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Prospective donors' perspectives on hematopoietic cell donation for cell and gene therapy research and development

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Abstract

Introduction: The debut of allogeneic cellular products makes the field of cell and gene therapy (CGT) heavily dependent on healthy donors providing hematopoietic stem cells (HSCs). This change in landscape will introduce new ethical quandaries for stem cell donors as their role evolves with the introduction of stem cell donation for CGT research and development (R&D). The objective of this study is to explore prospective donors' attitudes and perceptions towards donating cells for novel treatments R&D.

Methods: A survey was launched in 2019 targeting prospective donors on a UK unrelated blood stem cell donor register. The survey reported on participants' demographics, willingness towards donating HSCs for novel treatment research, and degree of comfort with the donor registry collaborating with and receiving payment from external organizations. A total of 20,000 potential participants were contacted. The survey was open for completion for two weeks between January and February 2019. Data analysis was performed using SPSS software (version 28.0.1.1). Moreover, 94 participants provided qualitative responses, which expanded upon and/or explained their quantitative responses.

Results: In total, 2440 prospective donors responded to the survey. Most participants (87%) indicated they would be willing if approached to donate for research and novel treatment development. Most participants were comfortable with the donor registry collaborating with external organizations (91%) and with the donor registry receiving payment (80%). Participants'

qualitative responses mapped on topics such as trust, informed consent, transparency, privacy, and commercialization.

Discussion:

The results are consistent with other studies in the literature assessing donors' willingness to donate blood for biobanking and embryos for stem cell research. A hierarchy of donation purposes emerged based on participants' responses, whereby therapeutic donations for patients in need take precedence over donations for R&D. This could be a consequence of current recruitment models to attract donors. In addition, it was evident that donors experience a moral obligation and keenness to influence the direction of any donations made. As advancement in the field may precede official regulatory guidance, donor organizations engaging in CGT should practice self-regulation to ensure the sourcing and supplying of donor cellular material to the commercial sector is conducted within a framework that safeguards donors' needs and wellbeing.

Abbreviations:

CGT: Cell and gene therapy(ies), HSCs: Hematopoietic stem cells, R&D: Research and development, AN: Anthony Nolan.

Introduction

Three decades of ongoing stem cell research and their potential use to cure human diseases and injuries have given rise to a transformative new category of therapeutics known as cell and gene therapies (CGT)[1]. The CGT industry is on a fast-tracked path towards successful translation into clinical practice. Several therapies, predominantly for haematological and immunodeficiency diseases, have already been authorized for clinical use [2]. Moreover, there is

a vast pipeline of developments for CGT to treat cardiovascular, neurological, and musculoskeletal diseases [3]. Globally, 1,340 clinical trials on CGT were taking place by the end of June 2022 [4]. In the UK, the number of CGT clinical trials is on the rise, with 168 ongoing trials in 2021, a 9% increase from 2020 [5]. In parallel, initiatives have been established to accelerate patient access to these therapies. In 2021, over 5000 individuals across the NHS and the industry received training in the delivery of advanced therapies to patients, including CGT [5].

The debut of allogeneic cellular products offers the potential to retrieve products in quantities that may be unattainable from autologous sources [6]. This makes the development of allogeneic CGT heavily dependent on healthy donors providing hematopoietic stem cells (HSCs). Consequently, the rapid growth of the CGT industry places stem cell donor registries under significant pressure to adapt. This is critical as such a transition introduces complex issues that might have several implications. First, the change in landscape will give rise to new ethical dilemmas as the conventional role of stem cell donors evolves with the introduction of HSCs donation for CGT research and development (R&D). Second, in order for advancements in CGT to continue, donor registries must be able to meet the increased demand of the CGT industry for HSCs without disrupting the existing donation structure for transplant patients. Third, sourcing and supplying donated HSCs entails a need for partnerships between stem cell donor registries and external organizations in the CGT industry. Partnerships could take place with pharmaceutical companies, universities, or other public and private institutions and could result in exchange of payment.

