Evidence for Policies Recognizing and Screening Gender-Diverse Blood Donors

Food and Drug Administration- Blood Products Advisory Committee
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Pride & Plasma

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Contents

Letter

Dear Food and Drug Administration; Blood Products Advisory Committee,

Blood donation has not always been an accessible nor equitable process for members of the LGBTQ+ community. With the revisions to the previous blanket MSM (men who have sex with men) deferment criteria, strides have been made by the FDA, CBER, and BPAC to reconcile past actions. However, transgender, nonbinary, and other gender-diverse individuals have been left to the side of this progress. These individuals not only serve the potential to contribute safely to the nation's blood supply, but have been subject to deferment criteria in opposition to their gender identity(ies) (e.g. transgender women and non-binary individuals subject to deferment criteria intended for men and male donors).

Attempts to create affirming environments for gender-diverse blood donors have been introduced, namely the language "In the context of the donor history questionnaire, FDA recommends that male or female gender be taken to be self-identified and self-reported", which was present in the 2015 and 2020 iterations of eligibility criteria. However, the preceding language does not consider individuals outside of the two poles of the gender binary. Additionally, there were no best practices, guidelines, or instructions provided for blood banks and donation facilities in regards to the screening and treatment of these donors prior to the language's disappearance in 2023 with the transition to the individual risk assessment.

Although not every individual trans+ individual chooses to pursue legal, medical, or surgical assistance with their transition, many do. The treatments, prescriptions, and

procedures that these individuals undergo result in a diverse pool of donors, whose needs and safety must be considered. Individuals undergoing testosterone administration may find themselves with higher concentrations of erythrocytes. While some cisgender men undergoing TRT (testosterone replacement therapy) are prescribed therapeutic phlebotomy to prevent the risk of clots and other adverse effects, transgender individuals prescribed the same medications have not been identified in the same risk.

Of additional importance, the Center's adherence to the gender binary for blood donors may contribute to the risk of Transfusion Related Acute Lung Injuries (TRALIs). If compliant with the 2015-2023 language of self-reporting and self-identification, transgender men and nonbinary individuals who were previously pregnant may not be asked about their history. These individuals may have higher concentrations of HLA-antibodies, and if allowed to donate platelets or plasma, may contribute to the risk of TRALIs in recipients or otherwise life-saving blood products.

In a time of critical national shortages, each and every blood center must ensure welcoming environments for all donors, but this is of particular importance when considering individuals subject to differential treatment in the past, such as members of the LGBTQ+ community. However, blood banks and donation facilities do not know how to ensure affirming experiences for these donors. We call upon the FDA, CBER, and the BPAC to regard this evidence and to finalize recommendations and policies for the screening, testing, and treatment of transgender, non-binary, and gender-diverse blood donors.

Background

Sex & Gender

Sex and gender are two separate concepts that may or may not be aligned. Gender, or an individual's internal sense of self, presentation, and outward expression. Sex is a person's biological status and may be identified as male, female, or intersex. We have included definitions from various professional organizations and LGBTQ+ groups to ensure an adequate understanding prior to presenting research and additional information about transgender, non-binary, and gender-diverse donors and individuals.

Definitions

Cisgender: individuals whose gender identity matches their sex assigned at birth[1]

Gender: attitudes, feelings, and behaviors that a given culture associates with a person's biological sex[1]

Gender Diversity: refers to the extent to which a person's gender identity, role, or expression differs from the cultural norms prescribed for people of a particular sex[1]

When using "gender-diverse", Pride & Plasma seeks to be inclusive of individuals who are impacted by the issues at hand, but may not identify as transgender, non-binary, or cisgender.

Gender-fluid: A person who does not identify with a single fixed gender or has a fluid or unfixed gender identity[2]

Gender Identity: one's sense of oneself as male, female, or something else (American Psychological Association, 2006). When one's gender identity and biological sex are not congruent, the individual may identify along the transgender spectrum (cf. Gainor, 2000; APA guidelines)[1]

Gender Non-conforming: individuals whose gender expression, gender identity, or gender role differs from gender norms associated with their assigned birth sex[1]

Genderqueer: refers to a person whose gender identity falls outside of the gender binary (i.e. identifies with neither or both genders)[1]

Intersex: a range of conditions associated with atypical development of physical sex characteristics (American Psychological Association [APA], 2006). Intersex individuals may

be born with chromosomes, genitals, and/or gonads that do not fit typical female or male presentations (OII-USA, 2013). Some examples of these conditions include ambiguous external genitals, inability of the body to respond typically to sex-related hormones, and inconsistency between external genitals and internal reproductive organs (APA, 2006)[1]

Nonbinary: An adjective describing a person who does not identify exclusively as a man or a woman. Non-binary people may identify as being both a man and a woman, somewhere in between, or as falling completely outside these categories. While many also identify as transgender, not all non-binary people do. Non-binary can also be used as an umbrella term encompassing identities such as agender, bigender, genderqueer or gender-fluid[2]

Sex: a person's biological status and is typically categorized as male, female, or intersex (i.e., atypical combinations of features that usually distinguish male from female). There are a number of indicators of biological sex, including sex chromosomes, gonads, internal reproductive organs, and external genitalia[1]

Transgender: is an umbrella term that incorporates differences in gender identity wherein one's assigned biological sex doesn't match their felt identity[1]

Transitioning: A series of processes that some transgender people may undergo in order to live more fully as their true gender. This typically includes social transition, such as changing name and pronouns, medical transition, which may include hormone therapy or gender affirming surgeries, and legal transition, which may include changing legal name and sex on government identity documents. Transgender people may choose to undergo some, all or none of these processes[2]

Transexual: refers to an individual who has undergone gender-reassignment surgery. This term has largely been replaced with "Transgender", but some individuals may still hold onto and prefer this term[3]

Transitioning[4]

Just as each individual's gender identity and gender-expression are both deeply individualistic, so is an individual's process of transitioning. There is no right or wrong way to "do gender", nor is there one process to reach a point of comfort in one's body. Some transgender, non-binary, and gender-diverse individuals. There are a multitude of assistive treatments, procedures, and processes that can help individuals reach this stage, some of which are included here.

