

Preferences

“You decide doctor”. What do patient preference arms in clinical trials really mean?

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Does it really matter if preferences are not rigorously assessed in trials?

It is well established that random assignment between experimental treatment and control arms is the gold standard in clinical trials to minimise differences between the groups being compared and safeguard against bias. There is, however, a fear that such random allocation may not accord with patients' preferences for the intervention or treatment, thereby compromising trial validity. It is possible that patients may resent not receiving their treatment of choice, and their negative attitude may lead to non-adherence to treatment or affect outcomes in some other way. Consequently, one option for trial designers is to include patient preference arms, whereby patients with no treatment preference are randomly allocated to experimental and control arms, while patients expressing a treatment preference are allocated to receive their preferred treatment.¹

Most of the debate about preference arms has focused on issues concerning increases in the sample size required, the types and stages of randomised design, and how to compare the groups. Ethical issues also arise, leading to concerns about those with strong treatment preferences being included in studies in the first place, especially those in which randomisation takes place irrespective of patients' elicited preferences (that is, to measure whether those who received their preferred treatment, or not, differed from the no preference groups). There is less information about how doctors' preferences for treatment influence their patients' preferences.²

A recent systematic review of the impact of patient and doctor preference for intervention in randomised trials, across a range of disorders, reported that elicitation of preferences led to a substantial proportion of potential participants (patients, including parents, and doctors) refusing randomisation. However, differences in outcome across the trials between randomised and preference groups were reported to be small, and where preference effects were noted

these were generally inconsistent.³ The authors of this study concluded that there was little evidence that preference substantially interfered with the internal or external validity of trials. The review included studies according to methodological criteria and if they “measured or recorded patient or physician preference” (page 1090). However, the reviewed studies varied widely in their approach to eliciting preferences, and preferences often appeared to have been simply noted in the consent to randomise procedures used. The methods used in most research on preferences include single item questions asking patients to state the option they would choose, Likert scales of the strength of the stated preference, and utility measurements (for example, rating scales, time trade offs, standard gamble methods)²; less commonly, preferences have been explored using discrete choice analysis.⁴ The question arises: does it really matter if preferences are not rigorously assessed in trials?

DO PREFERENCE ARMS REALLY REPRESENT PATIENTS' PREFERENCES?

It matters if preferences are not rigorously assessed because of the review's finding that there was little evidence that preference substantially interfered with trial validity. While this may be a valid conclusion, the result could also be simply attributable to each preference arm containing bias or a random mix of genuine preferences. Arguably, a preference can only be “true” if based on full, clear, and unbiased information about the treatment options: a preference is a value for alternative options for action after informed deliberation of their risks and benefits. And preferences need rigorous, standardised elicitation: research has shown that preferences are complex phenomena that may be informed by a wide range of constructs. That is, patients may have different reasons for expressing similar preferences—reasons based on past, or close

others' experiences; on misunderstandings of the different treatments; or on a plethora of other factors that range from justified fear to considered practicality.⁵ Patients can be affected differently by the same situation,⁶ and attach different significance to the same processes and outcomes,⁷ resulting in different treatment preferences. Additionally, when confronted with one or more unfamiliar treatments and asked to state a preference, a patient's immediate answer might not survive further reflection, or indeed, first contact with the treatment itself. Furthermore, we must be cautious in interpreting preference studies even when these do provide patients with apparently full descriptions of treatment options. It is well known that patients' and doctors' preferences for treatment can be influenced by “framing” effects (the presentation of information in different ways, negatively or positively, and in a different order), understandings of the concept of risk (relative or absolute risks); verbal (“rarely”, “sometimes”, “never”) or numeric (single figures, decimals, fractions, or percentages) descriptions of risks and benefits.⁷ Other influences might include recall bias in relation to the information on risks and benefits received; varying expectations; preference for the status quo or familiar scenarios; and, in the case of patients, by their doctor's preferences, perhaps because of patients' deference to doctors' dominance in the decision making process and the inclination of a substantial minority, especially older patients, to leave the decision “to the doctor”⁸ (despite the fact that doctors' and patients' treatment preferences, when measured in a standardised way, have been shown to vary).² All this can mean that the relation between stated and actual “true” preferences is weak. Surprisingly, there is little research examining the relation between patients' anticipated preferences for treatment, actual behaviour (treatment), and post-treatment preferences.⁹ Given these potential influences, then, it is not unexpected that the conclusion of one systematic review was that, while provision of information on risk reduced decisional conflicts and stimulated patients to be more active in treatment decisions, the effect on the outcome of these decisions (actual treatment) was uncertain.¹⁰

