard settings are in place for the draw flow and the return flow, and how these settings were determined.

For the draw flow rate, 11 (out of 16) organizations indicated they used standard settings. The standard settings range between 40 and 120 milliliter per minute; most use either 100 or 120 ml/min (both are used as standard setting in 3 organizations). Furthermore, 13 organizations indicated the draw flow rate was restricted at a certain maximum, which ranged from 80 to 150 ml/min (mode and median both at 120 ml/min).

When we asked the organizations how they had determined their standard or maximum setting, all 13 indicated they based them on suggestions by the manufacturer. In addition, 9 organizations indicated that (the prevention of) adverse events also played a role, 2 organizations also factored in yield, and 3 organizations mentioned other factors such as the donor's veins, experience, or donor comfort.

For the return flow rate, again 11 organizations indicated their organization used standard settings, while 5 did not. For the 11 that did, the standard settings ranged from 30-150 ml/min (median: 120 ml/min). Here too, 13 organizations indicated they used a maximum for the return flow rate, ranging from 90-150 ml/min (both median and mode at 150 ml/min). Almost all organizations indicated that the standard settings and/or maximum were set based on suggestions by the manufacturer (12 out of 13 organizations). Eight organizations indicated that (the prevention of) adverse events also played a role, and 2 organizations indicated that yield played a role as well.

6. Adverse events

Since donation has an impact on the body and venipuncture is a procedure performed by humans, donors may experience adverse events. In our inventory, we determined how and which adverse events are registered in the different organizations. Additionally, we asked what organizations do to prevent adverse events.

6.1 Preventing adverse events

Fifteen organizations shared information about what they did to prevent adverse events in their donors. The most frequently used method was advice on water loading or hydration before, during, and after the donation (12 organizations). Other methods included well-trained staff (to recognize potential adverse events early and/or put donors at ease; 7 organizations), special attention for new donors (5 organizations), provision of or advice about nutrition (e.g., salty snacks; 4 organizations), saline replacement (2 organizations), lower return cycle flow rates for new donors (2 organizations), and post donation monitoring (1 organizations).

6.2 Donor vigilance

All 16 organizations indicated they had a donor vigilance system in place, meaning they register and monitor donor adverse events. One organization is limited to registering only 1 adverse event per donor or donation, thus, they register the most severe adverse event if multiple adverse events occur during or after the donation. The remaining 15 organizations could register multiple adverse events per donor or donation if necessary, 12 of whom had no maximum to the number of adverse events registered. The other 3 organizations indicated they can only register 2 or 3 adverse events per donor/donation.

The majority of organizations indicated they also assess and register the grade or severity of adverse events (14 out of 16). One organization does not register the grade or adverse events, and one organization only does so when the clinical team is to follow up with the donor afterwards. Imputability (an assessment of the likelihood that the adverse events was caused by the donation) is assessed and registered in 8 organizations, while 3 organizations only do so in case of serious adverse events to donation (SAED) and 5 organizations do not register imputability.

In the survey, we asked whether the organizations register adverse events in 5 categories (following the 'standard for surveillance of complications related to blood donation' from the ISBT and AABB working groups on hemovigilance): Local symptoms, generalized symptoms, apheresis-related events, allergic reactions, and other serious complications (mainly major cardiovascular events). Nearly all adverse events that we presented were registered by the large majority (13-16 out of 16 organizations). For instance, all organizations register local symptoms such as hematoma and arterial puncture, generalized symptoms such as vasovagal reactions (both with and without loss of consciousness), apheresis-related events such as citrate reactions, local and generalized allergic reactions, and major cardiovascular events such as acute cardiac symptoms and myocardial infarction.

In the case of major cardiovascular events, 9 organizations did not have a certain timeframe for registering events, while 7 organizations did. Of the latter, 3 organizations only registered the event if it happened within 24 hours of the donation, 1 only when the donor is hospitalized within 24 hours, and one within 30 days. Ten organizations further required an assessment of imputability to be made in the case of major cardiovascular events. Of the 10, 7 registered all events regardless of imputability, 2 only registered the events that are assessed as possibly, probably or definitely attributed to the donation, and in one organization the standard operating procedures did not define imputability.

Additionally we asked whether the organizations registered potential long-term adverse events. Here, we found that 4 organizations register skin and vein fibrosis (scar formation) and 1 organization registers lowered bone density (osteoporosis).

7. Testing

Plasma collecting organizations test the donated plasma to ensure donor and patient health. All 16 organizations indicated that they test total protein levels of their donors, yet they test this at differing intervals. Most organizations measures total protein (at least) once a year (11 organizations) and many indicate they check it for new donors (4 organizations), or after a certain number of months/donations (e.g., after every 5th donation or every 4 months). Finally, one organization tests it on 1% of the total plasma components collected. Twelve organizations reported a lower limit (range 50-63 g/l) and 7 reported an upper limit (range 82-100 g/l) for the total protein. Most organizations defer donors temporarily when their total protein is too low or too high for 28 days to 3 months; almost all organizations take case-by-case decisions on temporary or permanent deferral.