These emerging topics are likely to influence stem cell donors when making their decisions to donate, making donor involvement a key parameter to consider. For example, research into donors' attitudes on donating biospecimens for biobanking and stem cells for induced pluripotent stem cell (iPSC) research recognizes altruism as the principal motivating factor to donate [7, 8]. Yet, some donors demonstrate concerns over donating stem cells and biospecimens for R&D purposes [8]. This is particularly prominent when research bodies associate with and receive funding from for-profit organizations [9]. Under such circumstances, donors exhibit concerns over privacy of genetic material, disclosure of information during informed consent, and commercialization [8-10]. Yet, trust seems to be a key influencer in guiding these views (Table 1). Public trust is essential in fostering public engagement and encouraging donation [11]. Consequently, the wellbeing of donors and the potential for harm and exploitation within this new paradigm of donation practice are key issues for stem cell donor registries to consider. Trusted donor organizations and stem cell registries must carefully determine how to navigate this transition without risking the disruption of the trust-based relationship with prospective donors. In order to achieve that, it is essential to understand prospective donors' perspectives on the sourcing of their stem cells by donor registries to external organizations for CGT development. Accordingly, a survey was launched in 2019 by Anthony Nolan (AN), a UK charity and stem cell donor registry facilitating life-saving stem cell donations from volunteer donors. The survey aimed to explore prospective donors' willingness to donate HSCs for novel treatment R&D and their degree of comfort with AN collaborating with and receiving payment from external organizations. In January 2019, there were 690,000 active donors on the AN register.

Table 1. Overview of ethical concerns related to stem cell donation for research and biobanking

Methods:

Sample selection

The population of interest included prospective donors on the AN unrelated donor register in the UK. Donors are accepted on to the AN register from 16 years of age and remain on the register until they are 60 years of age. Approximately 20,000 people on the register were contacted with the aim for a response rate of 2,000. The 20,000 people contacted were selected from the AN register, specifically from those who had opted into such communications from AN. A stratified sample was obtained using Alteryx, a data analytics tool, ensuring that donors from diverse geographical regions, ages, ethnicity, and gender were selected. In total, data was collected from 2440 registered prospective donors.

Survey design and administration

An email with a link to the digital survey and to the AN website was sent out informing potential participants about the research and the opportunity to complete the survey. A reminder email was sent out one week later. The survey was open for completion online for a period of two weeks during January and February 2019. The project received approval from Research Ethics Committee at [redacted]

Measures

The measurement instrument for the survey was developed in accordance with the guidelines of the FHM REC. To ensure comprehensibility, the draft survey was piloted by 10 volunteers on the AN Donor Panel who were invited to participate and selected to match the demographics of potential participants in the study. The measures of the survey assessed prospective donors' willingness to donate cells to be used for research towards developing new therapies, and their degree of comfort with AN collaborating with external organizations and receiving payment from these organizations. The survey constituted 21 items including the above-mentioned variables in addition to prospective donors' demographics. All the items used were closed-ended questions, except for the final item, which allowed participants to leave any comments they had about the survey. Items in the survey were scored either using nominal scales or ordinal scales. Demographics were assessed using multiple-choice questions. Sample items from the survey are provided in Appendix 1. The STROBE guidelines for reporting observational studies were followed [13].

Data analysis

Arrangement and cleaning of data was performed on Microsoft Excel. Date entry and analysis was performed using SPSS software (version 28.0.1.1). Descriptive statistics are reported for categorical variables. Comparison between participants' demographics and their willingness to donate for R&D, degree of comfort with AN collaborating with external organizations, and degree of comfort with receiving payment was performed using Chi-square testing for independence. A p-value of less than 0.05 was considered statistically significant. Participants were not encouraged to leave comments related to the survey. However, 94 participants provided qualitative responses which expanded upon and/or explained their quantitative responses. The

qualitative data was themed according to overarching broad topics. These topics mapped on participants' reasons for donation, concerns over donation, and facilitators of donation for CGT research and development.

Results

Demographic characteristics

The total number of participants was 2362 after missing values were removed from the data, achieving the expected response rate. Of these participants, (67%) were females and (33%) were males. Most participants were between 21 and 40 years of age, (14%) were over 51 years old. The overwhelming majority of respondents were white British (94%). Over half (52%) of participants were classified as having higher education, defined as attaining any undergraduate or graduate degree, whereas (48%) of participants reported high school level education. Most participants (86%) were in some form of employment, including self-employment or voluntary work (Table 2).

Table 2. Characteristics of participants

Participants' willingness to donate stem cells for research and novel treatment development

Most participants (87%) indicated they would be willing if approached to donate HSCs for novel treatment research and development. Those who were uncertain about whether they would be willing to donate constituted 12% and only 1% were unwilling to donate. Among the participants who were unsure of their willingness to donate, 92% were comfortable with the AN

collaborating with external organizations and 85% were comfortable with AN receiving payment from external organizations. There was no statistically significant association between participants' age, gender, and ethnicity and their willingness to donate for CGT development (p value = 0.713, 0.345 and 0.807, respectively). A statistically significant association was present between participants' willingness to donate for R&D and education level (p value = 0.011).

