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May 2018
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MAY 2018 CLINICAL RESEARCHER
HOME STUDY
Behind the Scenes of Clinical Trials

Ensuring Representativeness in Competencies for Research Coordinators

LEARNING OBJECTIVE
After reading this article, participants will be able to be able to describe why and how the Joint Task Force for Clinical Trial Competency framework domains of "Communication and Teamwork" and "Leadership and Professionalism" are important to the training of research coordinators.

DISCLOSURE
Lauren B. Solberg, JD, MTS; H. Robert Kolb, RN, CCRC; Alena Prikhidko; Linda S. Behar-Horenstein, PhD: *Nothing to disclose*

1. **Which of the following describes the Joint Task Force for Clinical Trial Competency (JTF) framework?**
    a. Narrow in scope in order to give clinical research professionals specific guidance for practice.
    b. Broad and applicable to individuals conducting, supporting, and managing research in varied professional capacities.
    c. Serves as a theoretical framework for the conduct of clinical research protocol development.
    d. A complex compilation of general duties in which research staff should have knowledge as decided by experts.

2. **How many competency domains does the JTF Clinical Trial Competency framework possess?**
    a. Seven
    b. Eight
    c. Nine
    d. Ten

3. **Which of the following is an example of the competency domain of "Communication and Teamwork"?**
    a. Obtaining additional continuing education on clinical research topics.
    b. Calibrating equipment provided by the sponsor.
    c. Collaborating with coworkers within and outside the CRC profession.
    d. Missing required team meetings.

4. **Which of the following would a clinical research professional operating at the experienced level of the "Communication and Teamwork" do?**
    a. Delay reporting serious adverse events until certain they were valid.
    b. Work in isolation and solve problems alone to impress management.
    c. Join a professional organization because it looks good on a resume.
    d. Incorporate feedback from colleagues into work when provided.

5. **Which of the following is a suggested new competency within the "Leadership and Professionalism" domain?**
    a. Advocating for the professionalization of the CRC role.
    b. Developing emotional intelligence.
    c. Promoting positive organizational culture.
    d. Enhancing executive research functioning among middle managers.

6. **According to the authors, professional identity can be established by which of the following?**
    a. Certification
    b. Enculturation
    c. Having an office
    d. Work history

7. **Which of the following is elicited by professional competence?**
    a. Confidence, engendering trust
    b. Annual salary increase
    c. Meeting study recruitment goals
    d. Respect

8. **Facilitating trustworthiness requires legitimate knowledge that has a structure and support that is which of the following?**
    a. Essential for fostering collegiality.
    b. Transferable and replicable.
    c. Similar to other clinical professions.
    d. Required for research participant retention.

9. **A true collaborative competence is which of the following?**
    a. Present with established emotional intelligence.
    b. Defined by clinical research leadership, which in turn creates an organizational culture that is positive and impactful.
    c. Required to meet contracted study goals.
    d. A social experience which fosters integration of group qualities into one's professional self.

10. **Collaborative engagements with a professional community potentiates which of the following?**
    a. Active network-building and sharing of resources.
    b. Friendly competition for recruiting similar research patient populations.
    c. The likelihood that staff may leave their jobs for another in their local clinical research community.
    d. Success at bringing new drugs and devices to market.

Expectations of Cell Therapy: An Evaluation of the Cardiovascular Cell Therapy Research Network PACE Trial

LEARNING OBJECTIVE

After reading this article, participants will be able to be able to describe the design, evaluation, and goals of a proposed instrument for assessing participant expectations in clinical trials that explore novel treatments for serious diseases.

DISCLOSURE

Shelly L. Sayre, MPH; Judy Bettencourt, MPH; Michelle Cohen, MPH; Rachel W. Vojvodic, MPH; Emerson C. Perin, MD, PhD; Phillip C. Yang, MD; Michael P. Murphy, MD; Doris A. Taylor, PhD; Patricia G'Sell, RN; Eileen Handberg, PhD; Lem Moyé, MD, PhD: *Nothing to disclose*

11. According to the authors, what has been a contributor to advancing healthcare?

a. The willingness of individuals to participate in clinical trials.
b. New medical interventions are predictably producing satisfactory outcomes in patients.
c. Greater life expectancy has prompted significant increases in federal health research funding.
d. Members of the Baby Boomer generation lead much better lifestyles than those of other generations.

12. Which of the following is noted as a possible influence on participation in clinical trials?

a. Pressure from family and friends on patients with terminal illness.
b. Ads instructing audiences to "ask your doctor" about a treatment option in trial.
c. Family medical history showing negative responses to medications already on the market.
d. Research misconduct revelations convince many people to delay seeking medical attention.

13. According to the article, which of the following is true about expectations for stem cell therapy?

a. It will have its greatest efficacy only among the youngest patients.
b. It will eventually be regulated out of existence as unproven science.
c. It will be of value in the treatment of a variety of health conditions.
d. Its use will be concentrated in less developed countries and regions.

14. The authors caution that which of the following is true about individuals' expectations of stem cell treatments?

a. A literature review found no instrument for assessing various factors of patients' expectations for such treatments.
b. It is better to have no expectations of benefit from the treatments, no matter how well-studied or expensive they are.
c. Principal investigators would prefer their study subjects to have high expectations for treatments until told otherwise.
d. It is better for the patient to keep his or her expectations private from everyone on the study team, even if asked about them.

15. Intermittent claudication is explained by the authors as which of the following?

a. Feelings of anxiety that come and go.
b. A symptom that may be attributed to hypertension.
c. A focal area for stem cell transplantation.
d. Pain and/or cramping in the lower leg during exercise.

16. Which of the following is true of the Participant Expectation Questionnaire (PEQ) described in this article?

a. It is not validated and would need to be so for future research.
b. It looks to gauge what research patients want to improve in national and international studies.
c. It will further the advancement of stem cell research.
d. It was administered one year after enrollment.

17. How much decline was found in expectation fulfillment in terms of the effectiveness of stem cells from the beginning of the trial to the end?

a. 10% decrease
b. 15% decrease
c. 20% decrease
d. 25% decrease

18. The purposes of randomization is which of the following?

a. To equally distribute expectations across treatment groups.
b. To conveniently disperse treatment to participants.
c. To organize ordinal data.
d. To complicate data analysis.

19. Although perceptions were distributed equally across the cell and placebo groups, what was the relationship between expectations and outcomes?

a. Participants with lower expectations were more likely to actually receive cells.
b. Expectations were much stronger in participants who perceived they had received cells.
c. Expectations and outcomes were equal among all treatment groups.
d. Outcomes were stronger in participants who did not perceive they had received cells.

20. According to the authors, patients are often not vocal with their physicians about which of the following?

a. How sick they truly are.
b. Their access to care.
c. Their thoughts about the prices doctors charge.
d. Their expectations regarding their treatment.

