

## Risk-based decision making and ethical considerations in donor compensation for plasma-derived medicinal products

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For years, policymakers have debated the appropriateness of compensating plasma donors for the manufacture of plasma-derived medicinal products (PDMPs). Recently, the Alliance of Blood Operators (ABO) developed a risk-based decision-making framework for blood safety. In light of these two parallel discussions, now seems to be an opportune time to reanalyze whether an absolutist position against compensation is any longer relevant or would be appropriate if evaluated utilizing a risk-based decision-making approach.

Meeting the health needs of patients by providing an adequate supply of safe and effective blood components and PDMPs is the principal goal of blood operators and the plasma industry. Data demonstrate a large and increasing unmet demand for PDMPs worldwide,<sup>1,2</sup> and there is a growing consensus that an insufficient supply of PDMP treatment products is a major safety risk to patients.<sup>3</sup> Accordingly, it has been argued that a “vein-to-vein” approach to risk-based decision making that encompasses patient needs, product safety, ethical treatment of donors, and other ethical issues should be adopted when considering topics like PDMP donor compensation.<sup>4</sup>

In 2010, an International Consensus Conference on Risk-Based Decision Making for Blood Safety noted that, “As blood systems are focusing more on responsible use of health care resources, questions arise as to the most effective way to manage risk at a level that is tolerable and sustainable. Because of the increasing complexity and inconsistency in blood safety decision making, it is timely to explore whether it is possible to create a better decision-making framework based on risk management principles that can be used in various jurisdictions, taking into account social values, ethics, politics, economics, public expectations, and the historical context in which we operate.”<sup>4</sup> In conducting the current analysis, we use these findings of the 2010 Consensus Conference and the subsequent framework developed by the ABO to integrate all stakeholder concerns into an overall risk profile to inform the decision-making process (the ABO Framework).<sup>5</sup> In particular, we draw on the two elements of the framework most relevant to our analysis: the assessment

component as a refresh of the ethical discussion around compensated plasma donation and the participation strategy for relevant stakeholder engagement that has been missing from past analyses of compensated plasma donation. We note that the economic considerations of compensation for PDMPs have been explored by Grabowski and Manning.<sup>6</sup>

In addition, we draw in part from the analytical structure of the Nuffield Council on Bioethics (Nuffield), which posed the question: How far can society go in its demands on people to act in what many regard as a good cause—that of providing bodily material to benefit others?<sup>7</sup> The welfare of the many patients who do and could benefit from PDMPs is central to our analysis, and the welfare of donors is a powerful complementary consideration.

There are notable distinctions between donor plasma destined for further manufacture into PDMPs and labile whole blood and its components (e.g., red blood cells [RBCs], platelets, and plasma) for direct transfusion. The latter does not routinely undergo significant processing designed to mitigate the risk from transfusion-transmitted

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infections. Our assessment differentiates the two and focuses on ethical issues as they relate to the unique features of compensating donors of plasma destined for manufacture into PDMPs when donated in countries with well-established regulatory structures.

### **Risk-based decision making and ethical considerations in donor compensation for PDMPs**

The World Health Organization (WHO) has identified PDMPs, in particular clotting factor concentrates and immunoglobulins, as essential medications that should be provided by governments for the health of their populations.<sup>8</sup> For hundreds of thousands of patients globally, PDMPs have been life-saving, transforming often-fatal diseases into manageable conditions that enable patients to live healthier and more satisfying lives. Today, nearly 70% of the plasma used to make PDMPs is derived from donors who are provided monetary compensation.<sup>9,10</sup> Global demand for PDMPs is increasing, while demand in developed countries for whole blood donation (RBCs) has declined.<sup>11,12</sup> Despite steady gains, the vast majority of patients worldwide still have no or suboptimal access to treatment. Access and supply issues persist in both the developed and developing world.<sup>13-15</sup>

Recent public policy debates around the topic of donor compensation for PDMPs include a 2013 meeting of representatives of Ministries of Health from 51 countries at which a document, known as “The Rome Declaration,” was adopted.<sup>16</sup> The Declaration built on prior resolutions of the WHO World Health Assembly. Among its many statements, it called upon nations to begin a programmed phase-out of PDMPs obtained from compensated donors. In 2014, the provincial government of Ontario, Canada, enacted legislation prohibiting compensation for blood or plasma donation, declaring that this action was necessary to protect the integrity of the public, voluntary donor system.<sup>17</sup> Subsequently, the Canadian debate has spread to other provinces as well as to the national parliament.<sup>18</sup> The disconnect between a rising global need for PDMPs and calls for widespread restrictions on plasma donor compensation make this an urgent matter for re-evaluation.

