VIEWS ON ALLOCATION CONCEALMENT METHODS IN RANDOMIZED CLINICAL TRIALS: A SURVEY OF CLINICAL TRIALISTS

BY

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A Thesis

Submitted to the School of Graduate Studies

in Partial Fulfillment of the Requirements

for the Degree

Master of Science

McMaster University

MASTER OF SCIENCE, 2013 McMaster University

(Health Research Methodology) Hamilton, Ontario

Title: Views on Allocation Concealment Methods in Randomized Clinical Trials: A Survey of Clinical Trialists

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Number of pages: vii, 54

ABSTRACT

Allocation concealment is the process of implementing the randomization sequence in a manner that prevents foreknowledge of upcoming group assignments. It protects against preferential enrolment of study participants, which could disrupt the prognostic balance that randomization aims to create in the first place. Envelopes are one method perceived by clinical trial authorities to adequately conceal allocation, despite evidence suggesting otherwise. We do not believe that envelopes are adequate, and we wanted to know the extent to which our sentiment resonated within the clinical trials community. We administered an internet-based survey to a random sample (n=1,926) of corresponding authors of recently published randomized clinical trials (RCTs). We sent non-responders up to two e-mail reminders starting from two weeks after the original invitation. We received 490 complete surveys (25.4% response rate) after collecting data for seven weeks. Most participants (61%) preferred central randomization to conceal allocation, yet a majority (64%) also accepted that envelopes are adequate. After they were shown examples that suggested envelopes' vulnerability, 11% of participants shifted their preference away from envelopes and 38% of participants became less accepting of envelopes. Compared to their initial ratings and after they were shown the examples, significantly more participants (69%) preferred central randomization ($p<0.001$), while significantly fewer participants (45%) accepted that envelopes are adequate ($p<0.001$). This study suggests that while

most clinical trialists prefer central randomization to conceal allocation, most also trialists accept that envelopes are adequate. Given that reports suggest that envelopes are vulnerable to manipulation, the dangers of using them seem underappreciated within the clinical trials community. However, this study also suggests that clinical trial authorities may be persuaded to change their positions on envelopes; and, unless they stop accepting that envelopes are adequate, front-line trialists will continue jeopardizing the integrity of RCTs.

ACKNOWLEDGEMENTS

I offer my sincerest gratitude to my thesis supervisor, Professor Gordon Guyatt, for his unwavering support throughout my academic training. He is a mentor, a colleague, a friend, and above all an inspiration for me to strive for the highest order of excellence in my work. I thank my supervisory committee, which included Professors Lehana Thabane, John You and Elie Akl, for their invaluable insights and privileged guidance. I am grateful to Qi Zhou for her assistance with conducting the statistical analyses, and to Nasir Hussain for his help with constructing the sampling frame. I am thankful to Lorraine Carroll, Kristina Vukelic, Deborah Maddock, and Laurel Grainger for their administrative support, but more importantly for their encouragement and friendship. I am indebted to my parents and my brother for their love and care.

DEDICATION

To RK, my sun on cloudy days.

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CHAPTER 1: INTRODUCTION

Background

Randomized clinical trials (RCTs) are based on the fundamental principle that study participants are randomly assigned to any one treatment group. Successful *randomization* in RCTs depends on two important processes: (1) generating a random allocation sequence to assign study participants to a group; and (2) implementing this sequence in a manner that prevents foreknowledge of group assignments. If either of these two procedures is corrupted, randomization has failed. The focus of this thesis is the second process – *allocation concealment*.

Randomization aims to balance prognostic factors between study groups to ensure that they are comparable at baseline. However, trial personnel, whether staff or investigators, may preferentially enrol study participants to one treatment group, and thus subvert randomization. For instance, they may believe that one treatment is better than the other for *some* participants, and therefore review upcoming group assignments to strategically enrol those patients into that treatment group. However, this violates the fundamental principle of RCTs and can disrupt the prognostic balance that randomization aims to create in the first place. Therefore, it is crucial that allocation sequences are concealed in RCTs.

