

How do we forecast tomorrow's transfusion: the future of hematopoietic stem cell donation

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Traditionally, hematopoietic stem cell (HSCs) donation has been used for the treatment of blood cancers via allogeneic hematopoietic cell transplantation (HCT). However, over the past three decades, the field of stem cell research and development (R&D) has witnessed extraordinary progress resulting in the approval of several stem cell-based therapies for the treatment of multiple rare diseases (1). To date, there are twenty five cell and gene therapies approved by the Food and Drug Administration (FDA) available for direct patient use in USA, and fourteen approved by the European Medicines Agency (2) for patient use in Europe as of 2021(3, 4). These therapies treat different types of blood cancers like leukemias and lymphomas, congenital immunodeficiencies, inherited blood disorders such as sickle cell disease, cartilage defects, and neurological disorders(5). However, many current ongoing trials on stem cell therapies encompass a wide array of conditions, including cardiovascular and liver diseases, rheumatoid arthritis and osteoporosis, metabolic conditions such as type 1 diabetes, and dermatological such as male pattern baldness (1, 6, 7). Consequently, as the speed of translational research on stem cells accelerates, it is not too far-fetched for us to envisage a future where cell therapies can be used for the treatment of diseases previously considered incurable. Nor is it unlikely that stem cells donated from a single donor might be used for the treatment of multiple people, as opposed to a single recipient.

When contemplating this exciting future for cell-based therapies, we must also reflect upon donors, and explore their readiness for their donations to be used for these purposes. Will donors still be willing to donate stem cells if these cells were to be used for the treatment of conditions deemed as not life-threatening, such as male-pattern baldness? How might such a change in direction influence donor recruitment in the future? Hematopoietic stem cell donor registries worldwide experience attrition amongst registered donors, with donor reasons accounting for 47% of transplant cancellations(8). Furthermore, the rise of the COVID-19 pandemic in early 2020 significantly impacted donor recruitment(9). As such, there is a need to determine how stem cell donations can be sought and a pipeline sustained for the development of cell-based therapies without disrupting the associated donation system of stem cells for patient transplantation. Therefore, it is imperative to consider where current and potential donors stand with regards to donating for multiple recipients and donating to treat quality-of-life (QoL) conditions, as opposed to life-threatening conditions. In this guest editorial, we provide a summary of factors that influence donors' decisions to donate for novel treatments, how these factors might impact the translation of stem-cell based therapies into clinical practice, what challenges might arise as a result of such donations, and recommendations on how to possibly overcome them.

In 2019, an online survey was launched by Anthony Nolan (AN), a UK not-for-profit organization and stem cell donor registry, to assess prospective donors' and donors' attitudes towards donating cells for novel treatments R&D. The survey was followed by seven focus groups, which took place with members of the public, prospective donors, and donors, to explore in-depth the issues raised in the survey. During the focus groups, participants were asked about issues such as their donation being used for multiple recipients and donating stem cells to treat QoL conditions. We provide a summary of our findings from the focus groups below, with short extracts from participants included.

Donations for multiple recipients

Participants were asked about donating cells to help one recipient and multiple recipients, and the benefits and losses that might arise from donating to multiple recipients. Some donors viewed donating for multiple recipients as beneficial, especially if there was no additional inconvenience or cost to donors. Some donors contemplated if donations being used to help multiple recipients might encourage more donors, and act as a “pull factor”, while other donors and public participants were keen to position the idea of helping multiple recipients as an “added bonus”, stating that helping one person is and should be sufficient when deciding to donate. In effect, the number of people being helped should not be a motivating factor when making the decision to donate.

Participants were also asked how they understood the relationship between donors and recipients and explored how important contact was between both parties. Some donors explained they would be disappointed if they were unable to learn of the outcome of their donations, but it would not change their mind to donate if needed. Other participants appeared indifferent to not being able to have contact with multiple recipients and drew comparisons with blood donation, whereby a donation was considered to help multiple anonymous people, and blood donors continuing to donate despite not receiving feedback on individual recipients. Yet, some donors did raise concerns surrounding the connection between donors and recipients, and that not being able to offer a level of contact might negatively impact upon the recruitment of donors. They expressed worry that donating to multiple recipients might diminish the connection between donors and recipients as the energy, drive, and urgency generated by donating to one specific person to save his or her life might be lost by donating to more than one recipient. These participants drew upon the influential power of “success stories” when donors and recipients meet and have a “Hollywood moment”, to encourage and motivate future donors. While not all donors felt the need to have their own “Hollywood moment”, they still appreciated hearing and reading about others’ success stories. Nevertheless, the majority of public participants prioritized the needs of recipients over the needs of donors when stating that it was more important to help multiple patients than donors to receive information on recipients. The points raised during the focus group discussion on donations for multiple recipients are summarized in Figure 1.