Participants' degree of comfort with AN collaborating with external organizations

Most participants were comfortable with AN collaborating with external organizations for novel treatment R&D (Table 3). There was no statistically significant association between age, gender, and ethnicity and participants' degree of comfort with external collaborations (p value = 0.207, 0.608, and 0.099, respectively). A statistically significant association was observed when comparing participants' level of education with their degree of comfort with AN collaborating with external organizations (p value < 0.001) (Table 4).

Participants' degree of comfort with AN receiving payment from external organizations

Most participants were comfortable with AN receiving payment (Table 3). There was no statistically significant association between participants' age, gender, and ethnicity and their degree of comfort with AN receiving payment from external organizations (p value = 0.135, 0.985, and 0.595, respectively). A statistically significant association was observed between participants' level of education and degree of comfort with AN receiving payment (p value < 0.001) (Table 4).

Table 3. Participants' degree of comfort with Anthony Nolan (AN) collaborating with and receiving payments from external organizations

Table 4. Comparison between participants' level of education and degree of comfort with Anthony Nolan (AN) collaborating with and receiving payment from external organizations

Qualitative responses

For some participants, the desire to help for the benefit of others was the main motivating factor behind their willingness to donate HSCs for R&D of novel therapies. Collaboration with external organizations was viewed positively and was considered as a step forward for AN to improve the overall health and quality of life of others. While some participants demonstrated keenness to donate HSCs for R&D unconditionally, others constructed a hierarchy of donation purposes. Some participants had concerns over infringement of privacy, especially if external collaborations with third parties like pharmaceutical companies were to take place. Others conveyed apprehensions over their donations leading to profiteering and expressed worry that this might compromise universal access to healthcare and lead to overpriced treatments.

Participants suggested that informed consent and transparency over the nature of collaborations could relieve some of their concerns. Finally, some responses conveyed a sense of distrust amongst participants towards collaboration with pharmaceutical companies. In contrast, a great deal of trust was instilled with regards to AN, and it seemed that this degree of trust alleviated some of the worries participants expressed concerning partnerships with external organizations.

Table 5. Summary of emerging themes underlying participants' reasons for donation, concerns over donation, and facilitators of donation for cell and gene therapy research and development

Discussion:

The overwhelming majority (87%) of prospective donors were in support of donating HSCs for novel treatment R&D. The results are consistent with other studies in the literature assessing donors' willingness to donate blood for biobanking and embryos for stem cell research [7, 14]. Some participants would donate stem cells for CGT development only if these cells were a by-product of the primary purpose of donation. Others demonstrated willingness to donate for CGT development only at an age when their stem cells are no longer viable for the treatment of patients. Underlying these responses is a hierarchy of donation purposes, whereby therapeutic donations for patients in need take precedence over donations for R&D. While most participants were amicable to HSCs donation for R&D purposes, some responses suggest current donors are relatively unacquainted with this purpose of donation. Generally, donor recruitment organizations approach eligible donors through campaigns that primarily appeal to the public and potential donors' sense of altruism and beneficence [15, 16]. Perhaps donors' construction of a hierarchy of value is a consequence of current recruitment models employed by donor organizations and stem cell registries to attract donors. Under such assumptions, stem cell donor registries could explore how changing the recruitment journey for donors (through the introduction of HSCs donation for CGT R&D in recruitment initiatives) may influence donors' current perceptions on the different purposes of HSCs donation.

A substantial number of participants felt comfortable with AN collaborating with external organization for the development of new therapies. Similarly, most participants were comfortable with AN receiving payment from external organizations. Nevertheless, many participants raised several considerations that would factor in their decision-making as prospective HSCs donors for CGT R&D (Figure 1). First, the involvement of external organizations was coupled with apprehensions related to privacy and security of genetic material, further substantiating the well-documented donor concerns over the risk of reidentification and the potential for discrimination based on retrieved genetic information [8]. Second, some donors exhibited a moral responsibility to maintain universal access to healthcare when deciding to donate and relayed concerns over collaborations leading to profiteering and inaccessible, overpriced therapies. Such perceptions go in line with the effect of commercialization in the context of stem cell research [17, 18]. This could be due to donors' fragmented trust towards pharmaceutical companies compared with trusted donor organizations and their perceived beliefs that commercial companies are not as altruistic in their endeavours as donor organizations might be. The publication of a recent high-profile study delineating under-reporting of payments made by pharmaceutical companies to patient organizations could further validate these concerns [19]. Nevertheless, many participants expressed a need for more information on the circumstances surrounding these collaborations prior to deciding on how comfortable they are with the stem cell donor registry partnering with external agencies.