Trial authorities, including the Cochrane Collaboration and the Consolidated Standards Of Reporting Trials (CONSORT) Group, recognize the

importance of allocation concealment, to the extent that they consider that only certain concealment methods *adequately* safeguard randomization.[1,2] For example, they state that posting the allocation sequence on an open bulletin board is *inadequate*, as upcoming group assignments are visible to trial personnel. Conversely, they accept that central randomization is an *adequate* method of allocation concealment. With central randomization, a trial methods centre generates the allocation sequences with the help of computer software, and conveys the group assignments, typically via telephone or internet, to trial personnel when needed.

Cochrane and CONSORT also accept sequentially numbered, opaque, sealed envelopes as an adequate method to conceal allocation. With these envelopes, group assignments are printed on cards and fitted into identical, opaque envelopes.[3] The envelopes are then sealed and marked to be opened in a sequential manner when a participant is ready to be assigned to a group.

However, it is striking that these groups consider that envelopes are adequate when there are anecdotes that suggest otherwise. First, in a multicentre RCT that compared keyhole surgery versus conventional open surgery for a “common surgical condition” (the authors do not specify), investigators found that using envelopes to conceal allocation corrupted randomization.[4,5] Specifically, they observed that, when they used envelopes, participants who were allocated to the experimental group (keyhole surgery) were significantly younger than those assigned conventional treatment (median age,

59 versus 63 years, $p<0.01$). The investigators did not notice any differences between the groups when they used central randomization to conceal allocation. Others have hypothesized that older participants would have taken longer to recover from keyhole surgery than younger participants, and thus would have made the experimental treatment appear worse than it otherwise was. In addition, authors of the *Users' Guides to the Medical Literature, A Manual for Evidence-Based Clinical Practice,* report the following anecdote:[6]

Some years ago, a group of Australian investigators undertook a randomized trial of open vs laparoscopic appendectomy. The trial ran smoothly during the day. At night, however, the attending surgeon's presence was required for the laparoscopic procedure but not the open one, and limited operating room availability made the longer laparoscopic procedure an annoyance. Reluctant to call in a consultant, the residents sometimes adopted what they saw as a practical solution. When an eligible patient appeared, the residents held the semiopaque envelopes containing the study assignment up to the light. They opened the first envelope that dictated an open procedure. The first eligible patient in the morning would then be allocated to the laparoscopic appendectomy group according to the passed-over envelope (D. Wall, written communication, June 2000). If patients who presented at night were sicker than those who presented during the day, the residents' behavior would bias the results against the open procedure.

Further, investigators of the Hypertension Detection and Follow-up Program,[7] a five-year multicentre RCT, report that envelopes were violated in their study:

> *Starting in October 1973, a staff member began opening the sealed randomization envelopes and selectively assigning to stepped care persons whom she knew and felt could be helped by the free hypertension treatment.*

As a result of the "problematic randomizations," the investigators excluded 446 participants from the analyses. Schulz also reports hearing of accounts of trial personnel corrupting envelopes by holding them up to the "hot lights" in radiology departments to reveal the contained assignments.[8] Personal communication with clinical trialists reveals similar attempts to subvert randomization. For example, Dr. Mohit Bhandari, an orthopaedic clinical trialist, notes:

> *Envelopes can be problematic and concealment can be threatened in a few ways. Coordinators involved in surgical trials have mentioned envelopes being 'bright-lighted' or 'simply opened' and passed over to match the allocation preference of the attending surgeon. These actions have often gone unreported and remain part of the 'untold' story of envelopes in randomized trials.*

Last, we have also identified two examples of RCTs in which using envelops to conceal allocation appeared to compromise the prognostic balance between study groups. One trial, the CAPPP study, compared angiotensin-converting-enzyme inhibition versus conventional therapy on cardiovascular morbidity and mortality in patients with hypertension.[9] A highly regarded clinical trialist, Professor Richard Peto, also criticized this trial for its failed randomization:[10]

The small but highly significant differences between the two treatment groups in prerandomisation [demographic variables] show that the process of randomisation by sealed numbered envelopes was frequently violated . . . . Presumably, at some centres those responsible for entering patients sometimes unsealed the envelopes before the next patient was formally entered, and then let knowledge of what the next treatment would be influence their decision as to whether that patient should be entered and assigned that foreknown treatment . . . . Perhaps it could still, at this late stage, be determined which centres sometimes broke the rules in this way, yielding inappropriate foreknowledge of the next treatment . . . . Unfortunately the present report cannot be taken as coming from a properly randomised trial.