The ABO Framework used in our analysis presents a structured approach. It provides a systematic methodology for setting the best course of action under uncertainty by identifying, assessing, communicating, and mitigating risk to optimize the safety of the blood supply. At the same time, it enables the proportional allocation of finite resources to mitigate the most serious risks, recognizing that the elimination of all risk is not possible. It details a series of contextual factors that affect decision making in the management of blood risks, such as social, economic, and, significantly, ethical perspectives. The importance and centrality of appropriate stakeholder consultation is at the core of the ABO Framework.

Stakeholders have a right to be consulted about decisions that affect them and issues in which they have a significant interest. Although blood and plasma collection share many common features, each presents unique issues that stakeholders may view differently. “Stakeholders of interest” will vary by issue but, at a minimum, should consider the following for consultation: professional associations, researchers, health institutions, health professionals, thought leaders, funders, regulators, industry partners, suppliers, patient advocacy groups, affected patients, donors (noncompensated and compensated), and the general public. Most notable among stakeholders is the need for consultation with blood and blood product recipients who ultimately bear the risk of blood (and plasma) safety decisions.<sup>4,19,20</sup>

The ABO Framework also recognizes the importance of adherence to well-established ethical principles, including autonomy, beneficence, non-maleficence, and justice, to ensure that the rights of both donors and recipients are respected. The ABO Framework expressly recommends that ethical questions take into consideration the “public expectations and social context in which we operate.”<sup>4</sup>

While we emphasize adequate supply of PDMPs as a central safety and ethical component in evaluating the acceptability of payment for plasma, there are other important ethical concerns that have been posited as reasons to prohibit compensation, as discussed below: 1) the safety of PDMPs and the welfare of patients, 2) the welfare of plasma donors, 3) potential societal harms of compensated donation, and 4) deeply held values and beliefs against compensated donation.<sup>3,19,21,22</sup>

#### *The safety of PDMPs and the welfare of patients*

Allocation of resources in proportion to the magnitude and seriousness of the risk and effectiveness of interventions to reduce risk is a core tenet of the ABO Framework.<sup>19</sup> One of the most persistent arguments against compensation for plasma donation is that it will threaten the safety of plasma products, resulting in significant harm to the patients who receive them.

Recognized failures in blood safety management in the 1970s and 1980s led to implementation of a highly rigorous safety regimen (both regulatory and voluntary industry standards), which minimizes the risk of repetition of these events. Today, multiple interrelated tools have been used to reduce the risks inherent in producing plasma for PDMPs.<sup>4</sup> Implementation of two separate donor medical screenings, pathogen testing as well as virus removal and inactivation procedures during the manufacturing process have resulted in a robust level of safety for PDMPs that has effectively eliminated the transmission of hepatitis B virus, hepatitis C virus, or human immunodeficiency virus in PDMPs.<sup>23,24</sup> To put this risk in perspective, each year, approximately 300,000 patients in the United States who

undergo routine surgery suffer from hospital-acquired infections at a rate of 2% to 5%, and 3% of those infections are fatal.<sup>25</sup> Although more than a dozen emerging infectious diseases of concern have been identified since 2000, they are often a greater concern for labile blood components than for PDMPs (for example, the US Food and Drug Administration excludes PDMPs from the recent donor exclusion requirements to address Zika virus), and in no case has the prevalence of an emerging infectious disease been linked to donor compensation.<sup>26-28</sup>

### *The welfare of plasma donors*

The health and dignity of plasma donors is relevant to the discussion of donor compensation for PDMPs within the ABO Framework; therefore, the voices of donors (compensated and noncompensated) should be part of the discussion. Key stakeholders, including global patient, donor, manufacturing, and blood organizations, agree that donations should be voluntary; that is, donors should not be *coerced* by measures that overwhelm their capacity to make an informed decision about whether to donate.<sup>3</sup> Even when giving voluntarily, donors could potentially be exploited by failing to adequately screen and monitor their health or by giving them insufficient information upon which to make an informed decision about donation. However, in well-regulated environments, prospective plasma donors are not exploited in these ways. Donation is preceded by a robust informed-consent process that includes a full explanation of the procedures and their risks. Donors then undergo a medical examination and are being medically monitored during the donation process.<sup>29-32</sup>