Consequently, transparency is paramount to secure donors' trust in not just the donor organization, but any possible collaborators. Full disclosure over the nature of the partnership project, the payment process between the involved parties, and any potential commercial value

that might arise will allow prospective donors to be fully informed when making their donation decisions. Further, donor organizations and stem cell registries should carefully consider anonymity concerns when drafting policies and practices on supplying donated HSCs to the private industry. Donors should be well informed on the General Data Protection Regulation (GDPR). Under this law, genetic data is listed as sensitive personal information that can be processed only if overt consent from the data subject has been obtained [20]. The above-mentioned matters require consideration by donor organizations and stem cell donor registries wishing to engage within the CGT industry. Donor organizations should practice self-regulation to ensure the sourcing and supplying of donor cellular material to the commercial sector is conducted within a framework that safeguards donors' needs and wellbeing. This is especially important as advancement in the field may precede official regulatory guidance on the facilitation of HSCs donation between donors and the commercial sector. Moreover, even though the results present a positive response from prospective donors to collaboration and income generation, stem cell donor registries need to consider how to meet the increased demand of the industry for donated cellular products whilst continuing to facilitate life-saving stem cell donations from volunteer donors.

Interestingly, most prospective donors' who were unsure of their willingness to donate for novel treatment R&D were in favour of AN partnering with and receiving payment from external establishments. This suggests that factors besides those raised in participants' responses may be involved in the decision-making process for donors regarding donations for CGT. The most common perceived incentive for HSCs donation among potential donors is the belief that donations save lives, and donors possess the ability within themselves to help [21, 22]. These

Figure 1. Overview of donor issues to be considered by stakeholders engaged in stem cell donation for allogeneic cell and gene therapies (CGT) research and development

beliefs represent the scaffolding by which the donor-recipient relationship is built and through which it remains anchored. However, Diamond et al. discuss how relationships constructed through donation can shift as the means and reasons for donations proliferate and become more complex [23]. The advent of allogeneic therapies serves as a prime example of such change by expanding the role of stem cell donors beyond its traditional boundary. Through the introduction a new purpose of donation, allogeneic CGT blurs the direct link currently present between donors and recipients. Understanding how this transformation is perceived by potential donors is crucial for the CGT industry to continue its growth at pace.

Implications for future policies and practices

It was possible to gain insight into the perceptions of some prospective donors on pharmaceutical companies, and the disparities that surface when comparing donors' views on private establishments versus trusted donor organizations. It was also evident that some donors experience a moral obligation and keenness to influence the direction of any donations made. Accordingly, it would be worthwhile to disentangle donors' perceptions surrounding the private sector and gain deeper insight into what is deemed to be 'ethical' engagement between trusted donor organizations and commercial institutions. Further inquiry into donors' perceptions on donation for CGT R&D is necessary to construct ethical policies and outline donation practices that ensure the safety and welfare of donors. Now is the time to reform the regulatory agenda and ensure donors are at the forefront of issues in need for consideration within this budding field.

Limitations

It is worthy to note the timing of the data collection in relation to the COVID-19 pandemic. The role pharmaceutical companies played in the recent pandemic could result in a shift in

perceptions and attitudes of prospective donors. For example, a recent study published by the Association of the British Pharmaceutical Industry revealed a 24% increase in the public's positive views of the industry since the pandemic [24]. It is therefore possible that a similar shift in perceptions may be present amongst prospective donors today. Another limitation of findings is related to the sample population. Most participants were white British and minority groups were scarcely represented. This reflects the general under representation of minority groups in stem cell donor registries and could therefore bias the results of this survey. Nevertheless, we believe the sample size of this study along with the sample selection method ensure generalisability as the range of participants was wide; both males and females ranging across several age groups and educational backgrounds were included, and all major outcomes were represented.

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 [redacted]

Data availability

Data is not available due to ethical restrictions. Due to the nature of this study, participants were recruited on the basis of informed consent and did not agree for their data to be shared publicly. Permission was not requested to share data when submitting the ethical approval form because of the commercial sensitivity around the aims and objectives of the wider research study and the resulting data analysis. We therefore are unable to deposit the data in a repository.