In their reply, the study authors acknowledged the "randomization problem" of the trial, yet they noted that "to execute the proposed analysis would be akin to throwing suspicion upon all the investigators in the study, something that [they

were] not prepared to do."[10] The other study assessed the risk of cesarean delivery in women given regional epidural versus systemic analgesia in labour.[11] We will describe the violations in detail later.

Both studies are part of the body of anecdotal evidence that suggests that envelopes are an inadequate method of allocation concealment. Yet, groups such as Cochrane and CONSORT continue to accept that envelopes are adequate. We believe that envelopes are inadequate, and we want to explore the extent to which our sentiment resonates within the clinical trials community. To our knowledge, there has not been an empirical study that has (1) collected trialists' views about the acceptability of envelopes as an adequate method of allocation concealment; and (2) assessed if these views could be influenced after trialists are shown examples that suggest envelopes' vulnerability. In addition, to our knowledge, no study has explored variables that may be associated with these views. Our study will thus be the first known empirical investigation of trialists' views on allocation concealment methods.

Objectives

The primary objective of this study is to determine clinical trialists' ratings of the acceptability of envelopes to adequately conceal allocation in RCTs before they are shown two examples that suggest envelopes' vulnerability. The secondary objectives of this study are:

1. To determine trialists' preferred method of allocation concealment in RCTs before they are shown the two examples
2. To explore whether trialists' demographics are associated with (i) their initial acceptability of envelopes; and (ii) their initial preferred method of allocation concealment
3. To determine change in trialists' (i) acceptability of envelopes; and (ii) preferred method of allocation concealment after they are shown the two examples
4. To explore whether trialists' demographics are associated with (i) their change in acceptability of envelopes; and (ii) their change in preferred method of allocation concealment
5. To explore whether trialists' views on the two examples are associated with (i) their change in acceptability of envelopes; and (ii) their change in preferred method of allocation concealment

CHAPTER 2: METHODS

Study design

We designed the study as an internet-based survey.

Study participants

The target group was a random sample of corresponding authors of recently published RCTs. We used PubMed (http://www.ncbi.nlm.nih.gov/pubmed) to search for participants. We used the following search limits to first identify eligible studies: (1) RCT [article type], (2) humans [species], (3) published in one of 119 Core Clinical Journals [journal category] [Appendix 1], (4) English [language], and (5) published between January 1, 2011 and December 31, 2012 [publication date].

Along with another health research methodology trainee, the student investigator independently screened the titles and abstracts of the resulting studies to: (1) check that an e-mail address for the corresponding author was available; and (2) confirm the randomized study design. Both individuals also extracted the full name (first and last) and e-mail address of the corresponding author from eligible studies. The student investigator removed duplicate e-mail addresses, created a final list of trialists, and used a software program (Microsoft Excel) to generate a random sample of the desired size.

Study administration

We created, hosted, and administered the survey via an in-house (Faculty of Health Sciences, McMaster University) survey program (LimeSurvey). The student investigator sent all participants an invitation e-mail that contained a unique link to the electronic survey.

In order to increase survey response rates, we abided by several of Dillman's guidelines for administering internet-based surveys.[12] For one, we personalized the invitation e-mails so they appeared to address each participant directly. Second, we kept the invitation e-mails brief. Third, we utilized a multiple contact strategy, by which we sent non-responders up to two e-mail reminders (again, personalized) that were two weeks apart. The survey was closed three weeks after sending out the second reminder. Thus, we sent a total of three e-mail waves (one invitation and two reminders) and collected data over seven weeks.

Survey composition

The survey consisted of six domains [Appendix 2]. Four domains consisted of 14 multiple-choice questions of varying styles, i.e. single and multiple response options, three-point and five-point Likert scales, etc. All questions were mandatory. Two domains consisted of the examples we found.

Examples

Participants were shown a table of the differences in baseline demographic variables between study groups in both trials. To understand the significance of the key differences, participants were shown the following summaries, which represented the state of clinical knowledge at the time each study was published:

Example #1 (CAPPP Study)

At the time, evidence suggested that beta blockers (conventional treatment, in this study) were better for people with heart disease. The [data] indicates that significantly more people with heart disease (medical history of myocardial infarction and ischaemic heart disease) were assigned to receive beta blockers (p=0.037). Also, evidence suggested that ACE inhibitors were better for patients with diabetes mellitus. The [table] indicates that significantly more diabetic participants were assigned to receive ACE inhibitors (p=0.048).