Internal Transition

These are practices and actions that an individual can participate in to begin the process of feeling at ease with their true gender identity. These include dressing differently, calling yourself a different name, using your voice differently all while in private.

Social Transition

Social transition begins when an individual is ready to progress from internal to external transition (private to public). These can include actions such as coming out to friends and/or family, changing the pronouns that you use, changing or modifying your name, dressing differently (such as binding or stuffing your chest, or tucking or packing your groin), and using your voice differently. These are methods of adapting your presentation in social settings, attempting to influence the perception of your gender by others, as well as making yourself more comfortable when publicly presenting as your gender.

Medical Transition

Medical transition can include prescriptions and medical treatments that alter your presentation. These processes vary based upon the intended presentation (masculine, feminine, androgynous), as well as an individual's intended outcome, or the extent of a change one is seeking to achieve.

Systemic effects and hematological impacts of hormone replacement therapy will be covered in the literature review, as related to the screening and testing of gender-diverse blood donors.

- **Masculine medical treatments**:

    - **Hormone replacement therapy**: initiated with the goal of initiation of secondary sex characteristics; deeper voice, facial hair, muscle growth, redistribution of body fat away from hips/breasts, delay or stop menstrual period
        - Achieved through the use of testosterone
    - **Voice Training**: initiated with the goal of producing a deeper, more masculine voice
    - **Fertility preservation**: saving eggs that can be used to have biological children in the future
- Feminine medical treatments:
    - **Hormone replacement therapy**: initiated with the goal of initiation of secondary sex characteristics; breast growth, redistribution of fat towards hips, decrease in overall body hair
    - **Voice Training**: initiated with the goal of producing a higher-pitched, more feminine voice
    - **Fertility preservation**: saving sperm that can be used to have biological children in the future
    - **Laser hair removal**: removal of body & facial hair

Surgical Transition

Gender affirming surgery(ies) are permanent procedures to help align an individual's body with their gender, gender identity, and transition process. Some examples of gender-affirming surgeries are included below.

- **Masculine/Androgynous surgical procedures:**
    - **Mastectomy/top surgery**: removal of breasts/breast tissue
    - **Laryngoplasty**: surgery to change vocal cords
    - **Hysterectomy**: removal of internal reproductive organs
    - **Phalloplasty**: construction of a penis using skin from other parts of the body
    - **Metoidioplasty**: surgical extension and increased flexibility of the clitoris
    - **Scrotoplasty**: surgical creation of a scrotum and testes
    - **vaginectomy/vulvectomy**: removal of the vagina and/or vulva, paired with other surgeries
    - **Nullification**: surgery that removes/hides external genitals
- **Feminine/Androgynous surgical procedures:**
    - **Breast augmentation**: top surgery, creation of breasts
    - **Laryngoplasty**: surgery to change vocal cords
    - **Tracheal shave**: decreasing down the size of an adam's apple
    - **Facial feminization surgery**: altering the size/shape of facial structures
    - **Orchiectomy**: removal of the testes

- **Vaginoplasty**: creation of a vagina, inverting the skin of the penis
- **Nullification**: surgery that removes/hides external genitals

Legal Transition

The practice of legally transitioning is the process of changing gender markers, names, and other information on government, financial, and other documents, accounts, and identification. These include, but are not limited to your drivers license, birth certificate, social security card, immigration documents, school, employer, dr/health insurance, and more. The accessibility of these processes and procedures vary greatly from state to state, and an individual's gender is no less valid if it does not match the identification assigned to them on a form.

Legal Recognition[5]

The difficulty of changing one's gender marker from M to F or F to M, as well as changing one's name through the legal process varies greatly by geography. Additionally, not every state has legal recognition of X gender-markers (an option other than M or F) on birth certificates or drivers licenses. The following is a list of states with the option of X identification on birth certificates and/or drivers licenses as of 2022.

State	Drivers License	Birth Certificate
Arkansas	x	
California	x	x
Colorado	x	x
Connecticut	x	
DC	x	x
Hawaii	x	

Illinois		x
Maine	x	x
Maryland	x	
Massachusetts	x	
Michigan	x	x
Minnesota	x	
Nevada	x	x
New Hampshire	x	
New Jersey	x	x
New Mexico	x	x
New York	x	x
Ohio		x
Oregon	x	x
Pennsylvania	x	
Rhode Island	x	x
Utah		x
Vermont	x	x

Previous FDA Language

2015 saw the revision of the lifetime deferral for MSM donors after 30 years, with the new policy implementing a 12-month policy. The update simultaneously introduced language for some gender-diverse donors.

> *"In the context of the donor history questionnaire, FDA recommends that male or female gender be taken to be self-identified and self-reported"*

Unfortunately, this policy was not inclusive of individuals who did not identify as male or female. It was a step in the right direction, but not fully applicable to the entire trans, non-binary, and gender-diverse community. The policy was still in place in the 2020 update that reduced the MSM deferral to 3-months.

In 2023, with the removal of blanket MSM deferral criteria, and the introduction of the individual risk assessment, the prior language was removed. However, all gendered language was also removed from the FDA's deferral criteria, a significant improvement in accessibility for transgender, non-binary, and gender-diverse blood donors. The Donor History Questionnaire 4.0 (DHQ 4.0) was also free from any gendered language or questions specifically asked of male or female donors.[6]

Evidence

At Pride & Plasma we believe that data should be used to inform best practices, that equitable treatment and scientific procedure should go hand in hand, and that research is best when it has practical implications. What started as an inquiry into current practices, medical transition processes, and the potential for more inclusive screening guidelines quickly grew into identification of the risk of patient harm due to oversight on already marginalized groups of people. With an understanding that an argument that "inclusive blood donor practices are the right thing to do", likely would not be sufficient; we hope that the evidence, research, and argument we propose spurs urgent action to ensure not only equitable access to donation on behalf of gender-diverse donors, but also ensuring that preventable risk of transfusion-related harm never meets those in need of life-saving blood products.