Determining which incentive for plasma donation is *altruistic enough* or which incentive is *too coercive* is relevant to evaluating issues of donor autonomy and justice. Nuffield specifically addressed the ethical acceptability of incentives where a health need is not being met by altruist-focused interventions, through the concept of an “Intervention Ladder” as a tool for considering the ethical acceptability of different forms of encouragement.<sup>7</sup> The important considerations are consequentialist: What real harms accrue at the highest rungs of the intervention ladder, where incentives are more direct and substantial, and what steps can be taken to avoid or mitigate those harms? Potential harms to be considered include the welfare of the donor and threats to the common good, such as crowding out voluntary donation systems and increasing social inequalities.<sup>5,7</sup> Nuffield is careful to make the point that most donations are motivated neither by pure altruism nor by pure self-interest and that the most direct incentives, including compensation, are not alone reason to prohibit an activity.<sup>7</sup> In the case of plasma, Nuffield concludes that donor compensation is “ethically vindicated” at the highest level of scrutiny, given “the importance of the need for plasma, the difficulties in sourcing it, and the

highly regulated nature of the donor recruitment and quality systems.”<sup>7</sup>

The majority of nationally coordinated blood services in the European Union and organizations in the United States, such as the American Red Cross, allow some type of incentive to encourage blood and blood component donation that makes the donation not completely altruistic on the Nuffield Intervention Ladder.<sup>7,33,34</sup> Examples of these incentives include: a free cholesterol test, a “frequent donor” rewards programs, or paid time off work provided by their employer. It is important to consider whether a donation in response to these incentives is more altruistic than the typical \$35 US dollars (USD) compensation provided to an individual for undergoing apheresis as a plasma donor for PDMPs.<sup>35</sup> Direct payment of cash or a cash equivalent provides a more fungible reward than, say, a free cholesterol test. The ethical relevance of fungibility, if it exists at all, would only mean that, by Nuffield standards, the circumstances (i.e., donor and recipient safety) surrounding the more fungible compensation should be more carefully scrutinized.

Plasma donors have also been labeled inappropriately as individuals who are “chronically unemployed” and live in economic circumstances that give them no other choice than to “sell” their plasma, thus becoming “professional donors.”<sup>36-38</sup> Under such circumstances, donor compensation for PDMPs would appear to increase social inequalities by creating and stigmatizing a “donor class” that relies on the compensation as their major source of income. However, data do not support this assertion. In the United States, plasma donors for PDMPs are compensated an average of \$35 USD per donation and donate 15 times a year, equating to \$525 USD per year.<sup>35</sup> The average living wage for a single adult in a moderate-sized US city, such as Cleveland, Ohio, is approximately \$20,000 USD per year.<sup>39</sup> Even for donors who give the maximum 104 times per year, the annual payment would be roughly \$3600 USD per year, which is well below a living wage. Given these considerations, the notion of the “professional donor” is an inappropriate label to apply to individuals who donate their plasma.

### *Potential societal harms of compensated donation*

The argument has been made that compensated plasma donor systems could have negative societal impacts by “crowding out” noncompensated donation<sup>21</sup> or harming an important sense of solidarity or social cohesion related to donation.

In their 2016 review of the potential “crowding out” issue, Lacetera and Macis note that, although extensive research has been conducted over the past decades, the results are inconclusive. “Earlier studies,” they note, were “usually based on small-scale (often nonrandom) samples, hypothetical surveys, and laboratory experiments.” In contrast, more recent research involves larger, more

representative samples for both retrospective studies and randomized field trials examining actual behavior.<sup>40</sup> The earlier, less rigorous studies were generally consistent “with the view that incentives backfire” in terms of quantity of blood supplied. However, more recent studies demonstrate that material incentives increase donations for whole blood “with no consequences on deferral rates.”<sup>40</sup> Despite the long-standing concern about crowding out, the empirical literature to support it is mixed at best.

The claim that compensation for plasma in a well-regulated environment harms an important sense of solidarity or social cohesion remains a powerfully symbolic argument, but there is an absence of evidence to support the assertion.<sup>40</sup> The strength of individuality and solidarity varies from country to country, a political reality that certainly should be taken into consideration in any international policy framework. The policy of some countries is to meet identified patient need for PDMPs by importing PDMPs produced from compensated donations<sup>41</sup> while at the same time advocating a seemingly contradictory policy of prohibiting donor compensation within their own borders. Such inconsistency has been labeled hypocritical<sup>42</sup> and runs counter to the principle of solidarity.

