

ENDGAMES

STATISTICAL QUESTION

Zelen's design

Philip Sedgwick *reader in medical statistics and medical education*¹, Daniel K Sokol *medical ethicist and barrister*²

¹Centre for Medical and Healthcare Education, St George's, University of London, Tooting, London, UK; ²Inner Temple, London, UK

A randomised controlled trial incorporating Zelen's design was used to investigate whether an intervention involving postcards reduced repetitions of deliberate self poisoning. Participants were patients aged over 16 years who presented to a toxicology service with deliberate self poisoning. The intervention consisted of eight postcards sent to the participants over 12 months, combined with standard care. Each postcard was exactly the same and invited patients to contact the toxicology service if there was anything they wished to discuss regarding their self poisoning. The control group received standard care alone. The main outcome measures were the proportion of patients having one or more repeat episodes of deliberate self poisoning and the number of repeat episodes of deliberate self poisoning per person in 12 months. In total, 772 patients were recruited, of whom 378 were randomised to intervention and 394 to control.¹

The researchers reported that the postcard intervention did not significantly reduce the proportion of individual repeaters, although it significantly reduced the number of repetitions of deliberate self poisoning per participant over the 12 month study period.

Which of the following statements, if any, are true?

- a) Patients consented to being allocated to treatment at random.
- b) All patients consented to participation in the trial.
- c) The principle of intention to treat was used to analyse the results.

Answers

Answer *c* is true, whereas *a* and *b* are false.

The aim of the randomised controlled trial was to investigate whether the intervention of postcards combined with standard care reduced repetitions of deliberate self poisoning, when compared with standard care alone. The randomisation of patients to treatment is widely acknowledged as an essential component of modern day clinical trials, and its advantages have been described in a previous question.² In obtaining informed consent, researchers must explain to patients that

randomisation will be used to allocate them to treatment. Informed consent is usually obtained before treatment allocation. However, in the above example Zelen's design was used.

Zelen's design is sometimes called a single consent design or, more generally, a randomised consent design. In the above example, Zelen's design involved randomising patients to intervention or control without their consent (*a* is false). Written informed consent for participation in the trial was sought only from those who were allocated to the intervention group (*b* is false) and then only after randomisation. Patients allocated to intervention could refuse their allocated treatment and receive standard care alone. Of the 378 patients who were randomly allocated to intervention, 76 refused and opted for standard care. Those patients who refused the intervention and received standard care were still part of the trial. Consent for participation in the trial was not obtained from those patients allocated to standard care (*b* is false). Patients in the control group were not aware that they were involved in a trial and that other patients were receiving an alternative treatment option.

In the above example the standard care group was not followed up. Data for the control group were collected from routine healthcare databases, with information obtained when patients presented again with deliberate self poisoning. Sometimes it is necessary to follow up the control group participants in a trial that uses Zelen's design. If so, consent is required, but participants in the control group will not be told that they are in a trial, only that they are in a study of their healthcare. The control group will remain unaware of an intervention group.

When Zelen's design for randomised controlled trials was proposed, an analysis by intention to treat was intrinsic to the design (*c* is true). The treatment groups were analysed as they were intended to be treated, with all participants included in the treatment groups to which they were originally allocated, regardless of whether they started or completed the treatment protocol. In particular, those patients who were randomised to the intervention but who refused their allocated treatment and opted for standard care (control) were analysed as though they had received the intervention. This maintained the composition

of the treatment groups achieved at baseline and reduced the potential for confounding resulting from an imbalance in baseline characteristics. Intention to treat has been described in a previous question.³ A per protocol analysis, described in a previous question,⁴ is not used in Zelen's design. A per protocol analysis includes only those participants who adhered to the treatment protocol to which they were originally allocated.

For most therapeutic trials Zelen's design is considered unethical. In particular, the randomisation of patients to a trial and their inclusion in it without their consent has caused much debate. The principle of respect for autonomy generally requires researchers to obtain consent before recruiting patients into a trial and randomising them to treatment. However, this requirement is not absolute, and there are circumstances where Zelen's design is ethically permissible. As for any clinical trial, the potential harms and benefits must be balanced in light of the specific facts of the proposed research.

Zelen's design has been criticised for withholding information about potentially beneficial alternative treatments from participants receiving the control treatment. However, although participants in the control group are in a trial, they are not undergoing a treatment that is any different from what they would have received anyway. Furthermore, patients allocated to the control group must still consent to standard care, as they would if not involved in the trial. Most importantly, Zelen's design does not subject patients to a new treatment without their consent. Participants allocated to the intervention could refuse their allocated treatment and receive standard care (control treatment).

The use of randomised consent designs in clinical trials can overcome difficulties that may occur if informed consent were obtained before randomisation. Obtaining consent is not always

without harm. The very process of doing so in a randomised controlled trial, however expertly done, can create much anxiety and confusion with little benefit. Informing patients of the treatment options before randomisation could have caused distress to those who were not allocated to the intervention. The researchers may have deemed it ethically dubious to raise hopes about the intervention in vulnerable patients, only to deny it to half of them through randomisation. Furthermore, informing patients in the control group about the intervention might have changed their behaviour and influenced the results. It is also possible that if patients in the control group were aware of the intervention they might have dropped out of the trial altogether through lack of motivation.

Randomised consent designs are a group of trial designs that include not only Zelen's design (single consent) but also double consent designs. In a double consent design, patients are still randomised to intervention or control without consent. Initially, all patients are offered the treatment to which they were randomised. However, patients in either group—intervention or control—can decline the treatment to which they were allocated and be offered the alternative. Double consent designs will be discussed in a future question.

Competing interests: None declared.

- 1 Carter GL, Clover K, Whyte IM, Dawson AH, D'Este C. Postcards from the EDge project: randomised controlled trial of an intervention using postcards to reduce repetition of hospital treated deliberate self poisoning. *BMJ* 2005;331:805.
- 2 Sedgwick P. Why randomise in clinical trials? *BMJ* 2012;345:e5584.
- 3 Sedgwick P. Analysis by intention to treat. *BMJ* 2011;342:d2212.
- 4 Sedgwick P. Analysis by per protocol. *BMJ* 2011;342:d2330.

Cite this as: *BMJ* 2012;345:e8505

© BMJ Publishing Group Ltd 2012