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BRIEF REPORT

TRANSFUSION

Repeat donation and deferral rates in US source plasma donors: Exploratory analysis from the IMPACT trial

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Abstract

Background: The IMPACT trial demonstrated the safety of a new personalized nomogram for plasma donation and provided an opportunity to explore short- to mid-term impact on repeat donation and deferral rates, and factors affecting these.

Study Design and Methods: In the IMPACT trial, participants were randomized to donate plasma using an established weight-based nomogram (control) versus a new personalized nomogram incorporating height, weight, and hematocrit (experimental). In this exploratory analysis, repeat donations (per donor, by study arm) were analyzed using negative binomial generalized linear regression models and descriptive statistics. The mean number of donor deferral events was compared between the two arms using logistic regression and count data modeling approaches and were analyzed by lead cause.

Results: The predicted mean number of repeat donations was similar between the control and experimental arms (6.82 vs. 6.62, respectively; $p = .22$). Overall, the predicted mean number of repeat donations was significantly higher in males compared with females ($p < .0001$). Naïve donors had on average 2.8/2.7 (control/experimental) fewer repeat donations compared with experienced donors. In 23, 137 donations from 3443 donors, 798 donors (376 control, 422 experimental, $p = .80$) had at least one deferral (for any cause). The predicted mean number of deferrals in all categories of interest was not statistically different between the study arms.

Conclusion: Similar repeat donation and deferral rates between arms suggest that the new nomogram did not result in disruptions to subsequent donation. Further longitudinal research on mid- to long-term effects is warranted.

KEYWORDS

deferral rate, IMPACT, plasma, plasma donor, repeat donation

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1 | INTRODUCTION

Plasma-derived medicinal products address a critical and growing clinical need. Source plasma collection from donors is essential for meeting the global demand.[1,2] The US is the leading collector of source plasma, contributing the majority of volume collected worldwide.[1,2] Plasma collection and target volume determination have followed a weight-based nomogram that the US Food and Drug Administration (Center for Biologics Evaluation and Research) issued in 1992.[3]

Recently, a more personalized approach to setting target volumes has been proposed. It includes additional parameters such as body mass index and hematocrit that are missing from the 1992 nomogram.[4] The IMPACT trial (NCT04320823) was designed to study the safety of such a personalized approach with respect to hypotensive donor adverse events. The trial compared two arms, the 1992 nomogram (control) and a new personalized nomogram (experimental).[5]

The study found that the new, personalized nomogram was noninferior as compared to the 1992 nomogram with regard to the primary safety endpoint of significant hypotensive donor adverse events.[5] Per one of the prespecified secondary endpoints, the study also found that donors in the experimental arm were, on average, able to donate significantly more plasma per donation.[5] In addition, a comprehensive safety analysis did not show any statistically significant increase in the risk of significant hypotensive as well as nonhypotensive adverse events (such as citrate reactions or phlebotomy-related issues).[5]

While the IMPACT trial was not designed as a longitudinal experiment with a fixed-visit structure, many study participants had multiple visits over the approximately 12-week study period (shorter in some study sites).[5] The large number of study subjects ($n = 3443$)

TABLE 1 Expected number of repeat donations

Donor, study arm	Number of donations	Observed mean donations in study, per subject	Predicted mean donations in study, per subject	*p*-Value
All donors, model-based predictions[a]				
All donors, control	11,775	6.82	6.82	.22
All donors, experimental	11,362	6.62	6.62	
By gender, model-based predictions[b]				
Male donors	15,913	7.11	7.06	<.0001
Female donors	7224	5.99	6.09	
Male, control	8036	7.14	7.16	.85
Male, experimental	7877	7.08	6.95	
Female, control	3739	6.22	6.17	.06
Female, experimental	3485	5.76	6.00	
By donation status, model-based predictions[c]				
Naïve donors	824	3.80	4.16	< 0.0001
Repeat donors	22,313	6.92	6.88	
Naïve, control	405	3.75	4.22	0.84
Naïve, experimental	419	3.84	4.10	
Repeat donors, control	11,370	7.03	6.98	0.21
Repeat donors, experimental	10,943	6.81	6.78	

