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Recruitment for placebo-controlled trials of interventional procedures: a patient-centred approach

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Placebo-controlled trials of interventional procedures present additional recruitment challenges compared to placebo-controlled drug trials and unblinded interventional trials. This is related to the additional risks a placebo intervention might pose to patients without any potential for physical therapeutic benefit. Patient reluctance to participate can lead to difficulty in recruiting to target and time.

Many reasons are cited by patients and medical teams when they decline to participate in placebo-controlled trials. However, educating patients and medical teams can alleviate concerns and ensure that, with fully informed consent, patients choose to participate in research that can be practice changing.

Patients often cite the feeling that they need to know what treatment they have had as a reason to decline participation. This desire to know is amplified in an interventional trial compared to a drug trial because of the more invasive nature of the placebo intervention. For example, in trials of renal denervation, patients randomised to the placebo intervention still undergo renal angiography[1]. Trial participants need to be prepared to be discharged from hospital after a procedure with no knowledge of what treatment they have had; this is not acceptable for all patients.

Both clinicians and patients often cite a desire for the patient to receive the active treatment as a reason not to participate because the idea of deferral of an intervention is not palatable to them. Of course it is understandable for participants and their clinicians to prefer to be in the intervention arm because of the possibility of therapeutic benefit, but we rely on the altruism of patients to assess interventions accurately, without bias, in order to better treat the patients of the future.

In this article we share our personal experiences of recruitment **(Table 1)** and how we have tried to address these issues in the placebo-controlled ORBITA[2] and ORBITA-2[3] trials. These two trials randomise participants to either percutaneous coronary intervention (PCI) or placebo in the catheterisation laboratory immediately after invasive coronary angiography and pressure wire studies, and once a deep level of conscious sedation has been achieved. If randomised to placebo, the patient remains in the catheterisation laboratory with auditory isolation and sedation for at least 15 minutes, before removal of the sheath.

Trust building: the researcher-participant relationship

For any trial, participation relies on the researcher-participant relationship. Also there is a link between recruitment rates and the nature of the trial. For example, an internet survey may have

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Table 1. Proposed recommendations based on our personal experiences of successful and unsuccessful conversations with potential participants.

Recommendation	Rationale and comments
Suggestion of participation in a trial should ideally come from the patient's own treating clinician.	– This helps to reassure the patient that the offer to participate has been carefully considered by their medical team. – The research option should first be discussed by someone who really knows their clinical details and has their best interests at heart.
Frame the conversation around the question the trial is trying to answer, and why placebo control is important to get the right answer.	– Patients often understand the placebo effect, are interested in the concept, and may be more willing to accept the possibility of placebo if they fully understand the rationale.
Highlight any personal benefits of taking part.	– In trials of symptom relief, taking part in a placebo-controlled trial can help patients to understand their symptoms better.
Approach patients in person if possible.	– In-person conversations help to build rapport. – The next best option is to arrange a convenient time to chat to the patient over the telephone, or preferably using a video link. – It helps to include a friend or family member during the discussion, if the patient wishes.
Avoid the term "sham"	– Negative connotations of the word "sham" can lead patients and clinicians to believe that the research is designed around "deception" which naturally adds to the burden of concern. – Instead, the word "placebo" should be used. – Placebo interventions should be seen as a normal part of research practice just as placebo medications have become acceptable to the public.
Be clear that a patient's decision to decline participation will not adversely affect their ongoing care.	– Transparency is paramount. This open approach increases trust and is essential to good clinical practice.
Allow sufficient time for recruitment conversations and to build a rapport.	– It helps to hear the patient's history in their own words. – Use open questioning, such as "What prompted you to see your doctor in the first place?" When a patient is describing their history, you can identify their priorities and pre-empt concerns or problems. – Patients may find it difficult to take time away from work to attend research visits and this may have economic implications. You can address this by offering flexibility in scheduling. – Patients often request more time to think, usually to talk it over with family and consider their options, so arrange a time for further discussion. – Do not be tempted to rush the patient into making a decision. Participation in research requires informed consent and part of that process includes giving the patient enough time to understand the proposal and have their questions answered.
Explain exactly what the procedure entails and the risk of a complication.	– Concealing or underplaying risks is not only unethical but also undermines the researcher-participant relationship. – Explain the risks in detail after quite a bit of time has been spent on understanding the patient's journey to that point and their priorities for treatment. Nothing should come as a surprise to the patient on their journey through the clinical trial.