In view of all this potential “noise” in preference elicitation, it might be considered as surprising if there was evidence that preferences, as currently measured, substantially interfered with trial validity. The possibility that preference arms in trials may not reflect true, informed, rigorously assessed preferences means that the results of analyses of the effects

of preferences on outcome are ambiguous. Asking a person if they prefer “tea or coffee” may result in a valid choice, given that such preferences are likely to be genuinely informed by familiarity with, and experience of, the two options. But in the case of treatment preferences, initially low patient knowledge of the processes, risks and benefits of the treatment options, means that such simplistic methods of questioning, which do not even consider the reasons underlying preferences, may be inappropriate for this complex topic. The conclusion can only be that the results of analyses of preference arms in trials must be viewed with caution, and the elicitation of preferences deserves more respect, with the application of better methodology to match the rigour of other aspects of trial design. If each preference arm in clinical trials does simply contain a random mix of genuine preferences, then this not only has implications for the rigour of research methodology, but also for the soundness of health policy on which such research is based.

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Speaker’s corner

A fascinating doctoral thesis

In early March 2004 I had the opportunity of travelling to Trondheim. Although not exactly paradise, this Norwegian city is interesting because it has the most northerly cathedral of Europe. It was built in the 12th century in the Romanesque style, and has been carefully preserved through the ages. The city was still partly covered by snow, but this was rapidly melting in a heavy rain. To find shelter I strolled into the cathedral bookstore, where I discovered a most fascinating doctoral thesis.

We all know that one can write doctoral theses about any subject, but this student had really found an extraordinary topic. He had written his thesis about weathering effects on the stone surface of Trondheim cathedral—a detailed study of how wind, precipitation, and frost have left their traces on this church. Pictures of roofs, windows, and walls showed the destructive influences of the hostile environment in which this church has been built. It was only through regular, careful repair that the building had survived, and this thesis was an attempt to contribute to protecting the building against future attacks on its integrity by proposing a few improvements of the design of its surface.¹ Quite clearly, its author had come to love this building dearly. It was difficult to escape the impression that the author had seen this cathedral as a living being—a grandmother whose hair, face, and skin have suffered from the wear and tear of time.

Browsing through this remarkable book I realised that this image of a building surviving in a hostile environment is actually a nice metaphor for human aging. Aging is a matter of accumulating damage to the body, plus a terrible design failure. It is a matter of being exposed to the wear and tear of time, plus a lack of sufficient repair mechanisms. The latter is evident from the fact that there are examples of species that do not show signs of aging. The oldest living organism in the world is a bristlecone pine (*Pinus longaeva*) nicknamed ‘Methuselah’. He is 4770 years old and lives at high altitudes

in a dry area in the White Mountains, east California (USA). Unlike human beings, bristlecone pines show no inherent signs of senescence, and even the oldest among these remarkable trees continue to produce cones with viable seeds.² Longevity in trees is achieved by characteristics such as retention of stem cells after each growth cycle, ability to replace complete damaged organs, a sectorized vascular system that permits part of a tree to survive when the whole cannot, formation of clones, and other biological mechanisms that human beings must do without.³

Can we live longer? Evolution has endowed us with biological systems that were intended to last for 40, 60, perhaps 80 years, and revolutionary advances in life expectancy are probably dependent on engineering these biological systems. Perhaps, if we unravel the secrets of bristlecone pines and other long lived organisms, we can bypass evolution and develop interventions that increase average human life expectancy at birth to 100, 120, perhaps 200 years. If we would prevent the death rate to rise after the age of adolescence, by radically improving our environment and drastically improving our design, life expectancy would increase to 1200 years,⁴ a value approximating that of bristlecone pines and Trondheim cathedral. The “only” remaining question is whether we would actually enjoy it ...

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