Injections of hope: supporting participants in clinical trials

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Understanding hope and better appreciating the personal investments of trial participants could improve patient experience and trial design, argue Emma Harding, Catherine Mummery, and colleagues

What you need to know

- The nature and scale of a participant's personal investment in clinical trials needs to be better understood in order to provide appropriate support for participants throughout and beyond trial involvement
- One fundamental but overlooked aspect of participants' experience is hope, and articulating and accounting for the impact of hope in the context of trials will be essential for enhancing support and improving trial design
- Sharing trials participants' experiences can better inform others' decisions about participation and lead to more representative trial cohorts and more robust outcomes

Public awareness of clinical trials has never been higher, and there is particular focus on predefined scientific outcomes and their implications for future policy and practice (Does this medicine slow the progression of disease? Does this vaccine lower the chance of disease onset?). In contrast, the experiences of the participants whose involvement is essential to producing these outcomes are often only heard when a trial ends in glory or disaster.[1 2]

Most of what is known about participants' experiences of clinical trials concerns the factors affecting their decision making about involvement. Studies indicate that, even at this early stage, the process is far more complex than a simple weighing-up of any potential medical benefit.[3 4] After enrolment, evidence about how participants and their study partners experience trials is sparse, even though measuring experience is encouraged to increase patient-centredness.[5] The literature that does exist suggests that it is complex: there are

positive benefits such as a sense of hope and purpose, but also significant physical, emotional, and practical burdens.[4 6 7] It is this often neglected psychological investment and impact we shine a spotlight on here.

A trial, with its repeated appointments, provides frequent opportunities to learn informally about the impact of trial involvement on participants and their families. We reflect on the complex array of factors that trial participants at our centre weigh regarding involvement in a trial—factors which continue to be in flux and renegotiated along the often bumpy journey through a trial. We look particularly at the role that hope has in sustaining the immense contributions of participants and their families, and we suggest that the development and delivery of enhanced support for all those involved in trials is essential for continued progress towards the hoped-for scientific outcomes. Individual participants are as central to the story of trials as are their healthcare workers, who, aside from injecting medication, can also inject hope.

Hope has philosophical, political, medical, psychological, spiritual, and other perspectives. Discussion across these fields is testament to the importance of hope as part of the human experience. It is distinct from optimism, which involves expectation—one needs to believe that a given outcome is likely in order to be optimistic about it. Hope merely requires that an outcome is possible and can be directed towards outcomes that seem almost impossible; this can be where it can be most helpful. Hope (and sometimes only hope) can be what sustains us through the most difficult of times. The possibility for hope to endure raises the issue of false hope—based on an unrealistic appraisal of the possibilities—which has important ethical implications within a clinical trial context, in terms of decision making around participation as well as ongoing communications with participants about trial results.

Hope among trial participants

Our work with dementia trials participants (living with a diagnosis of dementia or at risk of developing an inherited form of dementia) and their families has illuminated the many complex ways hope features before, throughout, and beyond their engagement in a trial.

Participants hope to meet the criteria to be accepted on to a trial; they hope that they have been randomised to receive the active drug or intervention; they hope that they will notice a halt in the progression of the disease, or an absence of or a decline in symptoms; they hope that these are not just random fluctuations but evidence that the drug is working; and they hope that the treatment for their condition might mirror the progress achieved in other conditions.[8] There is an additional, overarching and altruistic hope: participants describe their

hopes that they will be contributing to the greater good by being involved in a trial, that there is chance they will be helping to improve things for the next generation, and that their involvement will result in meaningful and lasting change for humanity (box 1).

Box 1. The journey of a trial—finding hope, purpose, and community
"I joined the trial in hopes of a cure. In addition to hope, I've found a supportive community, a sense of purpose, and incredibly helpful information. To me, the benefits of participating far outweigh the costs. I can look myself in the mirror and know that I'm doing everything I can (and the right things) to slow this disease—potentially for me, but more importantly for my children and the world. It is an emotional rollercoaster: thrills of hope, helping, and camaraderie combined with the sadness that comes with routine visits and communications. I imagine it would be easier to forget about my gene mutation for longer periods of time if I weren't in a trial, but then I wouldn't have my fellow participants and trial staff to help me get through the difficult times." (Trial participant)