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PEER REVIEWED

Ensuring Representativeness in Competencies for Research Coordinators

Lauren B. Solberg, JD, MTS; H. Robert Kolb, RN, CCRC; Alena Prikhidko; Linda S. Behar-Horenstein, PhD

[DOI: 10.14524/CR-17-0045]

Abstract

Providing educational programs designed to promote clinical research coordinators' (CRCs') implementation of competency skills is essential to workforce development; however, little is known about how programs address CRCs' needs. The purpose of this study was to assess CRCs' experiences in a six-month course. Using focus group methods, six participants revealed how the training assisted them in daily work.

The findings supported previous study results, and led to the identification of two competencies which are missing from the existing Joint Task Force for Clinical Trial Competency framework domains of "Communication and Teamwork" and "Leadership and Professionalism." The authors explain why these competencies are important for coordinators. The authors also discuss the instrumentality of qualitative research to ensure that competency domains reflect the needs of those for whom they are developed.

Introduction

The knowledge and skills of CRCs are fundamental to the success of those working in the profession and, in turn, the success of the research enterprise of institutions and investigators. The center of the CRCs' activities is human subjects research, with all its implications for ethics and participant safety.

CRCs undertake a variety of tasks, including requesting informed consent from participants, collecting and managing data or biological specimens, submitting regulatory documents to committees or agencies, and overseeing budget issues.{1} The multifaceted and, at times, highly technical nature of these activities can be daunting because they span broad and diverse work environments and require a highly specialized work force.

However, CRCs are generally trained in an on-the-job fashion, rather than by completing more formal training prior to working in these roles.{2} Furthermore, evidence suggesting that completing an academic program in clinical research results in CRC competence is not available.{3} Consequently, expanding workforce skills requires competency-based, focused training and evaluation efforts—both for novice and experienced professionals—in order to operate in today's complex research arenas.

Frameworks have been developed to guide trainings that focus on the implementation and application of competency-based skills in research coordination and management. One of these, the Joint Task Force for Clinical Trial Competency (JTF) framework, is intended to be broad and applicable to individuals conducting, supporting, and managing research in varied professional capacities.{3} This evolving framework currently includes the domains of "Leadership and Professionalism" and "Communication and Teamwork" among its eight competency domains.

After reviewing other established professional leadership programs{4} offered through University of Florida Training and Organizational Development and relevant literature{5} on leadership education, the authors of this article developed and implemented a training program for experienced CRCs on topics relevant to the JTF competency domains. This program was developed concurrently with other training

programs for CRCs in an effort to ensure robust training for our research workforce.{6–8}

In our literature search, we found a *Harvard Business Review* article that noted how "[m]embers of complex teams are less likely…to share knowledge freely, to learn from one another, to shift workloads…to help one another complete jobs and meet deadlines, and to share resources—in other words, to collaborate."{9} The article's authors explain a strong team leader is essential for success.

The purpose of the study outlined in the following sections was to assess CRCs' experiences in a six-month length course, and to describe if and how the training assisted them in daily work.

Methods

A single, 90-minute focus group was conducted with six experienced CRCs following completion of a six-month course. Topics addressed included navigating academia, vision and creativity, professional development, leadership, mentorship, and communication. The moderator (another researcher who was not a course instructor) explained the purpose of the study, and asked for consent to videotape the session using Zoom technology. The questions used during this semi-structured interview are shown in Appendix A.

A professional transcription service transcribed the audiotape. Questions were designed to ascertain how the training program addressed participants' professional needs, and to gain details on the following items pertaining to each individual participant:

- instructional preferences for in-class or online teaching and module content, and for a standardized coordinator curriculum
- essential skills or competencies
- whether their level of professionalization increased or decreased
- the ideal characteristics of a research coordinator
- how the coordinator training program influenced their role enactment

- if and how the training program influenced their sense of being/becoming an ideal CRC

All four authors of this article read the transcript independently, and each developed a list of emergent themes and sent it to the last author, who entered the collective themes into an Excel spreadsheet. The authors met and together developed a consensually agreed-upon list. Next, each author was assigned a subset of themes and was instructed to enter representative excerpts into the spreadsheet. After completing this task, another author checked the accuracy of the selected text passages.

Following data entry, the last author checked all areas of differences and sent a list to the primary analyst assigned to those areas where agreement was not reached. However, in all instances the primary and secondary analysts reached consensus. This process helped ensure the primary analyst stayed immersed in the data and enhanced their analytical acumen. The use of four analysts strengthened the credibility and dependability of the findings.

After conferring about the findings, the authors noted that some themes were similar to those found in previous studies.{6–8} However, two themes (elaborated upon in the Results section below) had not been identified in the JTF framework.

Results

As referred to above, this section presents two new competencies detected by the authors in this study that were not cited in the JTF framework.

For the domain of “Communication and Teamwork,” Table 1 deals with a new competency that refers to collaborating with coworkers within and outside the CRC role.

Table 1: Rubric for the Domain of "Communication and Teamwork"

Competency—Collaborating with Coworkers Within and Outside the CRC Role

Novice Level	Advanced Beginner Level	Experienced Level
Understands the importance of being attentive to tasks.	Understands the importance of seeking collegial input.	Understands that frequent collegial interactions often lead to better performance.
Example	**Example**	**Example**
Generally works in isolation from colleagues.	Intermittently seeks input or feedback from colleagues about work-related issues.	Frequently and while using one's own initiative, incorporates input or feedback from colleagues into work when input or feedback is provided.

Collaborating with coworkers within and outside the CRC role was described as a bi-directional process, whereby coordinators acquired and implemented rules and norms of professional conduct in their work. Research coordinators described mechanisms of learning these processes in the social environment. Specifically, they focused on developing managerial skills, recognizing variety and variability of research processes and the autonomy of other social actors in the complex research studies they were coordinating. In particular, they expressed the value of listening to and learning from others, as elaborated on in the following:

- Aileen extolled the importance of learning about "the decisions I make or how I communicate with the group" and reported that it was helpful.
- As a result of training, Harriet mentioned she now really "listen[s] more…[than] previously."
- Participants spoke about how learning from and about others assisted them in thinking about alternative ways to manage data or organize tasks.

- Joanne found it “helpful to get more information about organizing our studies…how people manage…their studies and what they do to be organized.”
- Participants also described learning about software and began to recognize the variety and variability in research processes.

These comments indicate that the novice coordinator initially works toward understanding the importance of being attentive to tasks. This practice is demonstrated when the CRC is observed working in isolation from colleagues. The experienced coordinator who appreciates frequent collegial interactions often performs better (as noted in Table 1).

The focus group results also led to the identification of a new competency within the JTF framework domain of “Leadership and Professionalism” that refers to advocating for the professionalization of the CRC role (see Table 2).