[a]Model-based predictions and the *p*-value are calculated using the GLE Negative Binomial Model regressing number of donations against the study arm adjusted for donation status, age, and weight. All adjustment variables are statistically significant (see Appendix).
[b]Model-based predictions and the *p*-value are calculated using the GLE Negative Binomial Model regressing number of donations against the study arm adjusted for donation status, age, and weight. All adjustment variables are statistically significant. For arm comparisons, male donations (female donations) vs study arm, the *p*-values associated with respective interaction terms are reported. The interaction terms are introduced only for the models aiming to estimate the gender vs study arm comparisons.
[c]Model-based predictions and the *p*-value are calculated using the GLE Negative Binomial Model regressing number of donations against the study arm adjusted for donation status, age, and weight. All adjustment variables are statistically significant. For arm comparisons, naïve donors (repeat donors) vs study arm, the *p*-values associated with respective interaction terms are reported. The interaction terms are introduced only for the models aiming to estimate the donor status vs study arm comparisons.

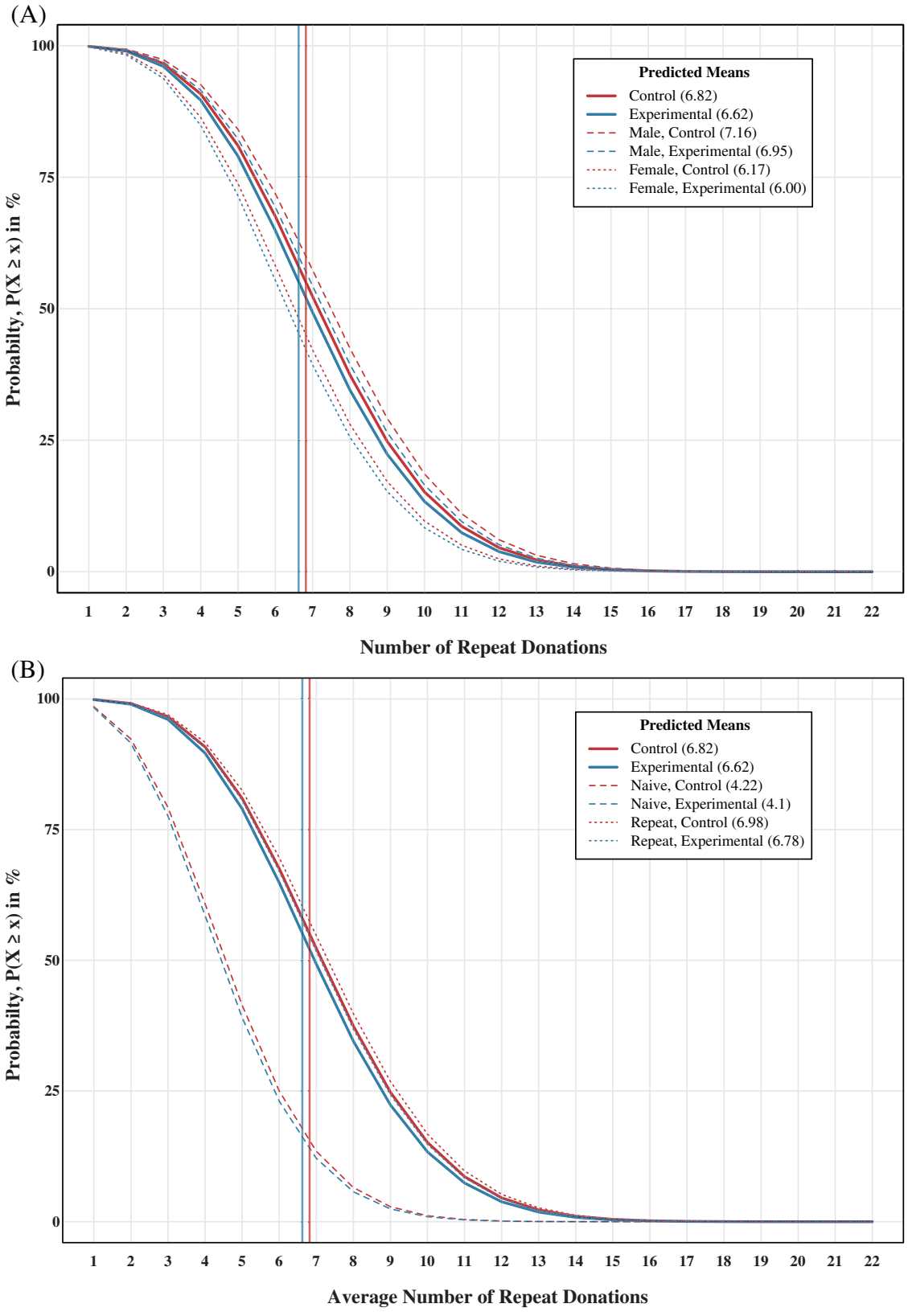

FIGURE 1 Cumulative distribution function for mean frequency of repeat donations—Model-based estimates. (A) All donors and gender subgroups; (B) All donors and naïve/repeat donor subgroups [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Analysis of deferrals by category in donors with at least one deferral: Model-based and descriptive summaries

Deferral type, study arm	Number of donors with at least one deferral	Mean number of donations in study, per subject[a]	Observed mean number of deferrals[a]	Predicted mean number of deferrals[a]	*p*-Value[b]
Combined, control	376	8.57	1.74	1.72	.8
Combined, experimental	422	7.91	1.73	1.75	
VS, control	195	9.09	1.70	1.67	.52
VS, experimental	211	8.26	1.73	1.76	
Protein, control	40	9.38	1.20	1.20	.73
Protein, experimental	49	9.43	1.29	1.28	
HCT, control	71	10.65	1.56	1.55	.63
HCT, experimental	58	8.45	1.43	1.44	

Abbreviations: HCT, hematocrit; VS, vital sign.

[a]Estimates are derived using the subgroup of donors with at least one deferral in the relevant category (combined, VS, protein, HCT).

[b]The *p*-values are associated with the null hypothesis: control = experimental. They are derived from the GLE Negative Binomial Model analysis (see model description).