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Appendix 1

Table 1. Questions included in survey assessing prospective donors' attitudes and perspectives on donating for novel treatment research and development

Table 1. Overview of ethical concerns related to stem cell donation for research and biobanking

Ethical concern	Context under which ethical concerns emerge	Reference
Trust	• Among the public, trust in university-funded research on preserved stem cells in biorepositories is high but decreases when researchers associate with private, for-profit institutes. • Collaborations with private preservation enterprises may be viewed by the public as a compromise to public/academic institutes' commitment to their mission of public service and would lead to a loss of trust in public/academic sectors.	Master, Z. et al. [9]
Informed consent	• Consent emerges in relation to subsequent commercialization of products and therapies that result from research on biobank samples. Consent as an ethical concern is also prominent when financial support by private bodies is provided to public biobanks, especially when this type of funding has not been attended to in the initial consent process.	Caulfield T. et al. [10]

Privacy	• The potential for genetic health information leading to reidentification is associated with great concern for iPSC donors. This concern relates to the possible risk of discrimination and stigmatization such information may lead to. • Involvement of private funders may aggravate privacy concerns for biobank participants. Participants may deem their privacy violated if data sharing were to take place with for-profit organizations, inevitably compromising the public's trust in biobanks.	Isasi R. et al. [12] Caulfield T. et al. [10]
Commercialization	• Potential donors for iPSC research demonstrate concerns over the distribution of any resulting commercialized therapies. These concerns are demonstrated in the context of the immortalization of cell lines and the distribution of profit if therapies were to arise from them.	Dasgupta et al.[8]

Table 2. Characteristics of participants

Characteristics of the study sample (n=2362)	Percentage
Gender	
Female	67%
Male	33%
Age	
16-20	14%
21-30	37%
31-40	20%
41-50	16%
51+	13%
Ethnicity	
White	94%
Asian or Asian British	1.9%
Black, Black British, Caribbean, or African	0.6%
Mixed or multiple ethnic groups	3.3%
Other ethnic groups	0.2%
Education Level	
Higher Education	52%
Lower Education	48%
Employment Status	
Employed full time	64%

Employed part time	22%
Not employed	14%

Table 3. Participants' degree of comfort with Anthony Nolan (AN) collaborating with and receiving payments from external organizations

	Collaboration with external organizations	Receiving payment from external organizations
Strongly agree or agree	2145 (91%)	1891 (80.1%)
Neutral	187 (8%)	387 (16.4%)
Strongly disagree or disagree	30 (1.3%)	84 (3.6%)
Total	2362 (100%)	2362 (100%)

Table 4. Comparison between participants' level of education and degree of comfort with Anthony Nolan (AN) collaborating with and receiving payment from external organizations

		Comfortable with collaboration	Uncomfortable with collaboration	Comfortable with receiving payment	Uncomfortable with receiving payment
Higher Education	**Count**	1087	23	947	60
	% Within Education Level	89%	1.9%	77.4%	4.9%
Lower Education	**Count**	1058	7	944	24
	% Within Education Level	93%	0.6%	83%	2.1%
Total	**Count**	2145	30	1891	84
	% Within Education Level	91%	1.4%	80%	3.6%

Table 5. Summary of emerging themes underlying participants' reasons for donation, concerns over donation, and facilitators of donation for CGT R&D

Themes	Participant quote
Altruism	"I am very happy to donate my stem cells to anyone that needs them or for research." (Female, aged 51+). "Very happy to participate in whatever way I could assist." (Male, aged 51+). "I like to think that there is collaboration which is wider than the initial cause that AN set up for. To improve the health and quality of life for current and future individuals, research and utilizing current resources such as the database of donors is a part of this." (Female, aged 40-51).
Hierarchy of donation	"I would be willing to allow some of the donation to be used if the majority of the donation was for a patient (i.e., the research sample was a by-product)." (Male, aged 40-51). "I'd be happy for my cells to be used for research with other companies provided that isn't the sole reason they were obtained - I'd rather know they were directly being used to treat someone." (Female, aged 21-30). "I would be happy to donate at an age where I would have to leave the register (so my cells are no longer viable for treating someone but hopefully still viable for research)." (Female, aged 21-30). "I appreciate the importance of research, but I feel strongly that I would not feel okay losing the ability to donate to someone when they need it." (Female, aged 21-30).