Table 2: Rubric for the Domain of “Leadership and Professionalism”

Competency—Advocating for the Professionalization of the CRC Role

Novice Level	**Advanced Beginner Level**	**Experienced Level**
Understands the importance of participating in institutional training activities.	Understands the importance of participating in governance activities beyond the institution.	Values the importance of seeking advanced training and leadership opportunities.
Example	**Example**	**Example**
Participates annually in training activities for CRCs.	Seeks membership in local, regional, or national CRC professional organization(s) or local networking group(s) for CRCs	Mentors or trains less experienced research coordinators.

The theme of the competency related to professionalizing CRC roles embraces professional identity development. It focuses on strong and assertive professional self-worth and establishes the need for recognition of the CRC as its own, distinctive profession.

Furthermore, professional identity is established through enculturation, as reflected in the following focus group comments:

- Harriet recommended that CRCs engage in group discussions to promote the "role of the coordinator…within the university." She found the training helped her "identify various resources" she could utilize, and remarked that participant interactions around training activities propelled research coordination toward a professional level. She emphasized it was necessary to "be assertive and … step up and fight for what you're worth." Through this course, she reported learning she did not have to settle for "okay, this is just the way it is," and reasoned that research coordinators could promote change.
- Helena noted that, despite the large role coordinators play in research, they "are not [well] represented" or regarded as professionals. She asserted they "deserved" greater recognition of their roles, since the effectiveness of study implementation often rests with their expertise and attention to detail.
- Lydia pointed out the necessity for assertive communication with principal investigators who may lack an understanding of the connection between their research goals and regulations requiring adherence.

These results lead to the development of a levelling rubric for the competency of advocating for the professionalization of the CRC role. This rubric describes characteristic behaviors that might be observed along the continuum from a novice research coordinator to an experienced one (as noted in Table 2).

Activities that typify the novice CRC role should help the individual begin to understand the importance of participating in institutional training activities. This competency may be marked by annual participation in CRC training activities. With increasing experience,

CRCs come to value the importance of seeking advanced training and leadership opportunities, as exemplified by their willingness to mentor or train less experienced research coordinators.

Discussion

The Association for Clinical Research Professionals (ACRP) is "working…to standardize [practice] in the clinical trial workforce."{10} Thus, it becomes increasingly imperative that the respective competency domains for CRCs are comprehensive.

While evaluating the findings of this project, it became evident to the authors that the JTF framework (see Table 3), as well as an independent analysis of the JTF framework,{11} omitted two important competencies from the "Leadership and Professionalism" and "Communication and Teamwork" domains that are essential for the success of research professionals.

Table 3: JTF Domains 7 and 8{3}

Domain 7: Leadership and Professionalism
Describe and apply the principles and practices of leadership, management, and mentorship in clinical research.
Identify ethical and professional conflicts associated with the conduct of clinical studies and implement procedures for their prevention or management.
Identify and apply the professional guidelines and codes of ethics that apply to the conduct of clinical research.
Describe the impact of regional diversity and demonstrate cultural competency in clinical study design and conduct.
Domain 8: Communication and Teamwork
Discuss the relationship and appropriate communication between sponsor, contract research organization, and clinical research site.

Describe the components of a traditional scientific publication.
Effectively communicate the content and relevance of clinical research findings to colleagues, advocacy groups, and the non-scientist community.
Describe the importance of team science and methods necessary to work effectively with multidisciplinary and inter-professional research teams.

For “Leadership and Professionalism,” we have identified a competency denoted as advocating for the professionalization of the CRC role, which is consistent with themes from earlier studies.{6–8} This competency reflects a desire to move toward creating a unique identity for CRC practice.

To reach professionalization, CRCs must be defined by practice and educational standards that support their role’s recognition in developing and maintaining a professional identity. Absent these conventions, CRCs are left working in a discipline that is ill-defined, not well understood, and largely unappreciated. For CRCs who are committed to a career in clinical research, the experience of advocating for one’s self and for others enables them to build a sense of personal power and self-identification.

Through the competency of advocating for the professionalization of the CRC role, learning and professional opportunities stimulate the intrinsic worth of CRC roles. This quality of faithfully representing oneself as a competent professional establishes dependability and credibility. By gaining self-esteem, the milieu of clinical research begins to look different, as synergy develops between self-perception and how others view CRCs.

Further, professional competence elicits confidence and engenders trust. To facilitate trustworthiness requires legitimate knowledge that has a structure and support which is transferable and replicable. This in turn strengthens and confirms the transformative transition to a professional identity. In this light, advocating for the professionalization of the CRC role becomes an essential competency.

The other crucial competency highlighted here, collaborating with coworkers in and outside the CRC role, falls within “Communication and Teamwork” and precipitates out of previous work.{6–8} Developing this competency would demonstrate that CRCs are better prepared to adapt to changing and complex environments which mirror current workforce practice.

This is particularly relevant to working within interdisciplinary groups, while trying to resolve conflicts. The psychosocial and communication facets of collaborative competencies transcend basic communication with sponsors on regulatory understandings, which is the primary focus of the JTF framework.

Instead, a true collaborative competence is a social experience which deepens appreciation of group norms, characteristics, values, and ideals and fosters integration of these qualities into one’s professional self as individuals make sense of personal and group behavior in socially constructed interactions.{12} In effect, collaborative competency requires a CRC to understand his or her immersion into a culture of research, which requires enacting culturally competent communication and understanding what communicating means in this context.

Conclusion

Collaborative engagements with a professional community potentiate active network building and sharing of resources. This process facilitates self-discovery, innovation, and empowerment to create a sense of forward career equilibrium, which in turn resonates with advocating for the professionalization of the CRC role. The JTF’s “Communications and Teamwork” and “Leadership and Professionalism” domains form a foundational matrix for the development of true competence.

Neglecting the importance of the intertwined competencies described in this article is a serious limitation if absent from any framework. Most coordinators have yet to understand competency training in terms of encountering a professional identity, or that there was even such a consideration. These additional competencies strengthen the intention of the professional competency movement as articulated by JTF and embraced by ACRP.