and study donations ($n = 23, 137$) allowed for some analyses of short- to mid-term effects on repeat donations and donor deferrals.[5]

Prior to this study, very little controlled prospective data were available from peer-reviewed literature regarding repeat donation and deferral rates or reasons for deferrals in source plasma donors. The IMPACT trial offered a unique opportunity to further elucidate these items.

2 | MATERIALS AND METHODS

The study design and methods of the IMPACT trial have been described in detail before.[5]

For this exploratory analysis, the IMPACT trial database was used to examine repeat donations per donor, by study arm. Repeat donations were analyzed in the framework of negative binomial generalized linear regression models as well as by using descriptive statistics. The negative binomial model had study arm, gender, age, weight, and donation status as independent variables.

In addition, all captured donor deferral events were analyzed by lead cause and compared between the two arms using logistic regression and count data modeling approaches. Confidence intervals and *p*-values associated with the study arm effects were reported. The differences or effects associated with *p*-values <.05 were assessed as statistically significant.

3 | RESULTS

Repeat donation frequency ranged from 1 to 22 with a predicted mean of 6.82 in the control arm, and 1 to 22 with a predicted mean of 6.62 in the experimental arm. The predicted mean number of repeat donations was similar between the study arms ($p = .22$), as suggested by the negative binomial model-based inference (Table 1).

The predicted mean number of repeat donations in males, while not different between the study arms (7.16 control and 6.95 experimental; $p = .85$), was significantly higher ($p < .0001$) than the predicted mean number of donations in females (also not different between the study arms: 6.17 control and 6.0 experimental, $p = .06$) (Table 1, Figure 1A).

Naïve donors had on average 2.8/2.7 (control/experimental) fewer repeat donations during the trial than donors with a prior donation history, without any significant difference between the study arms ($p = .84$ and $p = .21$ for naïve donors and donors with a prior donation history, respectively) (Table 1, Figure 1B). Donor age and weight had significant positive effects on the predicted mean number of repeat donations ($p < .0001$ for each); however, the magnitude of their effect was relatively small (coefficient estimate 0.012 ± 0.001 for age and 0.0019 ± 0.0002 for weight).