Literature Review

As seen with MSM (men who have sex with men) blood donation, very little research has been published on the topic of transgender, nonbinary, and gender-diverse blood donors. This may be due to the limited research on the community as a whole, a lack of inclusion on existing research (e.g. the ADVANCE Blood Study on feasibility of Individual Risk Assessment only including cisgender queer men), or various other reasons[7]. This required an expansion of research topics from strictly "transgender blood donors" to other related topics and criteria.

HRT/Transitioning

Not every transgender, non-binary, and gender-diverse blood donor pursues medical or surgical assistance in transitioning. One's adherence with hormonal, medical, or surgical transition assistance does not make one's gender identity less or more valid over other individuals. Each person's relationship with gender is different and there is not one

perfect way to meet congruence between one's body and one's gender identity. Hormone therapy is one method highlighted due to the subsequent effects on the circulatory system.

Hormone replacement therapy (HRT) is one method of medical gender transition. The intended effect of HRT is to achieve the normal range of testosterone (in transgender men, and some nonbinary/gender-diverse patients) or estrogen (in transgender women and some nonbinary/gender-diverse patients)[8]. "Donors who are not on hormonal therapy will have Hb and ferritin levels similar to other donors with the same sex assigned at birth. However, testosterone use will tend to increase Hb levels in trans men, while estrogen will decrease levels in trans women"[9].

For transgender women or nonbinary/gender-diverse individuals taking HRT estrogen, the hemoglobin and hematocrit levels were found to be within the standard female range following therapeutic administration. (information about the study/report) "blood cell findings revealed a different time course of change. After 3–4 months on GAHT, the HCT or Hgb levels of transwomen matched those of cisgender women, with levels remaining stable within the 'normal' female range for studies lasting up to 36 months".[10]

Exogenous testosterone administration has varying systemic effects. Some of which include acne, alopecia, decreased HDL cholesterol, increased triglycerides, and increased systolic blood pressure[8]. Testosterone administration can increase hemoglobin concentration, as well as increase red blood cell production. The magnitude of these effects varies based upon the prescription, strength, and route of administration. In a review of systemic effects of testosterone administration in transgender men, "intramuscular testosterone esters resulted in a mean rise in haemoglobin of 17 g/L (1.7 g/dL) and a mean rise in haematocrit of 4.7% in 1 year. Intramuscular testosterone undecanoate for 1 year

resulted in a mean rise in haemoglobin of 12–13 g/L (1.2–1.3 g/dL) and a mean rise in haematocrit of 3.3–5.0%".[8] "As related to blood pressure in transgender men, testosterone therapy resulted in an increase in systolic blood pressure of 4–12 mm Hg after one year, but no significant change in diastolic blood pressure".[8]

Erythrocytosis, or an increased concentration of red blood cells, can occur with testosterone administration, for both transgender and cisgender patients. This occurrence is significant enough that the FDA enacted mandatory warning labels for a risk of thromboembolism for all testosterone prescriptions in 2015.[11] "Secondary erythrocytosis, a potentially serious adverse effect of testosterone therapy as it is associated with an increased risk of thromboembolic events by an increase in blood viscosity".[12] As with many other aspects of this issue, research on the topic is limited to cisgender individuals, or has not been pursued related to gender-diverse groups. The exact incidence and prevalence of erythrocytosis related to HRT rather than testosterone replacement therapy (TRT), is not available.[13]

HRT and TRT are the same practice of administering exogenous testosterone for patients seeking to increase serum concentrations and systemic effects, with HRT indicating transgender, nonbinary, and other gender-diverse patients; whereas TRT designates cisgender male patients. Although the points and evidence in this brief is meant to be applied to HRT patients, the lack of data on transgender individuals limits our ability to include sources that solely included gender-diverse participants. As the goal of HRT is to reach testosterone levels equal to cisgender men, data is supplemented with samples and studies on TRT.

To prevent thrombotic events, or hypercoagulation in the result of increased viscosity and erythrocytosis, some providers prescribe therapeutic phlebotomy for patients

undergoing TRT[14]. This order requires individuals undergoing TRT to donate blood to decrease their red blood cell counts[15]. These individuals may be prescribed therapeutic phlebotomy at intervals more frequently than the typical minimum of 8 weeks between whole blood donations. This process is approved by the FDA, as evidenced by variances submitted by facilities to allow the practice[16, 17]. Although many of these programs are created and maintained through cisgender men who are undergoing TRT, the applications or benefits may be also achieved through transgender men and nonbinary or gender diverse persons undergoing HRT. If both demographics of donors are seeking to maintain testosterone levels within a defined threshold, they may see similar, if not the same side effects. These donors, who currently are not acknowledged by federal regulations or policies, may be some of the safest repeat donors from a donor-risk standpoint.

TRALI

Transfusion related acute lung injuries are the second leading cause of transfusion-related mortality. An issue prevalent enough to recommend deferral for previously pregnant women from donating plasma and/or platelets. These deferrals are a method of preventing patients from dying, from requiring mechanical ventilation, from requiring prolonged hospitalization, amongst other adverse effects. But the application of these deferral criteria related to platelets and plasma donations are not inclusive of all those who are high-risk.