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References

1. Baer AR, Zon R, Devine S, Lyss AP. 2011. The clinical research team. *J Oncol Pract* 7(3):188–92.
2. Bonham A, Califf R, Gallin E, Lauer M. 2012. *Developing a robust clinical trials workforce*. National Academy of Sciences.
3. Sonstein SA, Seltzer J, Li R, Jones CT, Silva H, Daemen E. 2014. Moving from compliance to competency: a harmonized core competency framework for the clinical research professional. *Clin Res* 28(3):17–23. https://www.acrpnet.org/crjune2014/
4. The UF Leadership Competencies Model. http://hr.ufl.edu/leadership@uf/
5. Grossman SC, Valiga TM. 2017. *The new leadership challenge: creating the future of nursing* (5th Edition). F.A. Davis Company. https://www.fadavis.com/product/nursing-leadership-management-challenge-future-of-nursing-grossman-valiga-5
6. Behar-Horenstein LS, Bajwa W, Kolb HR, Prikhidko A. 2017. A mixed method approach to assessing good clinical practice computerized online training. *Clin Res* 31(5):38–42. https://www.acrpnet.org/2017/10/09/mixed-method-approach-assessing-good-clinical-practice-computerized-online-learning/
7. Behar-Horenstein LS, Potter JE, Prikhidko A, Swords S, Sonstein S, Kolb HR. 2017. Training impact on novice and experienced research coordinators. *The Qual Report* 22(12):3118–38. https://nsuworks.nova.edu/tqr/vol22/iss12/3/

8. Behar-Horenstein LS, Kolb HR, Prikhidko A. 2018. Advancing the practice of CRCs: why professional development matters. *Therap Innov & Reg Sci.* http://journals.sagepub.com/doi/abs/10.1177/2168479017750128
9. Gratton L, Erickson TJ. 2007. Eight ways to build collaborative teams. *Harvard Bus Rev* 85(11):100.
10. Association of Clinical Research Professionals. Joint Task Force for Clinical Trial Competency. Competency Domains for Clinical Research Professionals. https://www.acrpnet.org/professional-development/competency-domains-clinical-research-professionals/
11. Calvin-Naylor NA, et al. 2017. Education and training of clinical and translational study investigators and research coordinators: a competency-based approach. *J Clin Transl Sci* 1(1):16–25.
12. Erikson EH. 1974. *Dimensions of New Identity*. New York, N.Y.: W. W. Norton.

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Appendix A:

Focus Group Questions for Evaluating the CTSI Research Coordinator Leadership Development Program

1. In what way has the UF CTSI leadership training program addressed your professional needs?

2. In your opinion what are the ideal characteristics of a research coordinator leader?

3. How has the UF CTSI leadership training program influenced how you perform your role as a research coordinator?

4. How will you use the information and skills learned in the UF CTSI research coordinator leadership program?

5. Has your confidence in your level of professionalization increased or decreased as a result of this UF CTSI coordinator leadership training program?

6. What aspects of the UF CTSI coordinator leadership training program influenced your own sense of being/becoming an ideal research coordinator?

7. Were the program co-facilitators (Bob Kolb and Lauren Solberg) effective? In what ways? How might they improve upon their role?

8. What is your opinion of the guest speakers who lectured?

9. Did you appreciate having speakers who are/were research coordinators, or would you have preferred someone without coordinator experience?

10. What were the most and least helpful out-of-class assignments?

11. What were the most and least helpful in-class activities?

12. Was the networking aspect of this program helpful for meeting your goals?

13. Would you recommend this program to a colleague?

14. What skills or competencies do you consider essential for coordinator leadership and professionalization that were not addressed in the UF CTSI coordinator leadership training program?

15. What else might you change about this program for future cohorts of research coordinators?

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PEER REVIEWED

Expectations of Cell Therapy: An Evaluation of the Cardiovascular Cell Therapy Research Network PACE Trial

[DOI: 10.14524/CR-17-0041]

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[*Editor's Note:* Tables and Figures associated with this article are available in a PDF in the library of the Clinical Trials Recruitment Interest Group of the ACRP Online Community.]

Clinical trials represent hopeful new therapies to many people. The majority of healthcare advances today are made possible by the willingness of individuals to take part in clinical trials.

There are many motivators for enrolling in clinical trials, including altruism, desire to play an active role in one's own healthcare, and a desire to gain early access to novel treatments.{1,2} What one might expect from participating in a clinical trial can be influenced by multiple sources, (e.g., media coverage of new research, acquaintances who have had treatment, or advertisements instructing audiences to "ask your doctor" for this latest treatment option).{3,4}

However, with "new" often being equated with "better," investigational treatments can be misconstrued as a panacea, generating unrealistic expectations even before a trial has begun. Expectations often run high in clinical trials that explore novel treatments for serious diseases. For example, expectations are that stem cell therapy will have an impact in a number of applications, (e.g., cardiology,{5-7} traumatic brain injury,{8,9} Parkinson's disease,{10} etc.). Accordingly, cell therapy has received increased media coverage over the last decade for both regulated and unregulated uses.{4,11-15}

Investigators are exploring how information about stem cell therapy (accurate or not) enacts the power of hope in both patients and caregivers.{16-18} Many for-profit clinics offer stem cells for a wide spectrum of diseases and make claims of success without regulated oversight, raising questions as to whether there is evidence of success or if findings are based solely on individuals' expectations. A review of the literature identified no instrument to assess participant expectations for cell therapy clinical trials with regard to symptom relief, improved quality of life, and treatment efficacy.

This study evaluated participants' self-reported expectations associated with enrollment in a clinical trial assessing the effect of stem cell therapy on intermittent claudication. The study also examined changes in participant expectations over time, and the relationship between their perceived treatment assignment and expectations.

Methods

The PACE Trial

The PACE trial (Patients with Intermittent Claudication Injected with ALDH Bright Cells) was a Phase II, double-blind, placebo-controlled, randomized trial conducted by the Cardiovascular Cell Therapy Research Network (CCTRN) and funded by the National Heart, Lung, and Blood Institute. The trial was designed to assess the safety and efficacy of autologous bone marrow-derived aldehyde dehydrogenase bright (ALDHbr) cells delivered to participants with atherosclerotic peripheral artery disease (PAD) with symptom-limited intermittent claudication. Intermittent claudication is pain and/or cramping in the lower leg during exercise (caused by reduced blood flow to the vessels) that is relieved by a short period of rest.

Following 1:1 randomization, 78 participants were treated with cells or placebo administered via direct intramuscular injection to the calf and lower thigh and followed for six months. Participation included eight visits over six months, with a total maximum time commitment of 31 hours. Visit ranged from one to six hours, with the longer visits at time of bone marrow

harvest and those including endpoint collection activities (MRI and treadmill testing). The design and outcomes of the trial are further described elsewhere.{19,20}

The Participant Expectation Questionnaire

The Participant Expectation Questionnaire (PEQ) was developed by CCTRN research staff and administered to participants as a first attempt to learn more about their cell therapy expectations and participation in a clinical trial studying it. It has not been validated, and will require this step if it is to be used in future trials. As the PACE trial demonstrated neither beneficial nor harmful effect of cell therapy on the primary measures of peak walking time or increased blood flow in the affected leg,{20} all questionnaires were combined into one cohort for this evaluation.

The PEQ included categorical and open-ended response choices (see Table 1) and construct models used in similar evaluations of pain medicine.{21} Categorical responses used a Likert scale format to assess several aspects of expectation relating to trial participation. Topic areas included symptom relief, effectiveness of cell therapy, and trial participation. The open-ended portion focused on what might influence expectations and included motivation to participate, knowing someone who had received stem cells to treat a disease, discussion of the PACE trial with anyone before participating, and availability of any person(s) to help the participant during the study. The PEQ was administered prior to study injection (baseline) and was repeated at the six-month follow-up visit.