In 23, 137 donations from 3443 donors, 798 donors (376 in control and 422 in experimental arms, $p = .80$) had at least one deferral (for any cause) (Table 2). A deeper analysis of individual causes for deferrals showed that 89 donors (40 control and 49 experimental) had deferrals associated with low protein levels, 129 (71 control and 58 experimental) had deferrals related to hematocrit levels, and 406 (195 control and 211 experimental) had deferrals associated with at least one of three vital sign parameters (pulse, blood pressure, and temperature) (Table 2).

Further analysis, focusing on estimation of the mean number of deferrals per donor with at least one deferral,

suggested that the mean number of deferrals in all categories of interest (any cause, low protein level, low hematocrit, or vital sign related) was not statistically different between the study arms (Table 2).

4 | DISCUSSION

Source plasma is the critical starting material for plasma-derived medicinal products, such as immunoglobulins and factor concentrates. Plasma donors should be valued for their contribution to the global supply. Their safety and comfort needs to be an absolute priority. The most frequent concern with higher-intensity plasma donations is hypotensive (hypovolemia/vasovagal) events.[6] Citrate reactions and phlebotomy-related issues are other short-term concerns.[6,7]

Mid- to long-term protein depletion has been suggested as a potential issue, particularly in frequent plasmapheresis donors.[8-11] The US regulations 21CFR630.15[12] and 21CFR640.65[13] have been put in place to ensure regular testing for protein levels and to prevent donors from falling below acceptable levels. Loss of bone density due to citrate-related calcium losses during repeated apheresis procedures has been raised as a theoretical risk,[14,15] but subsequent longitudinal studies did not confirm this.[16,17] Lastly, a Swedish case–control study identified a possible increased risk of non-Hodgkin lymphoma in frequent plasma donors.[18] However, a subsequent national cohort study by the same group concluded that there was no convincing evidence of an increased risk of any hematological malignancy.[19]

The IMPACT trial did not demonstrate differences in critical short-term donor adverse events (significant hypotensive or citrate- or phlebotomy-related issues),[5] and it was not designed to study mid- to long-term effects. However, the number and rate of repeat donations and the deferral rates attributable to specific causes, as observed in the large number of subjects and donations during the approximate 12-week trial period, may contribute to our understanding of potential longer-term effects.

Similar repeat donation rates between the study arms suggest that no significant disruptions to donor well-being were introduced with the new nomogram. Any substantial change in donor comfort, satisfaction, adverse events, or deferrals should have negatively impacted the repeat donation rate in the experimental arm.

Repeat donations were higher in donors with a prior donation history as well as in males. This is in line with prior observations.[20,21]

Donor deferrals patterns did not show significant differences between the two study arms. Of note, deferral rates related to low protein levels were similar, indicating that there was no meaningfully increased protein depletion in subjects in the experimental arm, despite the increase in collected plasma volume. This is in line with findings from another trial, where an intensified donation scheme did not lead to an increase in dropouts related to low protein levels.[22]

Further longitudinal research, such as an analysis of observational real-world data, will be needed to definitively answer the question of mid- to long-term effects. Specific protein concentration analyses in a longitudinal format (e.g., pooled analysis from the fractionation process) will be needed to answer questions related to plasma protein yield.

A limitation of this analysis is that the IMPACT trial[5] was not designed to study longitudinal mid- to long-term effects. This present study was an exploratory analysis that had not been prespecified. Repeat donation rates may have been biased by the small reimbursement provided to donors for each trial donation under study conditions (fixed amount, same for both arms). Moreover, information on first-time donor status relied on information provided by the donors and could not be verified for potential donations outside of the study collection network. Lastly, the IMPACT trial was conducted during the months of January to March, which are known to show lower hypotensive donor adverse event rates. This may have also had an influence on deferral and repeat donation rates as compared with other months.

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CONFLICT OF INTEREST

Dr Hartmann reports being employed by and holding equity interest in Haemonetics Corp. Mr Ragusa reports being employed by and holding equity interest in Haemonetics Corp., and holding a related patent, assigned to Haemonetics Corp. (US 2018/0344910 A1). Drs Burchardt, Manukyan, Popovsky, and Leitman report consulting fees from Haemonetics Corp.

AUTHOR CONTRIBUTIONS

All authors participated in design and execution of and the data collection for this work. JH and ZM analyzed the data for this exploratory analysis. JH wrote the initial draft, which was commented on and edited by all authors.

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