First-In-Human Stem Cell Trials in Huntington's Disease: A Bioethics Survey

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Background

Experimental treatment approaches and first-in-human Phase 1 trials are ethically complex. These studies create challenges for informed consent, impose burdens and risks to subjects and may offer little or no prospect of clinical benefit. Similarly, these studies create bioethical concerns for investigators, coordinators and study staff. These issues are understudied in the field of regenerative medicine generally and in the Huntington's disease (HD) population specifically.

Methods

An anonymous survey of HD patients and family members regarding attitudes and concerns about participation in a study that involved stem cells, gene therapy and neurosurgical implantation was approved by the Institutional Review Board at UC Davis. The survey was offered on the HDSA website from September - December 2014. Descriptions of adult stem cells, gene therapy and stereotactic neurosurgery were provided in the introduction to the survey. Respondents were asked a series of sociodemographic questions followed by open-ended questions. Respondents who completed sociodemographic questions and at least one open-ended question were included in the analysis. We conducted a mixed methods analysis using quantitative and qualitative approaches to analyze participants' responses.

Sociodemographic data were sorted and analyzed with descriptive statistics. Open-ended questions were assessed by a multi-disciplinary team of five individuals including a movement disorders neurologist, a study coordinator with a degree in linguistics, and three bioethicists with backgrounds in philosophy, rhetoric and medical anthropology. After individually test-coding open-ended questions, the team discussed and agreed upon a standard codebook, with which two team members independently coded all open-ended responses. The two coders and another team member then reconciled all coding by consensus.

Results

Of 268 respondents, 209 met our inclusion criteria and were separated into either Group 1: Individuals at risk or genetically tested for HD (n = 116) or Group 2: Family members or care providers (n = 93) (Figure 1). Respondents were largely Caucasian (96%), and more likely female (69%), with mean age of 52 years (range 18 – 79) and drawn from throughout the US (Table 1, Figure 2). Regarding attitudes about participation in a first-in-human trial for HD, 67% of individuals from Group 1 responded positively compared to 92% from Group 2 (Figure 3).

For Group 1, roughly one third were diagnosed with HD, one third were gene positive and not yet diagnosed, and one third did not know their HD gene status (Figure 4). Seventy-seven percent of these respondents had previously participated in research (Figure 5). Most respondents (72%) reported no ethical concerns regarding experimental approaches to the treatment of HD, and 67% indicated willingness to consider participation in such a study. The most important reason cited for considering participation in a Phase 1 study was to find a cure for HD (62%), and this was also cited as the most important benefit for study participation (57%). The most common perceived burden of participation in a first-in-human trial included concerns about access (38%), and the second most cited concern was fear of adverse effects in 29%. (Table 2)

Group 2 respondents were primarily spouses or partners (46%), followed by parents (22%), other relatives (15%), and care providers(11%) or siblings (6%). Sixty-five percent of these respondents had no ethical concerns regarding experimental approaches to the treatment of HD, with 57% expressing support for the decision of a family member who wished to participate in such a study. Group 2 respondents were more likely to express safety concerns and specific types of adverse events (including death) than were those from Group 1. Perceived burdens related to participation were logistical (39%) followed by psychological/emotional burden (20%) and physical risk (10%)(Table 2).

Figure 1. Study flowchart

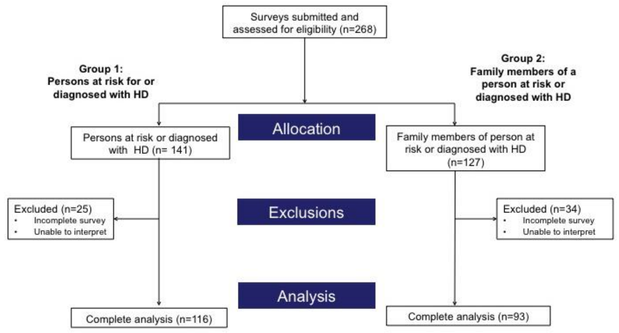


Table 1. Characteristics of respondents

	At risk or genetically tested for HD	Family members of individuals at risk or genetically tested for HD
Total, n	116	93
Age, y, mean (SD, range)	46.9 (14, 18-73)	56.9 (12, 22-79)
Gender, n (%)		
Female	66 (71)	80 (68)
Male	38 (32)	27 (29)
Race, n (%)		
White	112 (96)	86 (96)
Asian	1 (1)	2 (2)
Hispanic	2 (2)	2 (2)
Other	2 (2)	0
Education, n (%)		
<12th	3 (3)	1 (1)
High school Graduate	52 (44)	32 (34)
College Graduate	29 (25)	24 (26)
Graduate or Professional Degree	33 (28)	36 (39)
Employment, n (%)		
Student	3 (3)	1 (1)
Employed	53 (58)	50 (54)
Unemployed	17 (18)	5 (5)
Disability	19 (21)	36 (39)
Marital status, n (%)		
Single (never married)	21 (18)	4 (4)
Single (divorced or separated)	12 (10)	2 (2)
Married	83 (70)	68 (73)
Widowed	2 (2)	19 (20)