Statistical Methods

Text responses were independently coded by two coauthors using categories generated from the most common themes. Differences were adjudicated by a third coauthor. If participants gave more than one response, all were coded and included in analysis. For categorical data, frequency (counts and percentages) of responses to each item was tabulated. Comparisons of the distribution of response by perceived treatment assignment were carried out using Fisher’s exact test for dichotomous outcomes and chi-square statistics for the polychotomous responses. All computations were conducted using SAS 9.4. No corrections for multiplicity were employed in these exploratory analyses.

Results

Seventy-eight participants were randomized and received study product in the PACE trial. These participants completed a PEQ at baseline and six months post-treatment, and are the basis for this investigation.

Motivation for Participation

More than half of the participants decided to take part in the trial the same day the consent was reviewed with them by the research team (n=41; 53%), with most (n=64; 82%) reportedly discussing the trial with someone beforehand (i.e., a family member or physician). Almost all participants (n=73; 94%) said they had someone to help them during participation.

Principal motivations for trial participation were to reduce pain and avoid invasive treatments (n=33; 44%) and to get better (n=24; 32%). Other motivating factors included helping others by participating (n=13; 17%), improving mobility/quality of life (n=10; 13%), and following physician recommendations (n=5; 7%). A small minority of participants (n=10; 13%) knew someone who had been treated with stem cells.

Expectations Over Time Regarding Symptom Relief

Fifty-three participants (68%) had a well-established PAD history, diagnosed greater than three years before study participation, with the remaining (n=24; 32%) diagnosed within two years of study participation. The study utilized the Rutherford classification system, which categorizes PAD symptoms into acute or chronic limb ischemia to direct treatment regimens. Nearly all trial participants were Rutherford classification 2 or 3 (indicating moderate to severe claudication).{20}

As shown in Table 2, at baseline, 66 participants (85%) felt that stem cells would make them feel better in general. Sixty participants (77%) had a high expectation for either a large reduction or elimination of leg pain, and 51 participants (65%) agreed/strongly agreed that they would be able to walk without pain post-treatment.

At six months post-treatment however, 28 participants (36%) felt that stem cells made them feel better in general. Similarly, 28 participants (36%) reported their leg pain remained the same, and only 11 (14%) agreed/strongly agreed that they walked without pain after study treatment.

Expectations Over Time for Treatment of Disease

At baseline, 65 participants (83%) had high expectations for the effectiveness of stem cells at treating disease, despite the fact (noted above) that most did not know anyone personally who had received them. At six months post-treatment, 49 participants (63%) still agreed/strongly agreed that stem cells were effective at treating disease (see Table 2).

Expectations Over Time Related to Trial Participation

At baseline, 67 participants (86%) felt that taking part in the study would be easy; however, 59 participants (76%) expected some minor inconveniences and 25 (32%) anticipated being tired due to logistical complications of participation (see Table 2). At six months post-treatment, 72 participants (92%) agreed/strongly agreed that it was easy to participate, with 17 participants (22%) indicating minor inconveniences and 13 (17%) reporting feeling tired due to logistical complications.

Dislikes, Likes, and Future Expectations

When asked about dislikes regarding study treatment (see Figure 1a), 34% of the respondents indicated “none.” Respondents citing specific concerns primarily mentioned the magnetic resonance imaging scan and blood draws/needle use. When asked what they liked about study treatment (see Figure 1b), respondents mentioned the study team and seeing results or feeling better after treatment. In the end, the majority (90%) indicated a willingness to participate in another stem cell study.

Perceived Treatment Assignment

When the participants were asked which treatment they thought they had received, 26 participants (33%) indicated cells, 22 (28%) indicated placebo, and 30 (39%) reported they “did

not know." A clear majority of participants, 48 (61%) felt they could identify with being in either the cell or placebo group.

A subgroup exploration of the latter 48 individuals was conducted to assess differences. As shown in Table 3, the two perceived treatment groups were not significantly different in their expectations at baseline. Both groups expected a large reduction or elimination of leg pain (cells n=21, 81% vs. placebo n=18, 82%); to be able to walk without pain (cells n=19, 73% vs. placebo n=16, 73%); to feel better in general due to the stem cells (cells n=20, 77% vs. placebo n=21, 95%); and that stem cells are effective for treating disease (cells n=20, 77% vs. placebo n=19, 86%). Similar to the overall study cohort, both groups thought it would be easy to participate in the study (cells n=21, 81% vs. placebo n=19, 86%), though some recognized the potential for minor inconveniences (cells n=19, 73% vs. placebo n=17, 77%).

At six months post-treatment (see Table 3), differences between the two groups emerged—particularly for symptom relief. While only two (8%) cell-perceived participants felt their leg pain stayed the same, 13 placebo-perceived participants (59%) reported their pain remained the same ($p<0.001$). When asked about the ability to walk without pain, 10 cell-perceived participants (38%) agreed/strongly agreed while none in the placebo-perceived group agreed ($p<0.001$). The two groups also differed drastically on the idea that, in general, stem cells made them feel better (cell n=21, 81% vs. placebo n=2, 9%, $p<0.001$).

While the two perceived treatment groups differed on symptom relief at six months post-treatment, there were no significant differences related to effectiveness of treatment or trial participation. Both groups agreed that stem cells were effective for treating disease (cell n=20, 77% vs. placebo n=15, 68%); that it was easy to participate in the study (cell n=24, 92% vs. placebo n=20, 91%); and that they experienced only minor inconveniences (cell n=9, 35% vs. placebo n=6, 27%) (see Table 3). Overwhelmingly, members of both groups reported they would participate in another stem cell study (cell n=24, 92% vs. placebo n=21, 95%).

The same analysis was repeated utilizing the 48 participants' *actual* treatment assignments. There was no significant effect of actual treatment assignment on expectations at either baseline or at six months post-treatment.

The Interrelationship of Perceived Assignment and Actual Assignment

In order to assess the impact of actual therapy assignment on the relationship between *perceived* therapy and expectation variables, the analyses were repeated within each of the *actual* cell and placebo groups. In the subgroup of 48 participants, 24 were assigned to cells and 24 assigned to placebo.

At six months post-treatment, among those in the *actual* cell group, participants who *perceived* they received cells experienced statistically significant differences in leg pain reduction ($p<0.001$), walking without pain ($p=0.005$), and feeling better overall ($p<0.001$) compared to those who *perceived* they received placebo (see Table 4). Results at six months post-treatment in the *actual* placebo group showed that *perceived* therapy was only significantly associated with generally feeling better due to stem cells ($p=0.047$).