Hence, the feeling of loss when a study is paused or stopped entirely can generate considerable shock and disruption. Participants have to "find new things to fill the space" and maintain a fading hope that their hours of effort and commitment have not been in vain—that something will be learnt from their contribution.[9 10] This tenacity, the suggestion that hope can remain even when so much has been lost, is epitomised in George Frederic Watts' depiction of *Hope* (fig 1). Re-engaging with a trial (if it resumes) can generate complicated feelings, too. Participants experience a renewed sense of hope, but it is also "hard to shake off the feeling that that could happen again." In the case of dementia trials, decisions about recommitting have to be made against a backdrop of knowing "that you don't have a lot of time."

Hope is repeatedly recalibrated, moderated, and adjusted for as participants and their loved ones continually adapt to their changing everyday lives and circumstances in, around, and beyond a trial.

Fig 1 *Hope* by George Frederic Watts and assistants, 1886. Traditionally the figure of Hope is represented by an anchor. Seeking a more original approach to symbolism and allegory, Watts shows her blindfolded, seated on a globe, and playing a lyre with all but one of the strings broken. Hope's attempt to make music seems futile, and several critics argued that the work might have been more appropriately titled *Despair*. Watts explained that "Hope need not mean expectancy. It suggests here rather the music which can come from the remaining chord." (Reproduced with permission of the Tate under Creative Commons CC-BY-NC-ND 3.0 https://www.tate.org.uk/art/artworks/watts-hope-n01640)

George Frederic Watts, Tate

Understanding the investment of trial participants

Trials are often discussed in terms of the magnitude of financial investment by pharmaceutical companies, states, and other funders.[11] But conversations with participants reveal the magnitude of their personal emotional investment.[6 7] This is particularly pronounced among individuals in long running trials on a slowly progressive condition such as Alzheimer's disease, and in families with inheritable conditions where multiple generations may participate over decades (see box 2). Trial participation is an intense experience that can force the individual and those around them to confront the disease and the difficulties it generates. This is often challenging, but for some family members the repeated assessments can provide a helpful external source of validation for their otherwise subjective experience of decline.

Box 2. Family ties
In the DIAN-TU trial, led by Cath Mummery at the National Hospital, people who are at risk of a genetic form of Alzheimer's disease are asked to commit for a four-year period to being involved in a trial of anti-amyloid treatment. Despite the intensive nature of regular visits, infusions, and cognitive and imaging assessments, one participant wrote of his experience: "It's made a real difference to me being involved in the trial. For many years, I felt useless and unable to have any effect on a disease that has been rife in my family. I have lost so many, and unfortunately there will be a few more that will suffer the same fate. Early onset Alzheimer's is cruel. My father suffered with the disease for over 10 years. It is his untimely death that motivated me to try and do more for the family. If he was here today, I am sure that he would be involved in the trial. Being part of DIAN-TU and having such wonderful support has helped me grow stronger. It has enabled me to deal with many skeletons [in] my closet and leave them behind. The work that you do goes much further and deeper than a cure."

In addition to making physiological and emotional investments, clinical trial participants invest a great deal of time over an extended duration. For example, volunteers in presymptomatic familial dementia trials may be in their 30s or 40s, requiring time to be spent away from busy family and work lives. Many dementia trials last for four or five years, leading to dynamic relationships between all involved in the trial: participants, family members, and the study team. These relationships develop over time, often with the same study team members, and exemplify the social value that participation in clinical trials can have, beyond contributing to scientific progress. These relationships can instil hope and offer valued opportunities for ongoing connection, familiarity, and support: "The human contact of coming to a study is something else that would give us hope. [My husband] actually used to enjoy his visits, he enjoyed talking to the nurses, and he felt such support and hope from just being there" (partner of study participant)

Understanding the nature and value of these interpersonal relationships is critical to optimising support for participants at each stage of a trial, and importantly at the time a trial stops, when the feeling of involvement and support can become a feeling of abandonment.[12]

Enhancing future trials

There are moral, psychological and scientific benefits to improving the experiences of trial participants. Taking a more holistic view of the varied experiences of trial participants, acknowledging, accounting for, and learning to talk about the hope imbued in a trial, and planning ways to meet the emotional and social needs of trial participants may improve both the experience of participants and the scientific quality of trials.