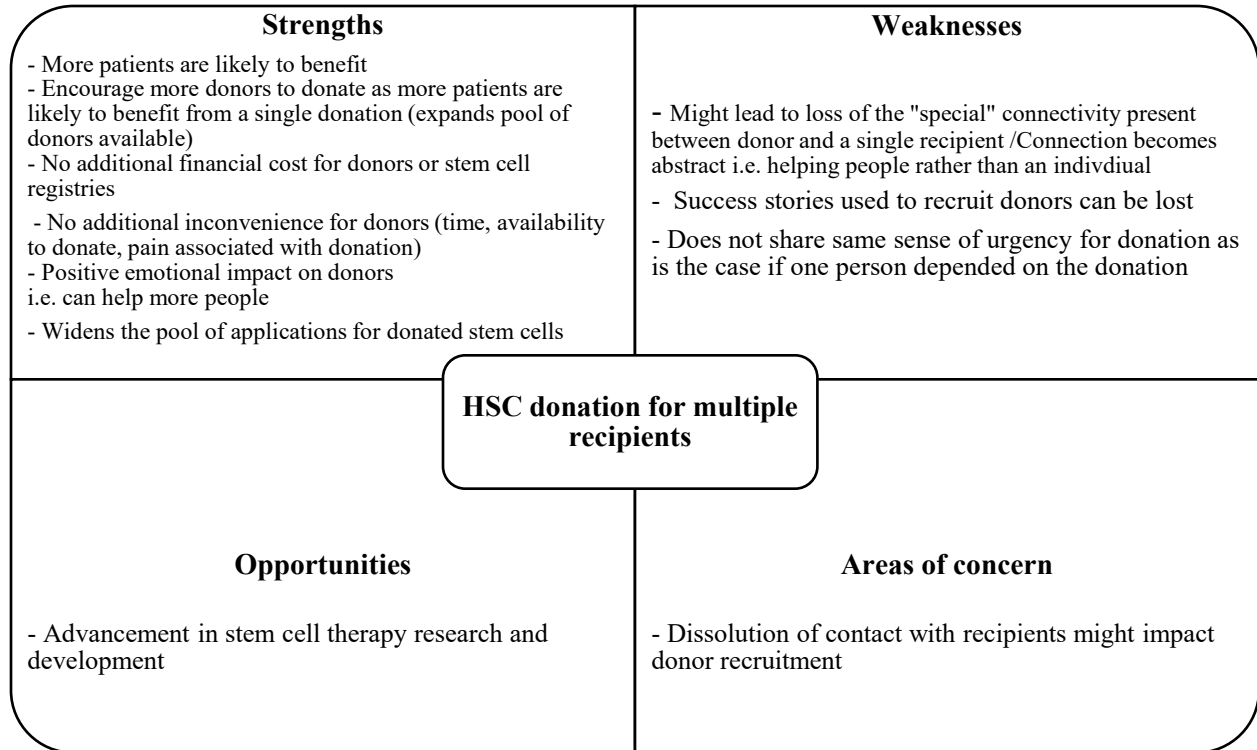


Figure 1. Situational assessment of stem cell donations made for multiple recipients

Donations for Quality-of-life Conditions

Participants were asked what health conditions they would be willing to donate their stem cells for e.g. conditions that were life threatening, or limiting a person’s QoL. Examples were given to help participants explore the topic such as rheumatoid arthritis, Parkinson’s disease, dementia, and male pattern baldness. Participants were also asked to discuss the level of commitment from donors for QoL conditions in comparison to life threatening conditions. The majority of donors and public participants considered it acceptable to ask people to donate HSCs for QoL conditions. Donors envisaged that the pool of donors might widen with the number of health conditions being addressed as the public were deemed to have a personal connection with at least one of the QoL conditions discussed. Some donors acknowledged that by AN helping QoL conditions it might increase awareness of their brand and work, and people might be more likely to fundraise for the organization. Participants presented this as an ethical decision for AN to make, and the ethics for such a decision should be considered, including the possibility of AN making a profit which could then be returned to research that supports AN’s mission.

Alternatively, many donors expressed reservations as it was anticipated that fewer people would donate, as the motivation to donate was typically based upon a personal connection with the illnesses being targeted. Donors were therefore concerned that the support for AN might decrease if the organization extended its remit to incorporate QoL conditions. A minority of donors were also unsure if people would donate for QoL conditions given the pain experienced when donating.