Example #2

At the time, professional associations recommended against giving regional epidural early in labour because of concerns about delaying labour and precipitating the need for caesarean section. The [data] indicates that women who were in early labour (cervical dilation of ≤1.5 cm) were significantly less likely to be assigned to the regional epidural arm (p=0.0017).

Further, participants were provided direct quotes that described the use of envelopes from the full texts of each trial:

Example #1 (CAPPP Study)

The randomisation sequence was... conveyed to the investigators by means of sealed numbered envelopes, one for each patient, with instructions to use the envelopes in numerical order.

Example #2

Group assignments were sealed in sequentially numbered, opaque envelopes that were opened only after cervical dilatation was determined to be less than 4.0 cm.

Last, participants were given the full citation of both trials, including the name of the trial authors, title of the study, journal, volume, issue, and page numbers, in case they wished to access the full texts.

Outcomes

The primary outcome of the study was participants' initial ratings of acceptability of envelopes (as an adequate method of allocation concealment), i.e. before they were shown the two examples. We assessed this by the extent to

which they agreed with whether envelopes are an adequate method of allocation concealment (question 8 on survey). Response options included: strongly agree, somewhat agree, neutral, somewhat disagree, strongly disagree. Participants who answered “strongly agree” and “somewhat agree” were considered to accept that envelopes are adequate.

A secondary outcome was participants’ initial preferred method for allocation concealment, i.e. before they were shown the two examples. We assessed this by their preferred method of allocation concealment (question 12 on survey). Response options included: prefer envelopes, prefer central randomization, no preference.

Sample size

We calculated the sample size based on the primary outcome of interest, i.e. the percentage of participants who, before shown the examples, accepted that envelopes adequately conceal allocation in RCTs. We used the following formulate to calculate the sample size (n):

$$\text{Margin of error} = \pm 1.96\sqrt{\frac{pq}{(n-1)}}$$

Assuming that 50% of participants would accept that envelopes are adequate (p = 0.5; q = 1 – p = 0.5) and a ±5 percent margin of error, we calculated that 385

participants were required. However, based on a complete response rate of 20%, including possible e-mail “bounce backs,” we needed 1,926 participants.

Survey pilot testing

We sent the survey to 10 individuals trained in health research methodology. These individuals were of varying age, gender, and educational background. All individuals had theoretical (coursework) or practical experience with clinical trials. They were asked to complete the survey and provide feedback on its length, comprehensibility, and their perceptions of its intended purpose. They were also asked to report any technical glitches that they experienced. We used participants’ feedback to change the survey as needed. After it was changed on the basis of the first round of feedback, we sent the survey to four more individuals, who were given the same instructions as above for pilot testing.

Data analysis

There were multiple lines of investigation. First, we calculated the percentage of responses to all questions and generated frequency tables. To meet the primary objective of the study, we calculated the percentage of participants who accepted that envelopes are an adequate allocation concealment method in RCTs *before* they were shown the examples. As described above, these were participants who responded as either “strongly agree” or “somewhat agree” to question 8 on the survey (level of agreement that

envelopes are an adequate allocation concealment method); participants who responded otherwise were considered to not accept that envelopes are adequate. Further, we computed the percentage of participants who accepted that envelopes are adequate *after* they were shown the examples (question 15 on survey). We compared the change in percentage of participants who accepted that envelopes are adequate after they were shown the examples using the McNemar's test. We calculated a p-value and set the threshold at 0.05 to determine if the change was significant. To compare the change in percentages, we only included those participants who reported their initial and later views.

We also calculated the percentage of participants who preferred using central randomization to conceal allocation *before* they were shown the examples. These were participants who responded "prefer central randomization" to question 12 on the survey (preferred allocation concealment method); participants who responded otherwise were considered to not prefer central randomization. In addition, we computed the percentage of participants who preferred using central randomization to conceal allocation *after* they were shown the examples (question 16 on survey). As above, we compared the change in percentages of participants who preferred using central randomization after they were shown examples, using the McNemar's test with the threshold at 0.05. Again, we only included those participants who reported their initial and later views.