Figure 2: Demographics of all respondents

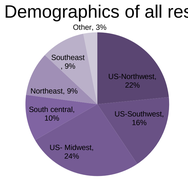


Figure 3: Participation in first-in-human trial

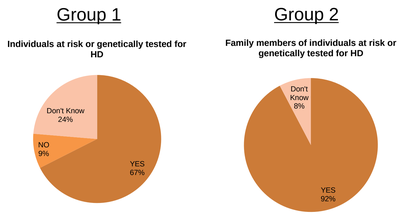


Figure 4. Respondent categories

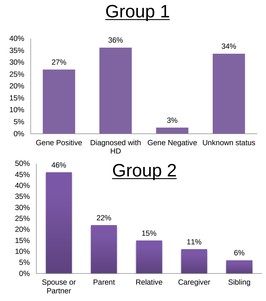


Figure 5. Previous participation in HD research

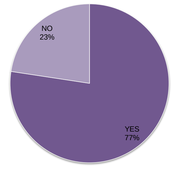
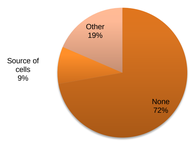


Table 2: Open-ended question responses (Group 1 and Group 2 included)

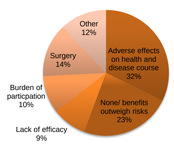
At risk or genetically tested for HD	Frequency (%)	Family members of HD individuals at risk or genetically tested for HD	Frequency (%)
What ethical concerns do you have about an experimental approach to the treatment of Huntington's disease?			
None	78 (72)	None	65 (65)
Source of cells	10 (9)	Embryonic stem cells	14 (14)
Other	9 (8)	Other	7 (7)
Risk to participant	7 (6)	Concerns are inconsequential	6 (6)
Informed consent and/or capacity	4 (4)	Safety	4 (4)
		Informed consent	2 (2)
		Surgery	2 (2)
How would you feel about being a participant (or having a family member) in a "first-in-human" clinical research study?			
Positive response	62 (54)	Positive	45 (43)
Conditional	15 (13)	Trepidation	15 (14)
Negative response	14 (13)	Deference to family members wishes	12 (12)
Do not know and/or uncertain	13 (11)	Uncertain	9 (9)
Mixed and/or conflicted	9 (8)	Risks verses benefits	8 (8)
Other	2 (2)	Proud and/or honored	7 (7)
		Hopeful and/or happy	6 (6)
		Negative	2 (2)
How willing might you be to (have a family member) participate in a study that involves stem cells, gene therapy, and brain surgery?			
Positive response	67 (58)	Unconditional Support	55 (57)
Unsure and/or cautious	20 (17)	Qualified and/or conditional support	25 (26)
Negative	14 (12)	Cautious and/or worried	6 (6)
Conditional	14 (12)	Negative	4 (4)
Other	1 (1)	Nothing to lose	3 (3)
		Dubious of methodology or chance of success	3 (3)
		Request for more information	1 (1)
What would be the most important reason for volunteering for this type of study?			
Finding a cure and/or treatment	62 (39)	Finding a cure and/or treatment	46 (32)
Help others	31 (19)	Help self and/or family	32 (22)
Family	29 (18)	Help others	24 (17)
Helping self	24 (15)	Hope	19 (13)
Knowledge/Advance Science	9 (6)	Quality of life	10 (7)
Other	4 (3)	Knowledge/advance science	8 (6)
		HD warrior/ purpose	4 (3)
What do you see as the biggest benefit from involvement in such a study?			
Finding a cure and/or treatment	57 (33)	Finding a cure and/or treatment	53 (39)
Help others	29 (17)	Help self	21 (15)
Knowledge/Advance science	22 (13)	Help others	18 (13)
Making a contribution	21 (12)	Empowerment	16 (12)
Helping self	20 (12)	Knowledge/advance science	13 (9)
Family	17 (10)	Hope	12 (9)
Hope	5 (3)	Other	3 (2)
		Nothing to lose	1 (1)
What are your biggest worries about involvement in this type of study?			
Adverse effects on health and disease course	40 (29)	Adverse effects	45 (36)
None/ benefits outweigh risks	29 (21)	None	15 (12)
Surgery	17 (12)	Lack of efficacy and/or does not work	13 (10)
Other	16 (11)	Death	12 (10)
Burden of participation	12 (9)	Other	10 (8)
Lack of efficacy	11 (8)	Worsen disease	8 (6)
Death	8 (6)	Psychological and/or emotional impact	7 (6)
Pain	7 (5)	The unknown	7 (6)
		Pain and/or discomfort	5 (4)
		Longer low quality of life	3 (2)
What do you see as the greatest burdens related to participation in such a study?			
Access (time, travel, cost)	46 (38)	Logistical burdens (time, travel, cost)	43 (39)
Risk of adverse effects	20 (17)	Psychological/ emotional burden	22 (20)
None and/or unsure	19 (16)	Physical risks	10 (9)
Impact on family	13 (11)	Aftercare	9 (8)
Psychological impact	9 (7)	Impact on loved ones	9 (8)
Uncertainty and/or unknown	5 (4)	None/ benefits outweigh risks	9 (8)
Post-trial support (team and/or family)	5 (4)	Lack of efficacy	4 (4)
Disclosure of gene status	4 (3)	Decision to participate	3 (3)
Additional thoughts or suggestions.			
Need and hope for cure	15 (19)	Gratitude/ support	14 (33)
Description of personal situation	13 (17)	Description of personal situation	12 (28)
Express of interest in participating	13 (17)	Question, request more info	5 (12)
Gratitude	13 (17)	Suggestion	5 (12)
Information request	7 (9)	Remark on urgency	3 (7)
None	6 (8)	Express of interest in participating	2 (5)
Other	6 (8)	Other	2 (5)
Remark on urgency	4 (5)		