TRALI can be caused by the transfusion of either human leukocyte antigen (HLA) antibodies. One of the leading hypotheses of TRALI pathogenesis is a two-hit process of neutrophil activation[18]. The “first-hit” in this theory is an existing inflammatory condition which leads to pulmonary endothelium activation as well as neutrophil accumulation. The

"second hit" is triggered by the transfusion of blood products, introducing HLA-antibodies to the recipient and resulting in an immune response. This underlying condition (i.e. infection, surgery) causes activation of the pulmonary endothelium, leads to sequestration and priming of neutrophils in the lung[19]. TRALI can be differentiated from TACO by the absence of echocardiographic abnormalities and less frequent BNP elevations[20], as well as with the assistance of laboratory testing, ultrasound, and clinical variables to determine fluid balance[21].

TRALI can be classified into multiple categories. Type 1 includes symptoms with the absence of acute respiratory distress syndrome (ARDS) symptoms. Type 2 includes either ARDS risk factors or existing acute ARDS. Direct risk factors for ARDS include pneumonia, aspiration of gastric contents, inhalational injury, pulmonary contusion, pulmonary vasculitis, and drowning[21]. Indirect ARDS risk factors include nonpulmonary sepsis, major trauma, pancreatitis, severe burns, noncardiogenic shock, and/or drug overdose[21].

Human leukocyte antigens (HLA) are cell markers that identify cells and cell components as either a part of an individual's body or alien[22]. These are identified by the immune system which may initiate an immune response when/if present. HLA antibodies are the immune system's response to these markers and can have critical system effects. Specifically, HLA antibodies play a role in platelet transfusion refractoriness; hyperacute, acute, chronic organ rejection; as well as being implicated as the primary cause in most cases of transfusion-related acute lung injury[23]. 80-85% of TRALI cases were associated with HLA/HNA[24]. TRALI cases have been indicated from all types of blood products, but plasma transfusions are most common.

Further, HLA antibodies are most common in previously pregnant donors, previously identified as multiparous women in both literature and deferment criteria[23]. The zygotal, embryonic, or fetal cells within a pregnant individual's cells can trigger HLA antibody production during the pregnancy, but these antibodies do not leave the immune system or circulation following birth, miscarriage, or abortion. A previously pregnant individual could have residual and/or increased HLA antibody levels for years or decades after a pregnancy regardless of the length or term reached.

Factors that affect the incidence of TRALIs include patient populations, such as those with existing hematologic issues, pediatric patients, or trauma patients; donor factors, such as previous pregnancies, miscarriages, or abortions; the type of blood product administered, the quantity and volume of blood products administered, and definition and diagnosable criteria used to identify cases, and the methods of symptom surveillance and reporting[25]. Other conditions that have been tied to TRALI and acute respiratory distress syndrome include sepsis and non-cardiogenic shock[18].

Prevention is implemented through the use of donor deferral through the history questionnaire, HLA screening, and increasing the percentage of plasma and/or platelet donations from male donors[19,26,] . Deferral criteria include a lifetime deferral for plasma and/or platelet donation for individuals with a history of pregnancy or a history of transfusion[19]. Some facilities may defer all women from donating plasma or platelets, as not all individuals are aware that they were pregnant if the pregnancy ended in the first weeks following conception[19,26]. Previously pregnant donors may be permitted to donate if testing for HLA antibodies is negative[25]. These methods have been effective, with an 80%

decrease in TRALIs when the American Red Cross implemented a male-predominant plasma donor program in 2007[24].

National incidence of possible transfusion-related acute lung injury (pTRALI) and transfusion-related acute lung injury (TRALI) from 2009-2021

Year	pTRALI			TRALI			Total	%	Rank
	Definite	Probable	Possible	Definite	Probable	Possible			
'09[27]							**13**	**30%**	**1st**
'10[27]							**18**	**45%**	**1st**
'11[27]							**10**	**33%**	**1st**
'12[27]							**17**	**45%**	**1st**
'13[27]							**14**	**37%**	**1st**
'14[28]							**13**	**43%**	**1st**
'15[29]	0	0	0	5	0	7	**12**	**32%**	**1st**
'16[30]	0	0	5	2	0	1	**8**	**19%**	**2nd**
'17[31]	0	0	4	0	2	3	**9**	**24%**	**2nd (tie)**
'18[32]	0	2	2	0	0	0	**4**	**13%**	**4th (tie)**
'19[33]	1	2	4	2	2	1	**12**	**27%**	**1st (tie)**
'20[34]	0	1	1	2	2	0	**6**	**21%**	**2nd (tie)**
'21[35]	0	1	4	1	1	0	**7**	**16%**	**2nd**
17-21[35]								***21%***	***2nd***

It is difficult to assess the national incidence of TRALI from a public standpoint, as only patient outcomes that result in mortality are mandated to be reported to the federal government, limiting the publicly available information related to and quantity of any

TRALIs that resulted in adverse effects other than death. Data on required mechanical ventilation, prolonged hospital stay, and intensive care placement are not readily shared nor accessible. Although the number of patients who die from TRALIs annually is not exceptionally high when compared to the number of transfusions administered, if they are preventable, actions should be taken at the point of donation, as has been done for years. However, these actions must be comprehensive.

A 2023 review calculated the incidence of TRALI among different blood products between 1991 and 2023[36]. The incidence rates per blood product were red blood cells (0.17 /10,000), platelets (0.31 /10,000), and plasma (3.19 /10,000). Without mandatory reporting of non-mortality TRALI cases, it is not possible to assess if TRALIs are occurring at greater, equal, or lesser rates of non-mortality TACOs. It is possible that TRALIs are more prevalent than TACOs when considering all outcomes other than death. Simply recognizing that TRALIs are no longer the leading cause of morality does not showcase the entire picture of incidence.