Seven out of 16 organizations also test total IgG levels for their donors. Frequency of testing IgG ranges from once a year (2 organizations) to once every 4 months (1 organizations) or every 5th donation (1 organizations). Five organizations indicated the lower limit, which ranges between 4 and 7 grams per liter (mode and median at 6 g/l). Three organizations indicated their upper limit was at 16 g/l. In these 7 organizations, the donor is temporarily deferred if the IgG levels are outside of the acceptable values, and the standard deferral time ranges between 3 weeks and 6 months (mode and median are 4 weeks).

Donors are tested for irregular blood group antibodies in 12 organizations. Seven of them test for antibody presence after a possible immunization event (e.g., pregnancy, transfusion), 6 perform the test at the first donation, 3 perform it at every donation, 2 perform it once every two years, and 1 performs it once per year. All organizations indicate that the results of the antibody tests should be negative; 9 organizations indicate that donors are deferred permanently if results are positive.

Eight organizations indicated they perform additional tests, such as blood type, AST and ALT (liver enzymes; once per year), ferritin (once per year), HLA antibodies presence (once for women), platelet, red cell, and leucocyte counts (performed on 1% of all plasma donations).

8. Miscellaneous

Participating organizations were all asked about competition in the market, the organizations' contingency plans, and ongoing studies related to plasma donor health.

With regard to competition, we found that 4 (out of 14) organizations were not the only plasma collecting organization that was active in the area/country. We asked them whether they shared information about plasma donations and adverse events with those other parties to prevent donors from donating too often at different organizations. One of the four organizations (Croatia) uses a nationwide registry to register all plasma donations, while the other 3 did not share information with other parties active in their area/country (Canada, Germany, Norway). For adverse events, 2 organizations make use of a nationwide adverse event registry while the other 2 organizations do not share information on adverse events.

We also queried crisis preparedness for the organizations, as the COVID-19 pandemic has shown that donations can go down in a short period of time. Out of the 16 organizations, 7 indicated they have contingency plans in place, while 6 do not. Three respondents did not know whether their organization has such a plan.

We also asked respondents whether they were aware of studies related to donor health protection that were about to start, ongoing, or recently finished in their organization. Seven respondents indicated that there were one or more studies in their organization. Most of the studies that the respondents

described were related to the effects of procedural changes (machines used, taking blood pressure in the pre-donation exam), donation intervals/frequency, or donor characteristics on parameters such as adverse events, protein levels, or the occurrence of infection.

Finally, we also asked respondents whether they could provide additional data about their collection and donor pool. For instance, we asked them whether they could share how much plasma was collected in a year, and how many active plasma donors they had. Ten out of 16 respondents were so kind to provide input for many of these additional data questions. For instance, 9 respondents reported how much plasma they collected in either 2021 or 2022, and results range from 240 liters in Latvia to 97527.8 liters in Germany. Seven organizations reported on the number of active plasmapheresis donors, and it turns out the size of the active donor pool ranges from 9 (in Malta) to 12,870 (Germany) and their average age ranges between 38 and 48. The percentage of women among the active plasma donors ranges from 0% (Malta) and 0.8% (Scotland) to 55% (Latvia) (median 41%). Latvia is the only country out of the 7 in which more than half the donor pool consists of women; men make up the majority of the donor pool in the 6 other countries. We are currently analyzing these data further and are preparing to write up the results for submission to a scientific journal in the transfusion field.

9. Conclusion

We observed large differences between organizations, but also some interesting similarities. For instance, we observed that all organizations register plasma-related adverse events and major cardiac events, and that all used similar selection criteria (e.g., vein suitability and hemoglobin/hematocrit levels; although sometimes with different acceptance criteria). Large differences were also found, for instance, in the number of active plasma donors (range 9-12,870) or the apheresis-machines used (10 different models from 5 manufacturers) including also blood flow rate.

Based on the responses, a 'modal' donation procedure was constructed:

The modal plasma donation is collected via apheresis from donors aged 18-65 with a minimum weight of 50kg. Donors can donate every 14 days, but once a month seems ideal. Hemoglobin is tested before every donation using a fingerprick and a photometer, and donors with values <125 g/l (women) or <130 g/l (men) are temporarily deferred. To prevent adverse events, the organization informs donors about the importance of hydration before, during, and after the donation, and offers refreshments on-site. Flow rate settings of the apheresis machines are usually determined mostly by the manufacturer, and may also be adjusted to prevent adverse events. For anticoagulation, either citrate dextrose-A (3% citrate) or tri-sodium citrate (4% citrate) is used, with a ratio of 1:16. Total protein levels are tested at least once a year and IgG levels 1-4 times per year; both may lead to temporary deferral. The presence of irregular antibodies is tested at every first donation and after every possible immunization event (e.g., pregnancy, transfusion), and positive results lead to permanent deferral for plasma donation. Finally, adverse events are registered with an assessment of grade and imputability.

The survey responses represent a range of perspectives from plasma collecting organizations inside and outside of the EU. The responses show that even though differences exist, there are also similarities that open opportunities for the development and implementation of best and uniform practices for the protection of plasma donor health.