Privacy	"The only issue I would wish to be reassured on would be the security of data sharing between AN and other organisations and the appropriateness of any payments between the parties... this would extend to DNA profiling, personal information security etc." (Male, aged 51+). "I would be happy if there was collaboration with third parties to save lives but would be concerned about third party data usage." (Male, aged 21-30).
Commercialization	"I wouldn't participate if there was any profit going to pharmaceutical companies." (Female, aged 31-40). "I feel comfortable about AN working with external organizations or receiving payment only if this doesn't compromise in any way, directly or indirectly, the affordability of treatments for everyone." (Male, aged 21-30). "I do not object to AN working with pharmaceutical companies, and getting paid for providing stem cells from donors, to help people in need. I would object if the pharmaceutical companies, then made millions off those stem cells and people in need had to pay a high price for their treatment." (Female, aged 51+).
Transparency and Informed Consent	"I would feel more comfortable if payments made to AN were publicized and the purpose of them were made clear." (Male, aged 21-30). "I would like to know more about how the money is used before I would feel comfortable with it." (Male, aged 21-30). "This would be greatly affected by who the agency/company/charity is…. this worry would be allayed if there were clauses within the contract which

	allowed the use of donations solely if the therapy developed from those was provided at a reasonable markup from cost." (Male, aged 31-40).
Trust	"I understand that provision of donations to third parties in exchange for money is a necessary evil…I hope some of your affiliates are also charitable organisations." (Female, aged 20-31). "I would be more cautious without significant safeguards, about AN working or receiving money from pharmaceutical companies, compared to, say, other charities." (Male, aged 51+). "I would be happy for AN to work with other organisations/be paid by them as long as it was for reasons that were compatible with what AN stands for…I trust AN to make ethical and fair choices in who they work with." (Female, aged 21-30).