a high participation rate despite the researchers developing no relationship with the participants. The more invasive or intrusive the study, the greater the number of study visits, or the higher the procedural risk, the more critical this relationship becomes. When the placebo intervention can carry risks which extend as far as death, the participant places a lot more trust in the research team.

Patients as partners

Patients often enjoy participating in trials. In particular, many are curious about the placebo effect and relish the chance to contribute to science. To harness this, we try to educate patients about why the trial is necessary and the potential impact it has for future patients. In designing ORBITA-2, we involved patients in the design, conduct and dissemination of future trial results. Our ORBITA focus group of previous participants was integral in shaping the aims, objectives and design of the trial. They also reviewed and amended all patient information literature and helped to design and pilot the smartphone app used in ORBITA-2. A former ORBITA patient was a co-applicant in grant applications and is a member of the trial steering committee. Engaging patients in research adds to the value of the research we produce and ensures that it remains patient focused and acceptable to potential participants.

Protocol considerations

The placebo intervention has to be sufficiently similar to the active intervention so that the patient does not know what they have had but should also carry as low a risk as possible. **Table 2** shows how the DITTO framework[4] can be applied to designing a placebo-controlled trial using the example of a trial of PCI.

Table 2. Optimising the design of a placebo-controlled trial of PCI using the DITTO framework.

DITTO framework item	Example
Deconstruct intervention into constituent components and co-interventions	– Anaesthesia – Arterial access – Coronary angiography – Coronary angioplasty – Haemostasis
Identify critical surgical element	– Coronary angioplasty
Take out the critical element	– Remove coronary angioplasty – Use of anaesthesia, access, coronary angiography and haemostasis are identical for placebo and PCI arms.
Think risk, feasibility and role of placebo in the trial when considering remaining components	– Anaesthesia, arterial access and coronary angiography carry a risk of complications. – However, these components are necessary to ensure that the treatment effect of PCI is distinguished from the effect of simply having coronary angiography and to ensure blinding of patients and staff.
Optimise placebo to ensure effective blinding of patients and trial personnel	– Use over-the-ear headphones for auditory masking. – Ensure patient cannot see cath lab monitors. – Sedation to a deep level of conscious sedation. – Similar procedural time for placebo and PCI. – Intervention not documented in the patients' notes. – Dual antiplatelet therapy for all. – Standardised handover to ward team. – Same post-procedural care on ward. – Limit interaction between blinded and unblinded staff. – Standardised discharge letter for all.

Trial management

Aside from trust and rapport building with the patient, management of the trial should be designed to remove barriers to participation. Here are some suggestions:

1. In trials designed to test existing therapies that form part of clinical practice, patients in the placebo arm should still be offered the active intervention once trial participation is complete.
2. All cost and time burden to partcipants should be minimised. Travel and refreshments, ease of access to medical care, and a dedicated contact telephone number for questions or concerns should be provided. It is important to allow flexibility in scheduling of study visits when approaching patients.
3. Ideally a patient should have one point of contact for the duration of the trial because, once they have built trust with a member of staff, it can feel disconcerting for the next visit to be handled by someone else. If the visit is going to be handled by someone else, the patient should be informed in advance.

As placebo-controlled trials become more frequent in procedural specialties, the need to recruit patients into these more complex trial protocols will become more important. Our personal experience of recruiting patients to placebo-controlled interventional trials has taught us that there are ways to improve recruitment rates and patient experience. With specific focus on the researcher-participant relationship and on the design of the study, these trials can be done and can provide novel data with the potential to have an impact on patient care.

Conflict of interest statement

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