Current Practices & Limitations

Research on transgender, nonbinary, and gender-diverse persons as individuals and as a whole has been significantly lacking when related to blood, tissue, and biologics. While identification of areas of growth for the screening, treatment, and testing of these donors has been published, solutions that address the needs and concerns of this community have not been uniformly shared nor implemented in the nation's blood centers. These donors can not only help ease shortages and decreased donations but must be acknowledged in an era of low donor turnout. Besides the necessity of ensuring welcoming environments for all donors, the failure to consider the differences of this sample when compared to the

general population of blood donors has resulted in potential risk for individuals receiving transfusions due to a lack of preventative measures applied to those at higher risk.

Current practices by many blood centers fail to consider these individuals while drafting, implementing, and reviewing donor screening mechanisms. Part of the issue is the outdated and limited capacity of blood establishment computer systems (BECSs)[9]. These programs and systems may only have two binary gender markers for selection by donors or staff. They may not have the capability to change a gender marker in the future if a previous donor has begun social and legal transition. Unfortunately, in a 2017 survey of US and Canadian blood centers, most American facilities did not allow the use of gender designations other than male or female (97%)[9]. However, a growing number of states and municipalities are transitioning towards gender markers beyond the gender binary, with X serving as an option for non-binary, gender non-conforming, and other gender-diverse. Even ignoring the ethical justification of acknowledging the existence of gender-diverse donors, the computer systems are not equipped or up to date with the necessary categories from a legal standpoint.

Further, this lapse in capability of categorizing gender-diverse donors has a critical implication on recipient outcomes. “In the United States and Canada, most questions on the questionnaires are identical; however, several questions differ according to female or male designation in the BECS. The “female” questionnaire will contain an additional question about recent pregnancy; there may also be a question about ever being pregnant, including miscarriages and abortions, to reduce recipient transfusion-related acute lung injury (TRALI) risk”.[9] Donors on TRT may be limited to donating RBC or whole blood rather than plasma or platelets[17]. Transgender men and some gender-diverse individuals should

be subject to the same donation eligibility as previously pregnant donors due to TRALI risk if undergoing HRT criteria.

The experience of gender-diverse blood donors is greater than just the questions asked of them. The environment, the attitudes of staff, and acceptance of their gender identity encourage or discourage initial and repeat donations. AABB publications include sharing pronouns and removal of gendered language, but these interventions do not solve the issue of outdated and limiting BCESs[37]. Other recommendations include using a donor's preferred or chosen name and gender, which may not be the same as the information on their legal documents[38]. Gender-diverse donors want to know why questions about their gender are asked, and if they aren't necessary, they should be avoided. Staff should maintain privacy and confidentiality during the donation process.

Conclusion

Under the language proposed in 2015 and 2020, transgender men, as well as nonbinary individuals who selected the male gender in the screening process may have been assigned the female sex at birth. These individuals, if screened as male, may not have, or may not currently be asked if they have ever been pregnant. If these individuals have previously been pregnant, they may have higher rates of HLA-antibodies in their bloodstream, which could be transfused to an individual, and result in a Transfusion-Related Acute Lung Injury, and possibly death.

The issue in the current screening and recommendation is not that transgender and gender-diverse donors exist, it is that the guidance (or lack of guidance(s)) ignores their unique needs and traits, and therefore allows them to fall through the cracks in risk-related deferrals. In order to ensure that all individuals are accounted for their individual risk, an

individual risk assessment should be applied to all individuals, not just those with a certain gender.

As done with the previous MSM (men who have sex with men) deferment criteria, all donors should be asked if they were ever pregnant, including cisgender men and transgender women. In order to ensure that no further individuals are at a risk of a preventable risk, the FDA should recommend screening all donors with all questions. Gender-diverse donors exist everywhere. They may be more likely to be first time donors compared to cisgender donors, are more likely to be younger than the existing donor population, and may donate more frequently. In a study of 282 transgender/non-cisgender donors at Memorial Blood Centers found that only 14.07% of donors who selected male/female (cis-gender) returned for a second donation, whereas 23.76% of donors who selected transgender or "other" as their gender returned for a second donation[40].

Further, the FDA should work with members of the transgender, non-binary, and gender-diverse community when formulating best practices that are both comprehensive and gender-affirming. Additionally, the FDA should fund, support, and initiate research to address the experiences, shortfalls, and benefits of blood donation amongst gender-diverse blood donors.

Recommendations

As the individual risk assessment for blood donors was finalized in May of 2023, blood centers should transition to and prioritize a universal, gender-neutral screening practice where all donors are asked the same questions, including questions about history of pregnancy, miscarriage, and abortion. Gender and sex are not synonymous and nor are they the same for every donor.

Shortages

National shortages in blood donations have impacted the ability to provide care to patients in need. This issue was exacerbated with the Covid-19 pandemic, and supply has yet to return to pre-pandemic levels. While looking at shortages at a systemic level, or a national level, revising eligibility for MSM donors, or creating policies inclusive of gender-diverse donors will not alleviate and solve all supply issues. But looking at the issue from a donor and recipient perspective, benefits will be felt. If donors are welcomed into inclusive environments they may be more likely to donate, and donate more frequently. One donation can be the difference between a life saved and a life lost. Enlisting new donors will save more than just one life, especially when considering the unique benefits that this demographic brings.

Transgender men and other gender-diverse donors undergoing testosterone administration may be some of the safest donors to give red blood cells due to the effects of HRT. Transgender women and other gender-diverse donors may currently be deferred from donating plasma or platelets if a blood center is affirming and following the previous language introduced in 2015 and 2020. However, these individuals would be able to donate platelets without an increased risk in HLA antibodies. With such a short shelf-life of platelets, enlisting donors is a critical practice in transfusion medicine.

In an era of chronic shortages of all blood products, blood donation facilities cannot afford to turn away donors, or to create unwelcoming or unaffirming environments for any donors. However, they do not know how to create settings that promote return donations. The FDA must step in to create guidelines and recommendations for national implementation.