Group 1

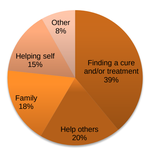
What ethical concerns do you have about an experimental approach to treatment of Huntington's?



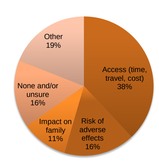
What are your biggest worries about being involved in this type of study?



What would be the most important reason for volunteering for this type of study?

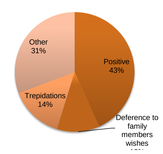


What do you see as the greatest burdens related to your participation in such a study?

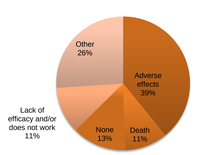


Group 2

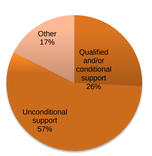
How would you feel about having a family member participate in a "first-in-human" clinic research study?



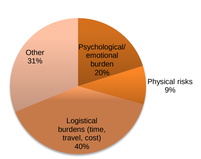
What are you biggest worries about having a family member involved in this type of study?



How willing might you be to have a family member participate in a study that invovles stem cells, gene therapy, and brain surgery?



What do you see as the greatest burdens related to your family member's participation in such a study?



Discussion

The goal of this survey was to explore attitudes and concerns of HD patients and family members about potential participation in a first-in-human experimental approach to treatment of HD utilizing gene-modified stem cells modified delivered by neurosurgical implantation. Results showed a broad support for participation in such a study from both patients and family members. The chief ethical challenge identified by both groups was concern for the source of stem cells, with some respondents objecting to the use of embryonic stem cells. Both patients and family members identified concerns about the potential risks of such a trial, and some raised concerns about the safety of neurosurgical implantation. Few respondents reported any ethical or safety concerns about gene therapy. While family members and caregivers were largely supportive of the decision by a loved one to participate in such a trial, they expressed more specific concerns about potential risks, including psychological, functional and medical side effects and possible death. The burden of study visits and logistics was important to both groups. Post-trial support for participants was identified as an important concern by family members. Both patients and family members reported potential benefits of study participation, including advancing scientific knowledge, taking an active stance against the disease, and helping others affected by HD. Additional thoughts from respondents included gratitude, support, remarks on urgency, and sharing of personal stories.

Limitations of this study included the survey format, which prevented respondents from seeking clarification about sources of stem cells, details of gene therapy and neurosurgical delivery of therapy. Strengths of the survey include a large response rate from a broad range of patients and family members directly affected by HD.

Conclusion

As basic research discoveries are translated to experimental treatments for HD it is our ethical responsibility as researchers to understand the beliefs and motivations of participants regarding these approaches. An appreciation for these ethical challenges inherent to this type of approach enables the investigators and participants to bridge communications gaps through a well informed consent process.

Acknowledgements

We would like to thank all the respondents who took the time to complete the survey by sharing their information and thoughts. We appreciate the contributions of the HD community immensely.

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