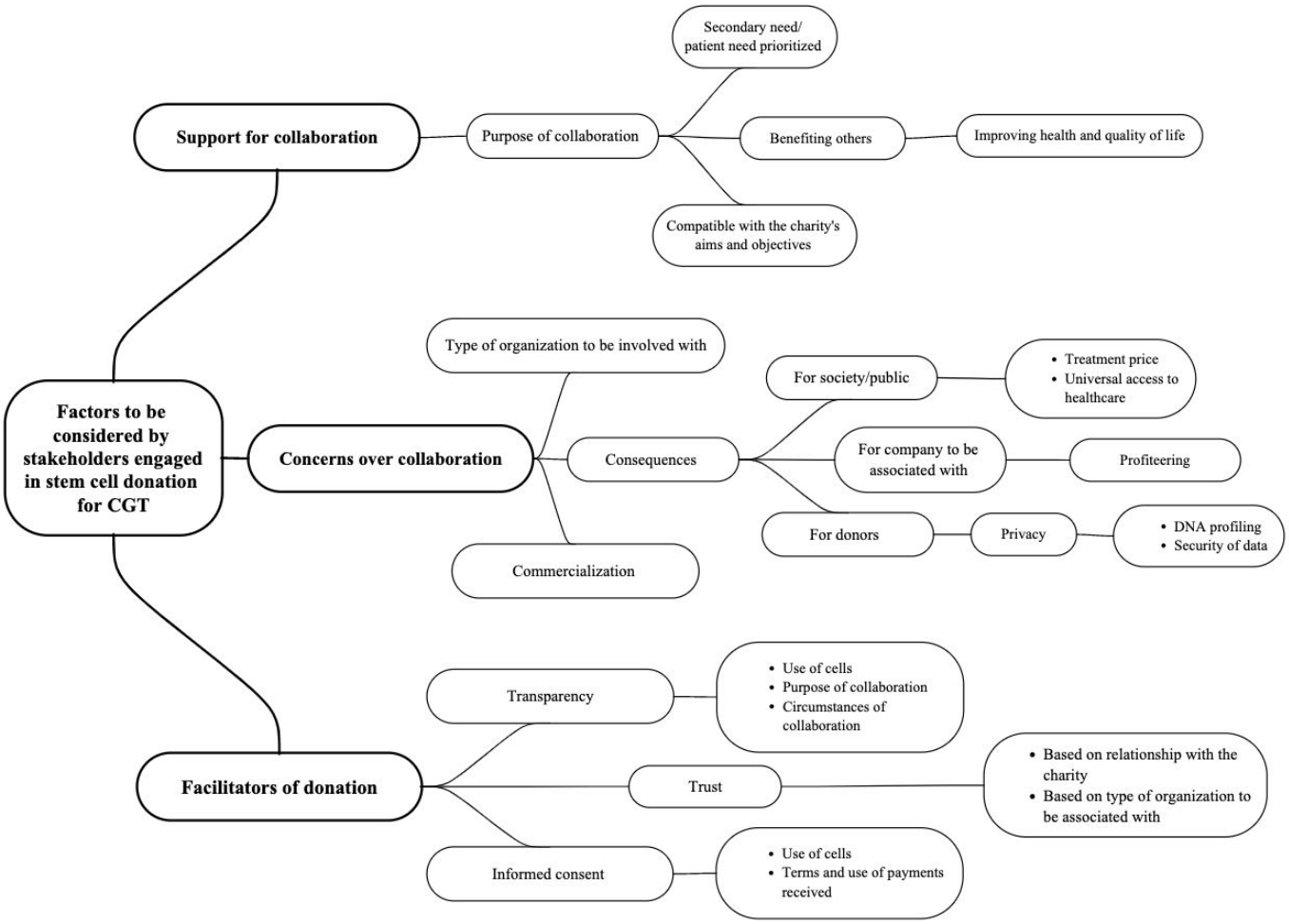

Figure 1. Overview of donor issues to be considered by stakeholders engaged in stem cell donation for allogeneic cell and gene therapies (CGT) research and development

Appendix 1

Table 1. Questions included in survey assessing prospective donors' attitudes and perspectives on donating for novel treatment research and development

Item	Question	Score
Understanding Stem Cell Transplants: How well do you understand the following topics?	Q1. The process of stem cell donation via the bloodstream (PBSC)	3-point Knowledge Likert scale
	Q2. The process of stem cell donation by bone marrow collection	3-point Knowledge Likert scale
	Q3. The work of the charity	3-point Knowledge Likert scale
Donating for new treatments: Donated cells can be used to help research and development teams working to develop new therapies.	Q1. Would you be willing to donate your cells for research that would help develop treatments to save and improve lives?	Nominal scale (Yes/No/Not sure)

To support development of therapies that save or improve lives, the charity could work with other organizations (e.g. other charities, pharmaceutical companies, or research and development groups that have developed expertise in modifying cells to target diseases). This support could be cell provision (supplying donated stem cells from donors like you) or services (like transport of the cells or consultancy). The charity would receive payment from these organizations, which would be used to further lifesaving work (e.g. by adding more donors to the register). How do you feel about the following statements?	Q1. I feel comfortable about the charity working with external organizations, if the blood or cells collected and the services provided help patients	5-point Agreement Likert scale
	Q2. I feel comfortable about the charity receiving payment for working with external organizations in this way	5-point Agreement Likert scale

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. (von Elm, 2014 #45)

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	2-4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5

Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	5
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6
Bias	#9	Describe any efforts to address potential sources of bias	5
Study size	#10	Explain how the study size was arrived at	5
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	6
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	6
Statistical methods	#12c	Explain how missing data were addressed	7
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	n/a
Statistical methods	#12e	Describe any sensitivity analyses	n/a
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	7
Participants	#13b	Give reasons for non-participation at each stage	n/a

Participants	#13c	Consider use of a flow diagram	n/a
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	7
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	n/a missing data removed
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	8
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
Main results	#16b	Report category boundaries when continuous variables were categorized	7
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	#18	Summarise key results with reference to study objectives	10-11
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	13
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	12
Generalisability	#21	Discuss the generalisability (external validity) of the study results	14
Other Information			

Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Included in Title Page to keep manuscript anonymous

Future Medicine

Methods Reporting Checklist
Version: 15th January 2019

Methods Reporting Checklist for Authors:

In accordance with the guidelines that emerged from a workshop led by the NIH, aimed at enhancing the scientific rigour and reproducibility of published results (accessed here), we have taken measures to ensure that we at Future Science Group are promoting good reporting standards. The checklist below is designed to establish if you have fulfilled the standards required by our journals.

Please check the below and indicate if the following information is available in your manuscript (or supplementary material). In cases where you have confirmed that the stipulated information is present in your article, please detail where it can be found by providing the page/paragraph/line number. If you feel that inclusion of this information is not applicable to your study, please indicate this in the column titled N/A.

For types of studies not covered by the methods checklist below, we recommend you consult the Equator Network website to identify a suitable guideline.