Recommendations

Issue 1- TRALIs, HLA Antibodies, and History of Pregnancy

Our Recommendation (1/2): We recommend asking all donors, regardless of sex, gender, or presentation about a history of pregnancy. Donors should not have to publicly identify their gender, nor their alignment of gender and sex to staff unless necessary. By asking all donors, including those who staff, facilities, and systems assume to be cisgender men about pregnancy history, donors with increased risk of HLA antibodies will be deferred from donating platelets and plasma.

Our Recommendation (2/2): Promote the reporting and public dissemination of data and information related to diagnosed TRALI cases that do not result in patient mortality.

Issue 2- Inclusive Environments, Screening, and Gender Options

Step 1: Promote Research on the Experience of Gender-Diverse Individuals:

Our Recommendation (1/2): In order to fully understand the current typical practice of screening and managing gender-diverse blood donors, research should be conducted with blood donation facilities. This research should be conducted with the goals of identifying current shortfalls, patient responses to current practices, and current affirming practices that can be utilized in other facilities. Other topics of concern include the relation between legal status of third gender markers as related to BCESs, donors who have transitioned after an initial appointment, and donor outlooks following the transition to an individual risk assessment.

Our Recommendation (2/2): It is possible that a review of current practices may not be sufficient to create new policies, even when paired with the existing literature on the topic. New research studies should be created, conducted, and disseminated similar to the ADVANCE Study.

Step 2: Draft Federal Recommendations and Guidelines for the Screening, Treating, and Interacting with Gender-Diverse Donors:

Our Recommendation (1/3): The usage and degree of medical and surgical assistance for gender transition varies greatly from individual to individual. Individuals who undergo surgical transition but not HRT would have hemoglobin and hematocrit concentrations greatly different than individuals who pursue only HRT. Because of this, two gendered, binary scales for vitals and laboratory results are not comprehensive to meet the needs for gender-diverse donors. A universal scale for hemoglobin, hematocrit, as well as body composition should be created to ensure that all donors can give blood safely.

Additionally, if donors are able to donate safely, they may experience fewer adverse effects and be more incentivized to make a repeat donation in the future.

Our Recommendation (2/3): As with the language in 2015 and 2020, donors should be able to both self-identify and self-select their gender. However, there should be additional options besides the binary “male/man” and “female/male”. Additional options should be available for gender-diverse donors, and donors should be able to easily alter their gender-selection if needed. Gender should be prioritized rather than biological sex or sex assigned at birth; this should also be clearly communicated to donors, facilities, and staff. This should be affirmed through language in FDA documentation, which was removed in the 2023 update for the Individual Risk Assessment.

Any new practices should not be limited to donors who have pursued, begun, or completed medical and/or surgical assistance with gender transition, as was the case by Canadian Blood Services (only permitting gender marker changes following a 3-month period post-op.). This would likely be alienating to individuals who do not wish to, or cannot pursue such treatments, as well as the significance that one's gender is not more or less valid following medical treatment.

Our Recommendation (3/3): One of the largest hurdles for implementation of inclusive practices and environments is the lack of facility control of BCESs. This has resulted in significant delays in implementation of FDA regulation changes, as was seen by prolonged application of the individual risk assessment. The FDA should advocate for improved access at the facility level of these systems, including the ability to add additional gender markers.

Step 2: Continual Monitoring and Solicitation of Feedback with the Transgender, Nonbinary, and Gender-Diverse Community:

Our Recommendation (1/3): Those impacted by these policies should be consulted during the drafting, public comment, and finalization of updates.

Our Recommendation (2/3): Response and adherence to guidelines impacting transgender, nonbinary, and gender-diverse donors should be collected following implementation of changes. These should be compiled by blood donation facilities nationally, and used to draft future improvements and changes by both FDA and AABB.

Our Recommendation (3/3): Intentional action should be made to explain why new policies are inclusive, improved, and more accessible to transgender, nonbinary, and gender-diverse donors. These donors may have poor relationships with blood donation facilities and the blood donation process due to unwelcoming environments and

unaffirming practices in the past. The same should be done with MSM donors who were previously deferred, as there is likely significant overlap between both demographics.

Issue 3- Testosterone, Erythrocytosis, & Therapeutic Phlebotomy; Transgender Women & Platelet Donation

Route 1: Our Recommendation:

Our Recommendation (1/2): The incidence of erythrocytosis amongst individuals prescribed and taking hormone replacement therapy w/testosterone should be better measured. On part of the FDA, variances for erythrocytosis should be promoted to blood donation facilities in an era of systemic shortages. Transgender men, nonbinary individuals, and other individuals who have secondary erythrocytosis following HRT should be considered in these programs.

Our Recommendation (2/2): Without the increased risk of HLA antibodies, transgender women, nonbinary individuals, and other gender-diverse individuals assigned male at birth, should be prioritized for platelet and/or plasma donation. Any blanket deferrals for all women donating plasma and/or platelets should be revised to not include transgender women as they do not hold the same risk as cisgender women for pregnancy attributed increases in HLA antibodies.