We conducted multiple regression analyses (summarized in Table 1), each of which corresponded to secondary objectives of our study. Most of the analyses were intended as exploratory, with only some analyses intended to test specific hypotheses. Some of the regression analyses considered the change in participants' acceptability of envelopes (becoming less accepting of envelopes versus other), and some addressed the change in their preferred method of allocation concealment (shifting preference away from envelopes versus other). Tables 2 and 3 summarize how we classified these changes. For all analyses, we calculated odds ratios (ORs) and p-values, and set the threshold at 0.05.

We conducted all statistical analyses using SAS software (version 9.2).

Research ethics

The Student Research Committee of the Hamilton Integrated Research Ethics Board approved this study.

CHAPTER 3: RESULTS

Survey piloting

All individuals (n=10) to whom we initially sent the survey completed the pilot testing. All respondents commented that the length of the survey was optimal, and most positively identified its intended purpose. Three participants, all non-clinicians, were unable to understand the examples and suggested modifications to the clinical summaries. Two participants reported technical glitches with the survey. We modified the survey, with special care taken to revise the clinical summaries, after consulting with two clinicians and the three non-clinician pilot testers. We later sent the survey to four additional individuals, two clinicians and two non-clinicians, all of whom completed the survey with high satisfaction.

Survey sample

We found 4,885 citations on PubMed that met the pre-determined eligibility criteria, i.e. article type, species, journal category, language, and publication date. Two individual independently screened the titles and abstracts of all studies, excluding 2,232 studies because they were not RCTs and 398 because they did not include the corresponding author's e-mail address. They removed 156 duplicate e-mail addresses and were left with 2,199 unique e-mail addresses.

The student investigator randomly selected 1,926 of these trialists and sent them an invitation to participate in this study.

Survey response rate

Figure 1 illustrates the three survey waves along with the corresponding response rates at each time point. We received 490 (25.4%) completed surveys by the end of the study period.

Demographic variables

Table 3 summarizes the demographic characteristics of the participants. Participants were mostly younger than 50 years of age (61.1%), male (65.3%), and reported having more than 10 years of experience in conducting clinical trials (65.2%).

Participants' initial views (before shown examples)

Acceptability of envelopes

348 (64.2%) (95%CI: 60%, 68%) of 542 respondents initially accepted that envelopes are an adequate method of allocation concealment in RCTs. Participants with more than 20 years of experience in conducting clinical trials (OR: 0.43; 95% CI: 0.21, 0.85; p=0.02) and those with 16 to 20 years of experience (OR: 0.50; 95% CI: 0.26, 0.96; p=0.04) were less likely to agree that

envelopes are adequate than those who reported having 5 to 10 years of experience (Table 4). We found no other statistically significant associations between participants' demographics and their initial acceptability of envelopes. The R^2 of this model was 0.06.

Preferred method of allocation concealment

321 (60.2%) (95% CI: 56%, 64%) of 533 respondents preferred central randomization to conceal allocation in RCTs. Male participants were less likely to prefer envelopes than female participants (OR: 0.57; 95% CI: 0.33, 0.97; p=0.04). Participants who identified their primary place of affiliation as academia were less likely to prefer envelopes than participants who identified otherwise (OR: 0.49; 95% CI: 0.28, 0.85; p=0.01) (Table 5). We found no other statistically significant associations between participants' demographics and their initial preferred method of allocation concealment. The R^2 of this model was 0.06.

Participants' views on the two examples

178 (36.3%) of 490 respondents agreed that the highlighted differences shown in both examples were due to chance, while 219 (44.7%) disagreed and 93 (19.0%) remained neutral.

249 (50.8%) of 490 respondents agreed that the highlighted differences were due to a failure to conceal allocation, while 126 (25.7%) disagreed and 115 (23.5%) remained neutral.

Changes in participants' views (after shown examples)

Acceptability of envelopes

Of the 490 respondents who rated the acceptability of envelopes before and after the examples were shown, 316 (64.5%) initially accepted that envelopes are an adequate method of allocation concealment, while 220 (44.9%) later accepted that envelopes are adequate (Figure 2).These percentages were signficantly different from each other ($p < 0.001$).