General Methods	**Yes – information is located on page/paragraph/line:**	**N/A**
1. I have detailed the exact sample size (*n*) for each experimental group/condition, as a number, not a range	7/2/142	
2. I have explained how sample size was chosen (in terms of having enough statistical power to make inferences about the sample)	5/1/96	
3. For animal studies, I have included a statement about sample size estimate (NB. applicable even if no statistical methods were used)		n/a
4. A description of the sample collection is included, enabling the reader to understand whether the samples represent technical or biological replicates (including how many animals, litters, culture, etc.)		n/a
5. I have defined how many times the experiment was replicated		n/a
6. I have detailed inclusion/exclusion criteria in cases where samples or animals were excluded from the analysis. I have detailed if the criteria were pre-established		n/a

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Methods Reporting Checklist

Version: 15th January 2019

7. I have clarified the method of randomization that was used to determine how samples/animals were assigned to experimental groups	5/1/101	
8. For animal studies: I have included a statement detailing whether or not randomization was used		n/a
9. For animal studies: I have included a statement detailing whether or not blinding was done		n/a
10. I have stated the extent to which the investigator was blinded to the group allocation during the experiment and/or when assessing the outcome		n/a

Statistical Testing	**Yes – information is located on page/paragraph/line:**	**N/A**
1. Statistical methods and measures have been defined: There is no need to describe very common tests, but more complex techniques should be described in the methods section. (For small sample sizes (n<5) descriptive statistics are not appropriate, instead plot individual data points)	5/1/113	
2. I have stated if tests are one-sided or two-sided		n/a
3. Statistical test results have been included e.g., *P* values	6/2/133	
4. 'Center values', such as median or mean have been defined		n/a
5. Error bars (e.g., s.d. or s.e.m. or c.i.) have been defined		n/a
6. I have stated if the data meet the assumptions of the tests (e.g., normal distribution)		n/a

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Methods Reporting Checklist
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7. I have clarified if there is an estimate of variation within each group of data and, if so, I have detailed if the variance is similar between the groups that are being statistically compared		n/a

Reagents	**Yes – information is located on page/paragraph/line:**	**N/A**
1. I have provided evidence that the antibodies were profiled for use in the system under study (assay and species), by giving a citation, catalog number and/or clone number, supplementary information or reference to an antibody validation profile (e.g., Antibodypedia, 1DegreeBio)		n/a
2. I have clearly identified the source of cell lines and reported if they were recently authenticated (e.g., by STR profiling) and tested for mycoplasma contamination		n/a

Animal Models†	**Yes – information is located on page/paragraph/line:**	**N/A**
1. I have reported the species, strain, weight, sex and age of animals		n/a
2. For experiments involving live vertebrates: I have either ticked to indicate that the necessary protocols have been followed in the Author Disclosure form or I have included a statement of compliance with ethical regulations and identified the committee(s) approving the experiments in my paper		n/a

† We recommend consulting the ARRIVE guidelines to ensure that other relevant aspects of animal studies are adequately reported.

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Human Studies[†] [‡]	**Yes – information is located on page/paragraph/line:**	**N/A**
1. I have identified the committee(s) approving the study protocol	5/2/109	
2. I have included a statement confirming that informed consent was obtained from all subjects/ indicated that this is the case in the Author Disclosure form	14/2/310	
3. I have reported the clinical trial registration number (at ClinicalTrials.gov or equivalent)		n/a

[†] For Phase II and III randomized controlled trials, we recommend that you refer to the CONSORT statement.
[‡]For tumor marker prognostic studies, we recommend that you follow the REMARK reporting guidelines.

Data and material sharing[†]	**Yes – information is located on page/paragraph/line:**	**N/A**
1. I have stipulated in the manuscript that all datasets on which the conclusions of the report rely are available on request	Data availability statement included 14/3/315	
2. I have provided accession codes for data that has been deposited in public repositories		n/a
3. If software has been used in the study: I have included information about the type of software and a statement describing if the software is available and how it may be obtained	6/2/128	

[†]We encourage the deposition of data to a discipline-specific, community-recognized repository where one exists, or a generalist repository if no suitable specific resource is available. Repositories can be found via sites such as re3data.org.

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Health economic evaluations	**Yes, see separate checklist:**	**N/A**
1. I have followed the separate CHEERS† checklist, available here.		n/a

† Husereau D, Drummond M, Petrou S *et al*., on behalf of the CHEERS Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMJ* 346, f1049 (2013).

Observational studies	**Yes, see separate checklist:**	**N/A**
1. I have followed the separate STROBE† checklist, available here.	Yes, uploaded as supplementary information	

† von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. BMJ. 335(7624), 806–808 (2007).

Systematic reviews & meta-analyses	**Yes, see separate checklist:**	**N/A**
1. I have followed the separate checklist established by PRISMA†, available here.		n/a

† Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 339, b2535 (2009).