Some donors were concerned that there may be insufficient donors available to support the work of AN for life threatening conditions if the organization also supported QoL conditions. Additionally, there were concerns raised by some donors that if people are asked to donate stem cells for QoL conditions, then they might also be asked to donate stem cells to enhance and improve the lives of 'healthy' people. Consequently, a hierarchy of illnesses formed during the focus groups, with degenerative conditions taking higher priority and conditions deemed "cosmetic" or based on "vanity" taking less priority. Public participants made a connection between "cosmetic" conditions and mental health, and how this might impact an individual's quality of life and therefore expressed their support for some "cosmetic" conditions. Finally, donors would wish to be informed if their donated cells were to be used for QoL conditions. Comparisons were made to the opt out process surrounding organ donation to reflect donors' wish for a layered consent so donors could decide how they would wish for their cells to be used e.g. research, treatment, researching QoL conditions, treating QoL conditions, researching life-threatening conditions, treating life-threatening conditions, and then decide which conditions are acceptable to them e.g. Parkinson's disease and leukemia etc.

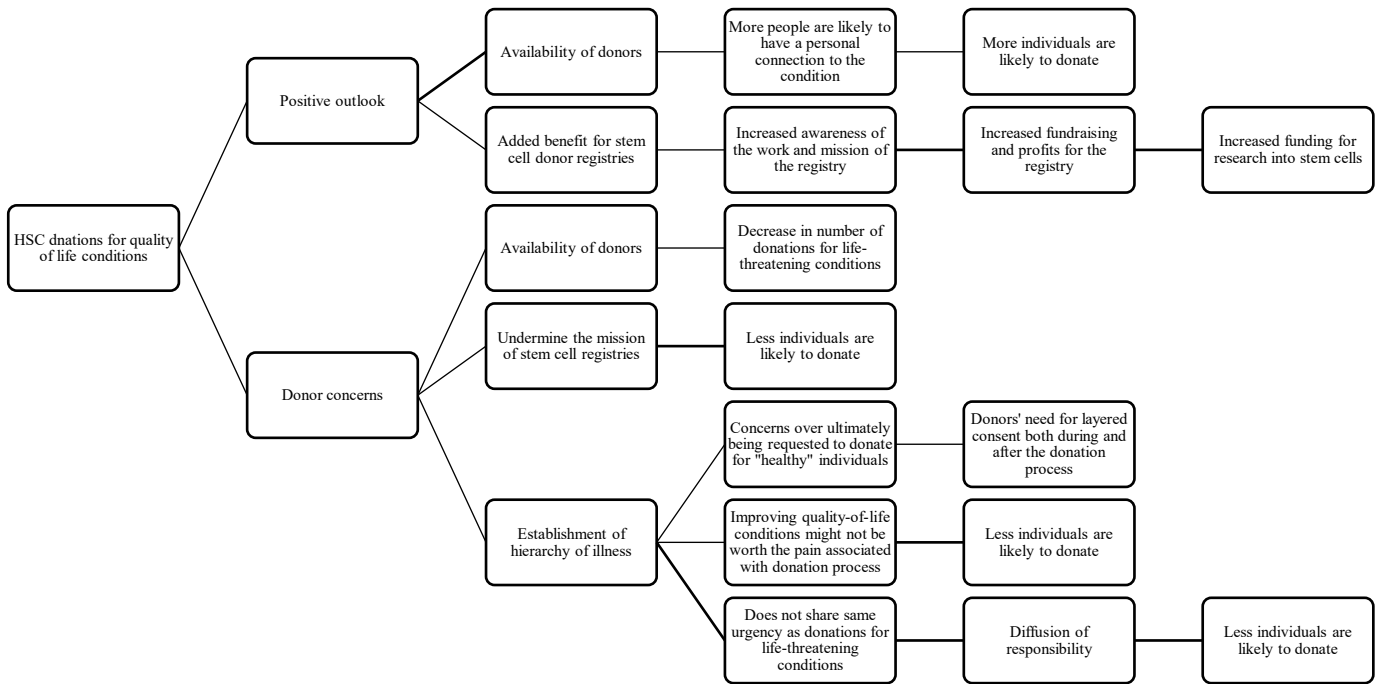


Figure 2. Overview of factors influencing decisions regarding HSC donations for quality-of-life conditions

Discussion

Conventionally, HSCs donations have always been linked to their direct use for HCT; a donor would undergo the process of stem cell collection, with the end goal of using these cells to save the life of an HLA-matched individual suffering from a life-threatening disorder. Therefore, HSCs donation intended for the manufacturing of cell-based therapies aimed at treating multiple individuals is relatively uncommon ground for donors presently. Yet, the initial responses from the focus group discussions are positive, with both donors and public participants being generally open to the idea of donating stem cells to treat conditions that significantly impact QoL.