Citations

1. American Psychological Association. (2015). *Key Terms and Concepts in Understanding Gender Diversity and Sexual Orientation Among Students.* https://www.apa.org/pi/lgbt/programs/safe-supportive/lgbt/key-terms.pdf
2. Human Rights Campaign. (2023, May 31). *Glossary of Terms.* HRC Resources. https://www.hrc.org/resources/glossary-of-terms?utm_source=ads_ms_HRC_20240306-HRC-AW-GS-Natl-GlossaryRP_GlossaryKeywords_a001-dynamic-rst_b:gender%20terms&gad_source=1&gclid=CjwKCAjwte-vBhBFEiwAQSv_xR1SFuE2pedOhtOopbWkEeL1fmrFjg3b1UHcwi-3iJXuADPRamDP1RoC5JUQAvD_BwE
3. American Psychological Association. (2023, March 9). *Understanding Transgender People, Gender Identity and Gender Expression.* https://www.apa.org/topics/lgbtq/transgender-people-gender-identity-gender-expression
4. Planned Parenthood. (n.d.). *What Do I Need to Know About Transitioning?* https://www.plannedparenthood.org/learn/gender-identity/transgender/what-do-i-need-know-about-transitioning
5. Migdon, B. (2022, May 31). *Here are the States Where You Can (and Cannot) Change Your Gender Designation on Official Documents*. The Hill. https://thehill.com/changing-america/respect/diversity-inclusion/3507206-here-are-the-states-where-you-can-and-cannot-change-your-gender-designation-on-official-documents/
6. Association for Advancement of Blood and Biotherapies. (2023, May 11). *Full-Length Blood Donor History Questionnaire (DHQ) v4.0*. https://www.aabb.org/docs/default-source/default-document-library/resources/dhq-v4-0/pdfs/dhq-v4-0.pdf?sfvrsn=c8022a9f_0
7. Custer, B., Whitaker, B., Pollack, L., Buccheri, R., Bruhn, R., Crowder, L., Steamer, S.L., Reik, R., Pandey, S., Stone, M., Di Germanio, C., Buchacz, K., Eder, A., Lu, Y., Forshee, R., Anderson, S., Marks, P. (2023). HIV risk behavior profiles among men who have sex with men interested in donating blood: the assessing donor variability and new concepts in eligibility (ADVANCE) study. *Vitalant Research Institute.* https://doi.org/10.1101/2023.04.08.23288320
8. Irwig, M.S. (2017). Testosterone therapy for transgender men. *The Lancet Diabetes & Endocrinology, 5*(4), 301-311. https://doi-org.uc.idm.oclc.org/10.1016/S2213-8587(16)00036-X
9. Goldman, M., Butler-Foster, T., Lapierre, D., O'Brien, S.F., O'Brien, A.D. (2020). Trans people and blood donation. *Transfusion, 60*(5), 1084-1092. https://doi-org.uc.idm.oclc.org/10.1111/trf.15777

10. Harper, J., O'Donnell, E., Khorashad, B.S., McDermott, H., Witcomb, G.L. (2021). How does hormone transition in transgender women change body composition, muscle strength and haemoglobin? Systematic review with a focus on the implications for sport participation. *British Journal of Sports Medicine, 55*(15), 865-872. https://bjsm-bmj-com.uc.idm.oclc.org/content/55/15/865
11. Oakes, M., Arastu, A., Kato, C., Somers, J., Holly, H.D., Elstrott, B.K., Dy, G.W., Kohs, T.C.L., Patel, R.R., McCarty, O.J.T., DeLoughery, T.G., Milano, C., Raghunathan, V., Shatzel, J.J. (2021). Erythrocytosis and thromboembolic events in transgender individuals receiving gender-affirming testosterone. *Thrombosis Research, 207*(1), 96-98. https://doi-org.uc.idm.oclc.org/10.1016/j.thromres.2021.09.005
12. Madsen, M.C., van Dijk, D., Wiepjes, C.M., Conemans, E.B., Thijs, A., den Heijer, M. (2021). Erythrocytosis in a large cohort of trans men using testosterone: a long-term follow-up study on prevalence, determinants, and exposure years. *The Journal of Clinical Endocrinology and Metabolism, 106*(6), 1710-1717. https://doi.org/10.1210/clinem/dgab089
13. Oakes, M., Kato, C., Yazdani, S., Deloughery, T.G., Milano, C., Shatzel, J.J., Raghunathan, V. (2020). The prevalence and management of secondary erythrocytosis in transgender individuals undergoing masculinizing therapy. *Blood, 136*(1), 13. https://doi-org.uc.idm.oclc.org/10.1182/blood-2020-140887
14. Kanias, T. (2021, October 18). *There's no need to sweat about red cells and testosterone replacement therapy.* Association for Advancement of Blood & Biotherapies. https://www.aabb.org/news-resources/news/article/2021/10/18/there-s-no-need-to-sweat-about-red-cells-and-testosterone-replacement-therapy
15. San Diego Blood Bank. (n.d.). *Testosterone replacement therapy*. https://sandiegobloodbank.org/hospitals/testosterone-replacement-therapy/#:~:text=Testosterone%20Replacement%20Therapy%20(TRT)&text=Those%20who%20are%20participating%20in,and%20viscosity%20within%20normal%20limits
16. Carter BloodCare. (2023, December 12). *Testosterone Therapy (TRT)*. https://www.carterbloodcare.org/education-center/types-of-donations/testosterone-therapy/
17. Hazegh, K., Anawalt, B.D., Dumont, L.J., Kanias, T. (2021). Toxic masculinity in red blood cell units? Testosterone therapy in blood donors revisited. *Transfusion, 61*(11), 3174-3180. https://doi-org.uc.idm.oclc.org/10.1111/trf.16658
18. Tung, J., Chiaretti, S., Dean, M.M., Sultana, A.J., Reade, M.C., Fung, Y.L. (2022). Transfusion-related acute lung injury (TRALI): Potential pathways of development, strategies for prevention and treatment, and future research directions. *Blood Reviews, 53*(1). https://doi.org/10.1016/j.blre.2021.100926
19. Muller, M.C.A., van Stein, D., Binnekade, J.M., van Rhenen, D.J., Vlaar, A.P.J. (2014). Low-risk transfusion-related acute lung injury donor strategies and the impact on the onset of transfusion-related acute lung injury: a meta analysis. *Transfusion, 55*(1), 164-175. https://doi-org.uc.idm.oclc.org/10.1111/trf.12816