Understanding, and enabling others to understand, the experiences of hope, acceptance of uncertainties, and multiple investments that characterise trial involvement is a first step to providing heightened care and support for individuals and families participating in trials (see box 3). Including appropriate participant support in trial protocols at the design stage signals that their contribution is not taken for granted and that the costs of participation are recognised beyond out-of-pocket financial expenses. This might include psychological support sessions built within the trial schedule, in particular around the beginning and end of a trial, or providing opportunities to share experiences with other participants. Weaving participant experience into recruitment and consent—for example, by sharing the learning and experiences of trials network members with prospective participants to complement patient information sheets and consent forms—may enhance informed consent and encourage wider participation. Platforms such as support group meetings or dedicated social media spaces for individuals to share their experiences with each other before, during and after trials may help to foster feelings of acknowledgement, shared understanding and connectedness about the relatively rare and often emotionally complex experience that taking part in a trial can be. For example, establishing a support group at a research site when a trial is abruptly stopped (such as the aducanumab trial in March 2019[13]) may allow participants, family members, and the study team to share feelings of loss, abandonment, and disappointment and reconcile those concerns with hopes for the future. Facilitating these sorts of platforms for sharing will require planning and commitment from study sponsors and institutional review boards, and careful consideration of participant confidentiality and communication

Box 3. Practical suggestions to improve support for trial participants

- Consider psychological support for trial participants and families
- Collect and analyse of psychological outcomes to model psychological impact of trial participation
- Identify positive and negative indicators of an individual's experience in trials
- Make participants heard to widen participation and enhance representation, such as:
  - Include those with lived experience in trial protocols
  - A dedicated consent process to address issues of confidentiality and enhance participant autonomy about sharing their experiences
  - Establishing an independent trial support group
- Development of guidance and training resources for trials and study centres to:
  - Identify vulnerable individuals before participation
  - Support participants and families throughout and beyond a study, including once a study has completed or if trial is unexpectedly paused or terminated
  - Build dynamic relationships between study team, participants, and carers over time

By enhancing trial enrolment and retention, better support for participants may contribute to more robust and representative outcomes. Poor representativeness of participants has negative implications for the validity and power of trials.[14] In addition, understanding the psychological impact of a trial on participants may enhance our interpretation of outcome measures and changes in outcomes over time (possibly including the magnitude of placebo effects).[15] For example, when does hope itself become an independent variable in a trial, or to what extent does hope and its fluctuations influence self-reported outcomes?

Better support and changes to practice for trials participants must also recognise and address any risks to the fundamental trials concept of equipoise, i.e. that expectations regarding the benefits of treatment and control must be balanced). For that reason, support should be given to all participants, whether they are on treatment or placebo. Enhancing the experience of trial participants should not alter that balance, nor alter hope itself, but increase resilience to the challenging aspects of being in a trial.

We propose key actions for specific stakeholders to facilitate enhanced support for and between trial participants to build on the positive experience of many participants who view trials as being about "more than a cure," recognising that trials inject and enable hope for many people living with serious and life limiting health conditions.

How patients were involved in creation of this article Patient involvement
This article has been shaped by informal conversations with trial participants and their carers and family members at the Dementia Research Centre over many years—conversations that have started before the trials and continued long after trials have finished, which have happened in 1:1 clinical research visits as well as PPI group meetings. Comments have been invited on this article at various stages from several participants, and it is co-authored by PR, who has been engaged in a trial as the study partner of the main participant and has personal experience of supporting a close family member throughout a clinical trial.

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Contributors and sources: EH contributed to the conception of the article, facilitated PPI discussions on the key themes reported within the article, and contributed to the writing of the article. PR participated in PPI discussions on the themes raised in the article and provided

comments on the manuscript to ensure the perspectives of those involved in trials were adequately represented. JW led team discussions on the philosophical themes of the article and offered comments on the manuscript. As co-lead of the Rare Dementia Support service, SJC contributed to the conception of the article, to PPI discussions on the themes raised in the article, and to the writing of the article. As head of clinical trials at the Dementia Research Centre, CJM contributed to the conception of the article, coordinated and facilitated PPI discussions on the themes reported within the article, contributed to the writing of the article, and is guarantor of the article.

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