Discussion

In the PACE trial, participants' motivations were largely driven by their desire for symptom reduction and overall improved feeling. Post-treatment, only 14% of participants agreed/strongly agreed they could walk without pain; however, 36% still agreed/strongly agreed that stem cells made them feel better in general. There was a 20% decrease in expectation fulfillment from the beginning of the trial to the end in the effectiveness of stem cells; a number that is not surprising in a trial that demonstrated neither beneficial nor harmful effects of cell therapy on its primary endpoints.

Most participants made the decision to participate in the trial the same day the consent form was reviewed, suggesting that much of the prior information they had was sufficient for them to feel comfortable to proceed. It is clear, however, that following the intervention, participants began to develop their own beliefs about their treatment conditions. Participants who ventured a guess were correct nearly half the time (n=22; 46%).

Since participants in a trial frequently try to guess their treatment assignment, we felt it was an important factor (beyond the control of the investigators) to explore, as these “impressions” can alter a participant’s compliance with attendance or influence adverse event reporting. Members of both the cell-perceived and placebo-perceived groups continued to respond favorably to the effectiveness of stem cells at treating their disease in the post-treatment period. They also responded similarly on questions related to trial participation and logistics; however, it is notable that those who perceived they received cells were more likely to report reduction in leg pain and feeling better overall than those who perceived they received placebo (85% vs. 18%).

Most striking is that 77% in the cell-perceived group also indicated their leg pain decreased compared to only 9% of the placebo-perceived group. Even though the vast majority of participants in either group were still experiencing pain when walking, nearly all indicated they would participate in another stem cell study.

In the perceived therapy versus actual therapy subgroup evaluation, perceived therapy produced a greater impact on expectations than actual therapy. This is to be expected, since one of the purposes of randomization is the equal distribution of expectations across treatment groups. However, the impact of perception appeared greater in those who actually received the cells. Thus, although perceptions were distributed equally across the cell and placebo groups, the relationship between expectations and outcomes was much stronger in participants receiving cells.

The equal distribution of perception across the randomized groups mitigates against unintentional unblinding of the actual group assignment to the participants. Despite these protective measures, there are likely subjective factors that may affect participants’ perceptions of their own outcomes and feelings after study intervention has occurred. Post-intervention expectations (e.g., placebo effect){22,23} may present a greater challenge in that they are intrinsic to the subject. This observation is the most intriguing of the findings and warrants further investigation.

Limitations

Although validation of the PEQ is warranted for future use, responses to the survey revealed that several factors shape the expectations of participants prior to considering a cell therapy trial. On evaluation at six months post-treatment, the inclusion of a “don’t know” option for perceived treatment assignment prevented full sample evaluation of the influence of perception on expectations. No interim assessments were collected between baseline and six months post-treatment to allow identification of any changes in the trajectory of participant expectations.

Since perception was asked only at six months post-treatment, one can question whether the perception of therapy induced the change in expectations or if the change in expectations affected the perception. Lastly, this investigation is limited to one trial of one cell type and its effect on one disease process, and it is not intended to be generalized.

As the field of cell therapy continues to expand, it will be important to know how expectations change with accumulated, reported experiences (both positive and negative) of many different types of stems cells in the treatment of different disease processes.

Conclusions

Patients are often not vocal with their physicians about expectations regarding their treatment, nor about possible logistical hurdles which threaten to hinder their clinical trial participation. The PEQ findings demonstrate high initial expectations were moderated over time, and perhaps even influenced by perceived treatment assignment, although the perception-response relationship in the cell group requires additional investigation.

Despite this, enthusiasm for the effectiveness of the treatment and participation in future trials remained. Eliciting and understanding participant expectations prior to enrollment in a stem cell therapy trial may help investigators have a more targeted conversation with potential participants. This discussion allows an opportunity to explain possible outcomes in realistic terms, benefiting both the trial and participants.

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In memory of our dear friend and colleague, Alan T. Hirsch, MD, we share these findings with the community in the hopes it will foster continued conversation between physicians and patients about the critical role of research in healthcare.

References

1. Center for Information & Study on Clinical Research Participation. 2015. CISCRP Perceptions & Insights Study--Report on Participation Experiences. Boston, Mass.
2. National Institutes of Health. NIH Clinical Research Trials and You. https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics
3. Lui H, Priest S. 2009. Understanding public support for stem cell research: media communication, interpersonal communication and trust in key actors. *Pub Und Sci* 18(6):704.
4. Bubela T, Li MD, Hafez M, Bieber M, Atkins H. 2012. Is belief larger than fact: expectations, optimism and reality for translational stem cell research. *BMC Medicine* 10:133-7015-10-133.
5. White IA, Sanina C, Balkan W, Hare JM. 2016. Mesenchymal stem cells in cardiology. *Meth Molec Biol* 1416:55-87.
6. Gyongyosi M, Wojakowski W, Lemarchand P, Lunde K, Tendera M, Bartunek J, Marban E, et al. 2015. Meta-analysis of cell-based CaRdiac stUdiEs (ACCRUE) in patients with acute myocardial infarction based on individual patient data. *Circul Res* 116 (8):1346-60.
7. Golpanian S, Schulman IH, Ebert RF, Heldman AW, DiFede DL, Yang PC, Wu JC, et al. 2016. Concise review: review and perspective of cell dosage and routes of administration from preclinical and clinical studies of stem cell therapy for heart disease. *Stem Cells Transl Med* 5(2):186-91.
8. Harting MT, Baumgartner JE, Worth LL, Ewing-Cobbs L, Gee AP, Day MC, Cox Jr CS. 2008. Cell therapies for traumatic brain injury. *Neurosurgical Focus* 24(3-4):E18-4/E17.
9. Tian C, Wang X, Wang X, Wang L, Wang X, Wu S, Wan Z. 2013. Autologous bone marrow