20. Roubinian, N. (2018). TACO and TRALI: Biology, risk factors, and prevention strategies. *Hematology, 2018*(1), 585-594. https://doi.org/10.1182%2Fasheducation-2018.1.585
21. Vlaar, A.P.J., Toy, P., Fung, M., Looney, M.R., Juffermans, N.P., Bux, J., Bolton-Maggs, P., Peters, A.L., Silliman, C.C., Kor, D.J., Kleinman, S. (2019). A consensus redefinition of transfusion-related acute lung injury. *Transfusion, 59*(7), 2465-2476. https://doi-org.uc.idm.oclc.org/10.1111/trf.15311
22. Nordquist, H., Jamil, R.T. (2023, April 24). *Biochemistry, HLA Antigens.* National Library of Medicine. https://www.ncbi.nlm.nih.gov/books/NBK546662/#:~:text=Human%20leukocyte%20antigens%20(HLA)%20are,can%20also%20have%20detrimental%20effects.
23. Triulzi, D.J., Kleinman, S., Kakaiya, R.M., Busch, M.P., Norris, P.J., Steele, W.R., Glynn, S.A., Hillyer, C.D., Carey, P., Gottschall, J.L., Murphy, E.L., Rios, J.A., Ness, P.M., Wright, D.J., Carrick, D., Schreiber, G.B. (2009). The effect of previous pregnancy and transfusion on HLA alloimmunization in blood donors: implications for a transfusion-related acute lung injury risk reduction strategy. *Transfusion, 49*(9), 11825-1835. https://doi-org.uc.idm.oclc.org/10.1111/j.1537-2995.2009.02206.x
24. Kuldanek, S.A., Kelher, M., Silliman, C.C. (2019). Risk factors, management and prevention of transfusion related-acute lung injury: a comprehensive update. *Expert Review Hematology, 12*(9), 773-785. https://doi.org/10.1080%2F17474086.2019.1640599
25. White, S.K., Schmidt, R.L., Walker, B.S., Metcalf, R.A. (2022). The epidemiology of transfusion-related acute lung injury: A scopy review and analysis. *Transfusion, 63*(1), 104-116. https://doi-org.uc.idm.oclc.org/10.1111/trf.17185
26. Juskewitch, J.E., Stubbs, J.R., Gandhi, M.J. (2021). Elevated rate of HLA antibodies in male covid-19 convalescent plasma donors: a risk factor for transfusion-related acute lung injury. *Mayo Clinic Proceedings, 96*(2), 500-502. https://doi-org.uc.idm.oclc.org/10.1016/j.mayocp.2020.11.007
27. U.S. Food and Drug Administration/Center for Biologics Evaluation and Research. (2013). *Fatalities reported to FDA following blood collection and transfusion: Annual summary for fiscal year 2013.* http://wayback.archive-it.org/7993/20171115110739/https://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM393080.pdf
28. U.S. Food and Drug Administration/Center for Biologics Evaluation and Research. (2014). *Fatalities reported to FDA following blood collection and transfusion: Annual summary for fiscal year 2014.* http://wayback.archive-it.org/7993/20171114162535/https://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM459461.pdf

29. U.S. Food and Drug Administration/Center for Biologics Evaluation and Research. (2015). *Fatalities reported to FDA following blood collection and transfusion: Annual summary for fiscal year 2015.* http://wayback.archive-it.org/7993/20171114162532/https://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM518148.pdf
30. U.S. Food and Drug Administration/Center for Biologics Evaluation and Research. (2016). *Fatalities reported to FDA following blood collection and transfusion: Annual summary for fiscal year 2016.* https://www.fda.gov/media/111226/download?attachment
31. U.S. Food and Drug Administration/Center for Biologics Evaluation and Research. (2017). *Fatalities reported to FDA following blood collection and transfusion: Annual summary for fiscal year 2017.* https://www.fda.gov/media/124796/download?attachment
32. U.S. Food and Drug Administration/Center for Biologics Evaluation and Research. (2018). *Fatalities reported to FDA following blood collection and transfusion: Annual summary for fiscal year 2018.* https://www.fda.gov/media/136907/download?attachment
33. U.S. Food and Drug Administration/Center for Biologics Evaluation and Research. (2019). *Fatalities reported to FDA following blood collection and transfusion: Annual summary for fiscal year 2019.* https://www.fda.gov/media/147628/download?attachment
34. U.S. Food and Drug Administration/Center for Biologics Evaluation and Research. (2020). *Fatalities reported to FDA following blood collection and transfusion: Annual summary for fiscal year 2020.* https://www.fda.gov/media/160859/download?attachment
35. U.S. Food and Drug Administration/Center for Biologics Evaluation and Research. (2021). *Fatalities reported to FDA following blood collection and transfusion: Annual summary for fiscal year 2021.* https://www.fda.gov/media/172382/download?attachment
36. White S.K., Walker, B.S., Schmidt, R.L., Metcalf, R.A. (2023). The incidence of transfusion-related acute lung injury using active surveillance: a systematic review and meta-analysis. *Transfusion, 64*(2), 289-300. https://doi-org.uc.idm.oclc.org/10.1111/trf.17688
37. Association for Advancement of Blood and Biotherapies. (n.d.). *Implementation of Individual Donor Assessment: Individual donor assessment primer.* https://www.aabb.org/docs/default-source/default-document-library/resources/aabb-ida-assessment-primer.pdf?sfvrsn=35da87e4_8
38. Association for Advancement of Blood and Biotherapies. (2022, November 9). *AABB22: Information about real-world donation needed to improve donation experience of gender-diverse donors.*

https://www.aabb.org/news-resources/news/article/2022/11/09/aabb22-information-about-real-world-donation-needed-to-improve-donation-experience-of-gender-diverse-donors

39. Reynolds, V., Van Buren, N.L., Gorlin, J.B. (2023). Confronting the challenge of gender nonconforming donors: A blood center's three-year experience. *Transfusion, 63*(7), 1284-1289. https://onlinelibrary-wiley-com.uc.idm.oclc.org/doi/10.1111/trf.17446