Participants were in support of HSCs donations for multiple recipients and highlighted the positive impact such donations might generate. This includes encouraging more individuals to donate and generating a positive emotional impact onto donors, as one donor equated donations for multiple recipients to “saving a nation”. Donors’ agreeableness to donations for QoL

conditions is crucial to expand our understanding of stem cell-based therapies and to advance their development. Nevertheless, we must also consider how such donations might impact donor recruitment for transplant patients given current concerns within the transplant community on donor attrition (8). As advancements in stem cell-based therapies expand, the need for donors will undoubtedly increase. This will be of concern to the transplant community, stem cell donor registries, and stakeholders involved in stem cell therapy research. Collaborative efforts need to be established on a regulatory level in order to maintain the advancement of novel therapies, without compromising cancer patients' access to unrelated HCT.

Interestingly, the donor-recipient relationship was a prominent subject during the focus groups. In particular, donors and public participants highlighted the importance of maintaining contact between donors and the role it plays in motivating donors to register and donate. Participants used terms such as "special feeling" to refer to the emotional experience generated by donating to save a person's life. They queried if the connection with the recipient/s could become abstract, and the "success stories" used in campaigns to recruit donors could become lost when more than one recipient is involved. Others worried that donors might feel less compelled to donate if one person does not depend on their donation, as is the case with HCT, and instead might leave it to other members of society to donate. These responses not only suggest that the donor-recipient relationship plays a significant role in influencing donation decisions, but that underlying the portrayal of this relationship is a power dynamic. Recipients were described as "not having what was needed within themselves" for their health to improve, and donors demonstrated awareness of their "own power to change someone's life". Such portrayal is not unexpected as this imbalance of power, and its potential to culminate in saving a life, has long been employed in donor recruitment campaigns and on social media by international stem cell agencies, donor organizations, and stem cell donor registries to disseminate success stories of matched donors and recipients and encourage more donors (10). By engaging with readers' emotions and thoughts, these stories act as powerful tools to aid in educating individuals and spreading awareness. In fact, a recent initiative in Canada employed the use of a library of stem cell donation stories on social media in an effort to encourage more donors to join a local stem cell register(11). The results of this initiative revealed that when employed to improve donor recruitment, success stories can be highly efficacious, as the total number of recruited donors

increased by 15% within the first five months of its launch (11). The study also found that the knowledge and attitudes of eligible potential donors towards stem cell donation improved, reaffirming the significant influence of success stories. Consequently, a shift from the current narrative utilized in donor recruitment campaigns (emphasizing notions such as “saving lives” and “becoming heroes”) towards a narrative that highlights the importance of improving quality of life and the influence cell-based therapies have on the health of multiple individuals, may be necessary to encourage more donations for the development of these therapies.

Conclusion

While the responses generated during the focus groups indicate a promising future for the field of stem cell therapy R&D, the issue of maintaining donor availability for cell-based therapies without disrupting the flow of donations for transplantations remains a concern. The literature is rich with studies exploring alternative sources of stem cells, ranging from adipose-derived stem cells to menstrual blood-derived stem cells, and their potential role in regenerative medicine (12, 13). These discoveries may offer a transformative solution to the issue of donor availability and could increase donor recruitment given the easier and painless process of collection (12). Despite that, a more urgent solution is required should we continue to envision a future where cell therapies hold the ability to cure Diabetes, Alopecia, or Alzheimer's. In 2011, the ruling of *Flynn vs. Holder* made financial compensation for peripheral stem cell donation legal in the United States, sparking heated debates on whether stem cell donors should be paid for HSCs donation. (14). Soon after, the World Marrow Donor Association (WMDA) released a statement rejecting donor remuneration for HSCs donation, asserting that donor payment will have detrimental effects on both donors and recipients (15). However, the increasing dependency on HSCs donation for cell therapy R&D might reignite the debate on donor payment. As the WMDA embarks on updating its statement on HSCs donor remuneration, lessons learned from previous experiences with donor payment for research purposes must be considered to understand how current evidence on donor payment translates in the context of HSCs donation for cell therapy R&D and to ensure donors' welfare remains a priority. Finally, stem cell donor registries may wish to consider introducing chronic conditions and the impact these conditions have on patients' lives in recruitment campaigns to increase public and prospective donors' knowledge

and decrease ambivalence. Nevertheless, more studies are needed to explore in depth the motivators and barriers of prospective donors towards donating stem cells for QoL conditions.

Consent statement

Informed consent was obtained from all individual participants in this project. The project received approval from the Research Ethics Committee at the Faculty of Health and Medicine (FHM REC) at Lancaster University.

Funding Statement

This project was funded by Anthony Nolan.

Disclosure of interest

C.A. Donor Care Physician at Anthony Nolan

L.M. Past chairperson and current member of the institutional review board (IRB) at Anthony Nolan

Acknowledgments

We wish to acknowledge the generous financial support from Dr Philip Welch that has funded Dr Lina Hamad's research assistant role whilst writing this paper.

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