mesenchymal stem cell therapy in the subacute stage of traumatic brain injury by lumbar puncture. *Exper Clin Transpl* 11(2):176-81.
10. Shen Y, Huang J, Liu L, Xu X, Han C, Zhang G, Jiang H, et al. 2016. A compendium of preparation and application of stem cells in Parkinson's disease: current status and future prospects. *Frontiers Aging Neurosci* 8:117.
11. Kolata G. 2016. A cautionary tale of stem cell therapy abroad. *The New York Times* 19.
12. MS stem-cell treatment 'success.' *BBC News*. http://news.bbc.co.uk/2/hi/health/7858559.stm
13. Taylor-Weiner H, Graff Zivin J. 2015. Medicine's wild west--unlicensed stem-cell clinics in the United States. *NEJM* 373(11):985-7.
14. Dama G. 2010. A point of view: stem cell tourism: "other side of the river is not greener." *BMJ* 341:6203c.
15. Board on Health Sciences Policy, Board on Life Sciences, Division on Earth and Life Studies, Institute of Medicine, and National Academy of Sciences. 2014.
16. Kim YS, Chung DI, Choi H, Baek W, Kim HY, Heo SH, Chang DI, Na HR, Kim SH, Koh SH. 2013. Fantasies about stem cell therapy in chronic ischemic stroke patients. *Stem Cells Dev* 22(1):31-6.
17. Petersen A, Seear K, Munsie M. 2014. Therapeutic journeys: the hopeful travails of stem cell tourists. *Soc Health Illness* 36 (5):670-85.
18. Han S, Choi H., Kim YS, Lee KY, Lee YJ, Koh SH. 2016. Analysis of the expectation of stem cell therapy in patients with Alzheimer's disease. *Dement Neurocogn Discord* 15(4):129.
19. Perin EC, Murphy M, Cooke JP, Moye L, Henry TD, Bettencourt J, Gahremanpour A, et al. 2014. Rationale and design for PACE: patients with intermittent claudication injected with ALDH bright cells. *Am Heart J* 168(5):667-73.
20. Perin EC, Murphy MP, March KL, Bolli R, Loughran J, Yang PC, Leeper NJ, et al. 2017. Evaluation of cell therapy on exercise performance and limb perfusion in peripheral artery disease: the CCTRN PACE trial (patients with intermittent claudication injected with ALDH bright cells). *Circulation* 135(15):1417-28.
21. Robinson ME, Brown JL, George SZ, Edwards PS, Atchison JW, Hirsh AT, Waxenberg LB, Wittmer V, Fillingim RB. 2005. Multidimensional success criteria and expectations for treatment of chronic pain: the patient perspective. *Pain Med* 6(5):336-45.
22. Kaptchuk TJ, Goldman P, Stone DA, Stason WB. Do medical devices have enhanced

placebo effects? *J Clin Epidemiol* 53(8):786-92.
23. Stewart-Williams S, Podd J. The placebo effect: dissolving the expectancy versus conditioning debate. *Psychol Bull* 130(2):324-40.

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Supplemental Materials for

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Expectations of Cell Therapy: An Evaluation of the Cardiovascular Cell Therapy Research Network PACE Trial

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Table 1: PACE Participant Expectation Questionnaire

#	Baseline[a]	Six-Month Follow-up[a]
1	When were you diagnosed with PAD? *Responses: 0-12 months, 1-2 years, 3-5 years, Greater than 5 years, No response*	Please indicate which treatment you think you received. *Responses: Stem cells, Placebo, Don't know*
2	I expect my leg pain to be reduced after study treatment.	My leg pain was reduced after study treatment.
3	I expect to feel better overall after study treatment.	I felt better overall after study treatment.
4	I expect to be able to walk without pain after receiving study treatment.	I walk without pain after receiving study treatment.
5	I am confident that treatment with stem cells will decrease my leg pain.	My leg pain decreased after being treated with stem cells.
6	I expect to have some minor inconveniences related to my participation in this study.	I had some minor inconveniences related to my participation in this study.
7	I think stem cells are effective for treating disease.	I think stem cells are effective for treating disease.
8	I expect to be tired due to logistical complications of participating in the study (i.e., driving to clinic, wait time to see doctor, etc.).	I was tired due to logistical complications of participating in the study (i.e., driving to clinic, wait time to see doctor, etc.).

9	I think it will be easy to participate in this study.	It was easy to participate in this study.
10	In general, I expect stem cells to make me feel better.	In general, stem cells made me feel better.
11	What is your hope for this treatment with regard to your leg pain? *Responses: Small reduction in pain, Moderate reduction in pain, Large reduction in pain, Elimination of pain, No response*	During this study, did your leg pain: *Responses: Increase, Decrease, Stay the same, Not sure, No Response*
12	Do you know anyone personally who has received stem cells to treat a disease? *Responses: Yes, No, No response*	What was the hardest part of being in this study? *Text response*
13	How long did it take you to decide to participate in this research study using stem cells for your Peripheral Artery Disease (PAD)? *Text response*	Based on your experience from this study, would you participate in another stem cell study? *Responses: Yes, No, No response*
14	Did you discuss the study with anyone before deciding to participate? *Responses: Yes, No; If Yes, text response*	What about the study treatment did you like? *Text response*
15	What motivated you to participate in this PAD study? *Text response*	What about the study treatment did you NOT like? *Text response*
16	Do you have a person(s) who will help you during your participation in this study? (For example, drive or accompany you to study visits, remind you to take your temperature, etc.) *Text response*	If you had to do this again, would you prefer biological treatment (stem cell or gene therapy) or conventional therapy (revascularization or pills) for your leg pain? Please explain: *Text response*

[a] Responses based on the following 5-item Likert scale: Strongly Agree, Agree, Neither Agree Nor Disagree, Disagree, Strongly Disagree (unless otherwise noted). "No response" was also an option for each question.

Table 2: Expectations of Participants at Baseline and Six Months Post-Treatment

	Expectations at Baseline			**Expectations at Six Months Post-Treatment**		
	Strongly Agree/Agree	**Neither Agree/Disagree**	**Strongly Disagree/Disagree**	**Strongly Agree/Agree**	**Neither Agree/Disagree**	**Strongly Disagree/Disagree**
	Expectations for symptom relief					
Leg pain	60 (77) – *Large reduction or elimination of pain*	11 (14) – *Moderate reduction in pain*	4 (5) – *Small reduction in pain*	33 (42) – *Leg pain decreased during study*	28 (36) – *Leg pain stayed the same/not sure during study*	6 (8) – *Leg pain increased during study*
Leg pain reduction after study treatment	59 (76)	11 (14)	2 (3)	34 (44)	15 (19)	25 (32)
Leg pain decreased due to stem cells	60 (77)	14 (18)	1 (1)	27 (35)	16 (21)	29 (37)
Walk without pain	51 (65)	17 (21)	4 (5)	11 (14)	13 (17)	48 (62)
Feel better overall after treatment	58 (74)	12 (15)	2 (3)	34 (44)	25 (32)	15 (19)
Generally feel better due to stem cells	66 (85)	11 (14)	0 (0)	28 (36)	27 (35)	16 (21)
	Expectations for treatment of disease					
Stem cells are effective	65 (83)	8 (10)	0 (0)	49 (63)	17 (22)	3 (4)
	Expectations related to trial participation					
Minor inconveniences	59 (76)	13 (17)	4 (5)	17 (22)	16 (21)	40 (51)
Tiredness due to logistical complications	25 (32)	30 (38)	20 (26)	13 (17)	10 (13)	51 (65)
Easy to participate	67 (86)	7 (9)	4 (5)	72 (92)	2 (3)	4 (5)

Participants who chose the option “no response” as their answer are not reflected in the table; thus percentages across columns do not add up to 100%.

