BJPsych Open (2015)
1, e3–e4. doi: 10.1192/bjpo.bp.115.000919

Editorial

Ethical considerations in placebo-controlled randomised clinical trials

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Summary
Ethical considerations in standard medical care and clinical research are underpinnings to quality medicine. Similarly, the placebo-controlled double-blind randomised clinical trial is the gold standard for medical research and fundamental to the development of evidence-based medicine. Researchers and clinicians are challenged by ethical concerns in the informed consent with a need to maximise understanding and minimise therapeutic misconception. This editorial expands on themes raised by Chen *et al*'s article 'Disclosing the Potential Impact of Placebo Controls in Antidepressant Trials' and serves as an invitation for further submissions to *BJPsych Open* on ethics, research design and informed consent.

Declaration of interest
None.

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The historical gold standard for pharmaceutical medical research is the placebo-controlled double-blind randomised clinical trial (RCT).[1–3] This research design, which is used in monotherapy, add-on adjunctive and 3-arm (investigational drug, active comparator and placebo) RCTs, is consistent with the Food and Drug Administration and European Medicines Agency regulatory requirements for investigational new drugs – proving superiority of the investigational drug over placebo.[1,4–6] There is an ongoing debate regarding the use of placebos in RCTs varying from methodological and ethical justification of placebos to the specific language required for a truly informed consent, especially in vulnerable populations including, but not limited to, psychiatric, paediatric, geriatric, cognitively impaired, low literacy and incarcerated patients.[2,3,6–13] Further, recent papers address whether overprotection of vulnerable patients prevents their inclusion in research and discuss the socioeconomic factors implicit in the newly termed 'structural coercion'.[14–16] *BJPsych Open* is pleased to add to this important discussion by publishing 'Disclosing the Potential Impact of Placebo Controls in Antidepressant Trials' by Chen *et al*.[17]

Chen *et al* focus on a major concern for all clinical research, ethical considerations in the informed consent. The authors studied the impact of using an enhanced informed consent on enrollment for a simulated placebo-controlled antidepressant RCT. The enhanced consent gave the study patients a greater quantitative understanding of the potential for therapeutic improvement – 40% with enrollment in the placebo-controlled RCT compared with 65% with non-enrollment in the RCT but with continued individualised psychiatric care. Two key findings were noted: (a) significantly decreased percent willingness to enroll in a placebo-controlled RCT in patients receiving the enhanced consent; and (b) increased altruism as reason for enrollment comparing the enhanced to standard consent. These findings are not surprising for emphasising that comparative lack of therapeutic benefit from enrollment in a placebo-controlled RCT in moderately depressed patients should result in preferentially seeking individualised treatment; however, this paper is important for it clearly documents the expected difference in enrollment and discusses associated implications while acknowledging limitations to research methodology.

Maximal understanding of the research process (purpose of the study, voluntariness, withdrawal, randomisation, therapeutic benefits/risks associated with treatment/non-treatment and societal benefits) with minimal therapeutic misconception is fundamental to a meaningful and ethical placebo-controlled RCT informed consent.[18–22] Nonetheless, a series of articles have noted that ~50% of all patients enrolled in RCTs have an incomplete understanding of one or more components of the informed consent.[18,19] Clearly, this lack of understanding in a significant portion of research patients is not acceptable for a truly informed consent and has resulted in four methods being tested for increased understanding – enhanced consents (as in Chen *et al*'s study), prolonged discussions, multimedia and test/feedback.[23,24] In a recent meta-analysis, only prolonged discussions and enhanced consents were statistically associated with an increased understanding of the informed consent.[24] Evaluation of the research methodology used for these positive findings noted that greater improvement in understanding occurred in simulated as opposed to 'real-life' RCTs for enhanced consents, whereas for prolonged discussions 'real-life' RCTs had a greater understanding.[24]

The enhanced informed consent used by Chen *et al* increases transparency of the intended RCT, for it addresses one key issue which each enrollee must comprehend – relative therapeutic outcome.[17] The enhanced consent in this study does not address in greater detail methodology – both the standard and enhanced consents lack mention of voluntariness, ability to withdraw and a brief study protocol which might include secondary study benefits including additional laboratories. Further, in both standard and enhanced consents there is only a very brief description of placebo (three words – 'a sugar pill'). This limited description of placebo is commonplace as noted in one recent review of 359 placebo controlled RCTs; this review also found that none of these RCTs included references to placebo or nocebo effects.[25] Since placebo and nocebo effects play important roles in both therapeutic and research interventions, discussions of such are important in clinical practice, research and informed consents.[25–27] The enhanced consent used in Chen *et al*'s study decreases only in

part therapeutic misconception for the methodology description is limited and no references are made to placebo and nocebo effects.[20–22] By enhancing the consent with only reference to relative therapeutic outcome, the authors have studied whether this difference alone impacts willingness to enroll; however, methodology with placebo and nocebo effects impacts an enrollee's ultimate decision. As such, future enhanced consents should have a greater inclusion of methodology as well as a brief description of placebo and nocebo effects.

The authors correctly identified a principal limitation of their study – as a simulation, this study addressed willingness to enter a potential RCT as opposed to actually having enrolled in an RCT. As such, the reported findings may be significantly different in 'real-life' research studies.[24] Further, the results found in this study may vary based on the severity of illness. For the enhanced consent, the authors suggested comparative improvement rates for enrollment *v.* non-enrollment in the RCT for moderate depression; would those improvement rates be different for mild or severely depressed patients and how would these different rates impact enrollment? Would comparative improvement rates and enrollment vary based on specific psychiatric illness and associated severity? Further, enhanced informed consents are generalisable to non-psychiatric medical illnesses and to surrogate consents where these same questions can be posed.

Chen *et al* comment that decreased willingness to enroll using the enhanced consent should result in increased costs based on their simulation study. This may not be the case, for two reviews of actual accrual rates using multiple methods to improve understanding informed consents reported no decline in recruitment.[23,24] Further, retention rates should be higher based on increased understanding with realistic expectations. As such, one might find similar or even decreased cost in studies. The authors also state that 'one cannot expect ethics to be always without cost'.[17] Perhaps a more valid consideration is that not being ethical in both research and standard medical care is too great a cost for medicine to permit. Thus, it is mandatory for increased efforts to maximise ethical interventions.

As with all worthy research, Chen *et al*'s article in addressing one important issue has raised multiple questions requiring future studies. Further research on enhanced informed consents, as well as other methods used to increase understanding of informed consents, should address: (a) willingness to enroll in 'real-life' RCTs with measurement of actual accrual and retention in different illnesses; (b) measurement of understanding and therapeutic misconception, including vulnerable populations and surrogate consents;[21,28,29] and (c) impact of methodology (research design and randomisation), placebo and nocebo effects, and severity of illness on enrollment. *BJPsych Open* welcomes further submissions on these topics.

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First received 30 Apr 2015, accepted 1 May 2015

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