#### *Deeply held values and beliefs against compensated donation*

Although the preceding ethical arguments against plasma donor compensation for PDMPs are based on empirical claims, deeply held beliefs often derive from gut feelings, sacred texts, and established social values.<sup>22</sup> They may or may not be supported by empirical evidence.

Deeply held beliefs are often described as “protected” values, meaning “values that people are not willing to trade off no matter what the cost of doing so may be.”<sup>43,44</sup> Some argue that compensation for plasma donated for PDMPs is an affront to “human dignity”<sup>45</sup> and, in and of itself, is wrong because it degrades “human dignity overall, since the human body cannot be attributed any material value.”<sup>40</sup> The concept of dignity has been used to represent long-held traditions abhorring utilitarian uses of or payment for the human body (e.g., in dissection, autopsy, and organ retrieval for transplantation).<sup>40,43</sup> However, these aversions were overcome when the “forbidden” practices demonstrated tangible benefits to well-being, and regulation and informed consent increasingly protected people from exploitation. To this point, Joel Feinberg (a leading American legal and political philosopher) has written, “Granted that it is important that we respect certain symbols, it is important that we do not respect them too much. Otherwise, we shall respect them at the expense of the very values they symbolize and fall into the moral traps of sentimentality and squemishness.”<sup>46</sup>

## CONCLUSION

Contemporary policy debate should be enhanced by a greater and more systemic process of stakeholder engagement and use of an analytical framework for decision making such as that set forth in the ABO Framework. Given advances in PDMPs and donor safety, one of the remaining threats to safety is a policy that undermines an adequate and sustainable supply of PDMPs.

Actions that limit patient access to treatment without considering supply issues raise the possibility that global patient needs will be eclipsed in pursuit of ethical ideals that are both impractical and unnecessary.

Failing to recognize unmet need ultimately limits patients’ access to PDMPs and effectively denies access to adequate health care. The safest drug that no one can afford or that arrives too late is of no benefit to a patient.<sup>47</sup> Given increasing demand and periodic shortages in some PDMPs, most notably immunoglobulins, a careful assessment of any change in donor policy is essential to determine its potential impact on the supply and availability of PDMPs.<sup>14</sup> As clinical indications for PDMPs evolve and new uses are identified, it is important to ensure that the availability of PDMPs keeps pace with the needs of existing and future patients. This is a compelling moral duty, particularly when alternative treatment options are often not available. It could even be considered an ethical imperative for blood establishments to proactively consider an option that includes compensation of plasma donors, taking a risk-based approach with implementation only where adequate safeguards exist.

By rigidly focusing on protected values unsupported by data as a reason for prohibiting compensated plasma donation, some critics have used a cultural symbol in a manner that threatens to undermine the very values the symbol represents: in this case, the health and dignity of patients badly in need of PDMPs. No tenable ethical basis exists for banning compensated donation for PDMPs, and, as such, both compensated and noncompensated donation should be permitted to coexist.

## CONFLICT OF INTEREST

This work represents the independent thinking of the authors. Mark W. Skinner, JD, is President and CEO of the Institute for Policy Advancement, Ltd.; he has received independent research funding from Bayer, Baxter, Biogen, SOBI, and Novo Nordisk; he participated in the development of the Alliance of Blood Operators Risk-Based Decision Making Framework; and his institution has received fees or honoraria for his attending advisory boards, consultancy, or giving educational presentations from Bayer, Grifols, and Novo Nordisk. P. Ann Hedlund Hoppe is the President of Hoppe Regulatory Consultants and has received consulting service fees from several companies who collect source plasma and manufacture plasma derivatives or medical devices as well as

from the nonprofit blood sector. Henry Grabowski, PhD, is Professor Emeritus and Director of the Program in Pharmaceutical Health Economics at Duke University and consults on behalf of several of health care companies. Richard Manning, PhD, is an economist employed by the consulting firm Bates White who provides economics expertise and consulting services on behalf of various interests in health care and life sciences. Raffi Tachdjian, MD, MPH, is an Assistant Clinical Professor of Medicine and Pediatrics at the University of California-Los Angeles. James F. Crone serves as a volunteer board member of the GBS-CIDP Foundation International, of which Grifols is a benefactor. Stuart J. Youngner, MD, is a Professor of Bioethics and Psychiatry in the School of Medicine at Case Western Reserve University and is a member of the Medical Board of Directors and the Donation Board of Directors of the Musculo-Skeletal Foundation, through which he receives funding for research and teaching the ethical issues of tissue and organ transplantation.

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