Table 3: Sub-Group Exploration-Expectations by Perceived Treatment Group at Baseline and Six Months Post-Treatment

	Expectations at Baseline[a]			**Expectations at Six Months Post-Treatment[a]**		
	Perceived Cells	**Perceived Placebo**	**Difference**	**Perceived Cells**	**Perceived Placebo**	**Difference**
	n (%)	n (%)	*P-value*	n (%)	n (%)	*P-value*
	Expectations for symptom relief					
Leg pain	21 (81) – *Large reduction or elimination of pain*	18 (82) – *Large reduction or elimination of pain*	*p=1.000*	2 (8) – *Stayed the same*	13 (59) – *Stayed the same*	*p<0.001*
Leg pain reduction after study treatment	20 (77)	19 (86)	*p=0.478*	22 (85)	4 (18)	*p<0.001*
Feel better overall after study treatment	19 (73)	19 (86)	*p=0.307*	22 (85)	4 (18)	*p<0.001*
Walk without pain	19 (73)	16 (73)	*p=1.000*	10 (38)	0 (0)	*p<0.001*
Leg pain decreased due to stem cells	19 (73)	19 (86)	*p=0.307*	20 (77)	2 (9)	*p<0.001*

Generally feel better due to stem cells	20 (77)	21 (95)	*p=0.106*	21 (81)	2 (9)	*p<0.001*
	Expectations for treatment of disease					
Stem cell effectiveness	20 (77)	19 (86)	*p=0.478*	20 (77)	15 (68)	*p=0.532*
	Expectations related to trial participation					
Minor inconveniences	19 (73)	17 (77)	*p=1.000*	9 (35)	6 (27)	*p=0.756*
Tiredness due to logistical complications	11 (42)	6 (27)	*p=0.368*	5 (19)	4 (18)	*p=1.000*
Easy to participate	21 (81)	19 (86)	*p=0.710*	24 (92)	20 (91)	*p=1.000*

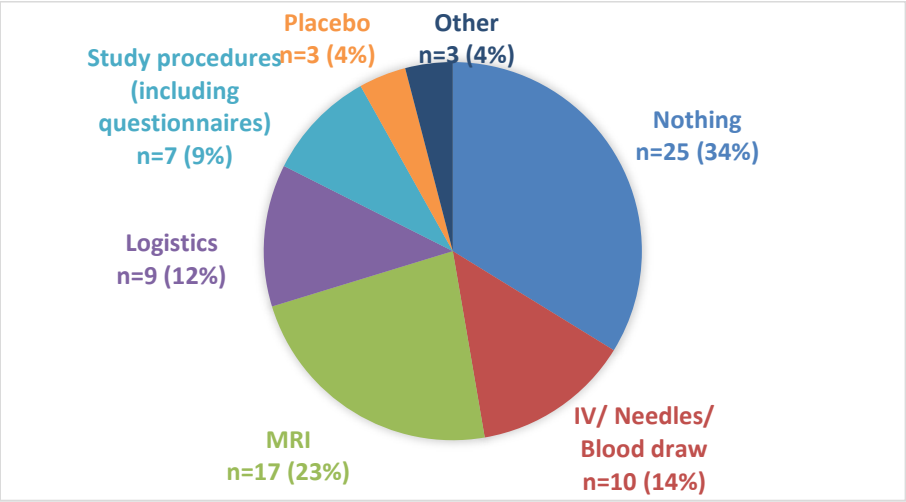
[a] Unless otherwise noted, data reported in this table reflect responses from two items of the scale (Strongly Agree/Agree).

Table 4: Sub-Group Exploration—Expectations for Symptom Relief at Six Months Post-Treatment When Controlling for Actual Assignment

	Expectations at Six Months Post-Treatment[a]					
	Participants receiving Cells (n=24)			**Participants receiving Placebo (n=24)**		
	Perceived Cells	**Perceived Placebo**	**Difference**	**Perceived Cells**	**Perceived Placebo**	**Difference**
	n (%)	n (%)	*P-value*	n (%)	n (%)	*P-value*
	Expectations for symptom relief					
Leg pain reduction after study treatment	12 (100)	0 (0)	*p<0.001*	10 (71)	4 (40)	*p=0.211*
Feel better overall after study treatment	12 (100)	1 (8)	*p<0.001*	10 (71)	3 (30)	*p=0.095*
Walk without pain	7 (58)	0 (0)	*p=0.005*	3 (21)	0 (0)	*p=0.239*
Leg pain decreased due to stem cells	12 (100)	0 (0)	*p<0.001*	8 (57)	2 (20)	*p=0.104*
Generally feel better due to stem cells	12 (100)	0 (0)	*p<0.001*	9 (64)	2 (20)	*p=0.047*
Leg pain (Stayed the same)	0 (0)	8 (75)	*p<0.001*	2 (14)	4 (40)	*p=0.192*

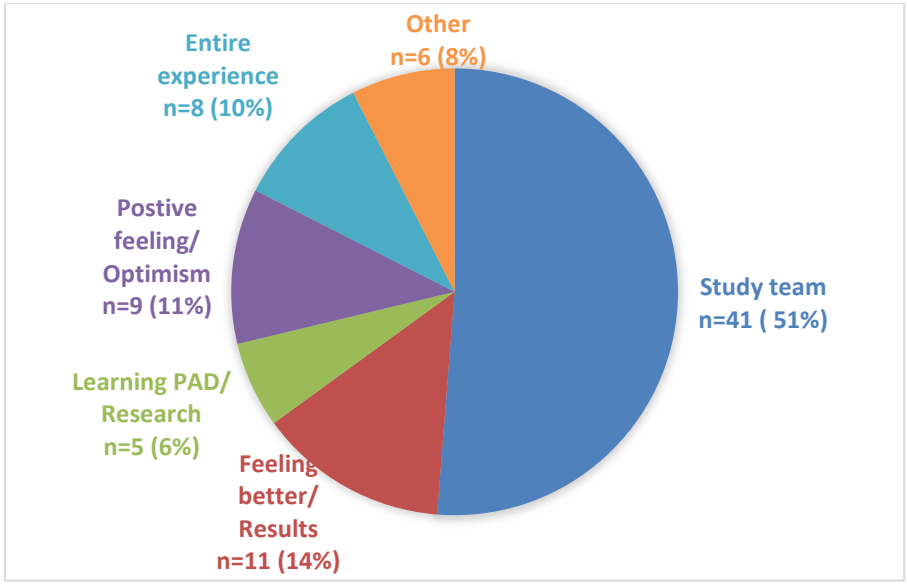
[a] Unless otherwise noted, data reported in this table reflect responses from two items of the scale (Strongly Agree/Agree).

Figure 1a: What Participants Disliked about Study *(open-ended question)*



This chart represents what participants disliked about participating in the PACE trial. Percentages are based on 74 responses. Participants could indicate more than one response.

Figure 1b: What Participants Liked about Study *(open-ended question)*



This chart represents what participants liked about participating in the PACE trial. Percentages are based on 80 responses. Participants could indicate more than one response.