Data also showed that, after shown the examples, 188 (38.4%) participants were less accepting of envelopes while 33 (6.7%) participants were more accepting of envelopes.

Also, male participants were less likely to become less accepting of envelopes than female participants (OR: 0.65; 95% CI: 0.43, 0.999; $p = 0.049$) (Table 6). Participants with more than 20 years of experience in conducting clinical trials were less likely to become less accepting of envelopes than those with 5 to 10 years of experience (OR: 0.46; 95% CI: 0.22, 0.96; $p=0.04$). We found no other statistically significant associations between participants' demographic characteristics and their change in acceptability of envelopes. The R^2 of this model was 0.05.

Participants who agreed that the differences shown in the two examples were due to chance were less likely to become less accepting of envelopes

versus participants who did not agree (OR: 0.53; 95% CI: 0.34, 0.81; p = 0.003) (Table 7). Further, participants who agreed that the differences shown in the two examples were due to a failure of allocation concealment were more likely to became less accepting envelopes versus participants did not agree (OR: 2.04; 95% CI: 1.37, 3.03; p = 0.001). The R^2 of this model was 0.08.

Preferred method of allocation concealment

Of the 490 respondents who reported their preferred method for concealing allocation before and after the examples were shown, 299 (61.0%) initially preferred central randomization to envelopes (Figure 3). Later, 338 (69.0%) preferred central randomization over envelopes. These percentages were significantly different from each other (p < 0.001). Data also showed that, after shown the examples, 56 (11.4%) participants shifted their preference away from envelopes and 4 (0.8%) participants shifted their preference towards envelopes.

We found no statistically significant associations between participants' demographics and their change in preference (Table 8). The R^2 of this model was 0.05.

Further, we found no statistically significant associations between participants' views on the two examples and their change in preference (Table 9). The R^2 of this model was 0.01.

CHAPTER 4: DISCUSSION

Main Findings

This study showed that almost two-thirds (64%) of experienced clinical trialists initially accepted that envelopes are an adequate method of allocation concealment in RCTs (Figure 2). After they were shown the two examples, a significantly smaller percentage of trialists (45%) accepted that envelopes are adequate.

This study also demonstrated that 3 in every 5 clinical trialists (60%) initially preferred using central randomization instead of envelopes to conceal allocation in RCTs (Figure 3). Later, after shown the above examples, a significantly greater percentage of trialists (69%) preferred using central randomization versus envelopes.

Strengths

This study has several strengths. First, the study used a systematic approach to construct a sampling frame, which included trialists across several clinical disciplines. Second, from that sampling frame, we targeted a randomly selected cohort of trialists. Third, we pilot tested the survey, taking special care to maximize its comprehension and face validity. Fourth, our large sample size allowed for precise estimates of key variables.

Limitations

A major limitation of the survey is the low response rate: only 25% of the surveys were completed despite three survey waves. This rate, however, did provide enough respondents to adequately power the results of the survey using our *a priori* criteria, i.e. expected response rate of 20%. Still, the low response rate remains a concern, as the views of respondents may differ significantly from those of non-respondents, thus resulting in a biased estimate of the community. Another limitation of the survey is the potential uncertainty surrounding the representativeness of the sample, given the challenges of constructing a good sampling frame. For instance, we restricted our target audience by the year in which they published their trial. However, this was done to minimize the possibility of e-mail "bounce backs" as a result of old, inactive e-mail addresses. Still, it remains possible that our target audience may not have been representative of today's clinical trials community.

Upon reflection, there are several aspects of the study that I would change. First, I would use a more widely recognized tool, such as SuveyMonkey, to create, host, and administer the survey. Due to a technical glitch with the current survey tool (LimeSurvey), I could not use available strategies to gain insight into the extent to which response bias affected survey results.[13] Second, it is possible that the electronic link to the current survey appeared foreign (relatively unknown survey website) to participants, thus discouraging them from

accessing the survey. Third, I would also explore the possibility of a reputable organization, such as the Society for Clinical Trials (SCT), administering the survey It is possible that an e-mail invitation (and reminders) from a group like SCT versus me would increase response rates. Fourth, I would pilot the survey in a face-to-face setting with potential testers to elucidate issues that may otherwise remain hidden, for instance, in an e-mail message. Fifth, I would remove certain demographic questions from the current survey and add new questions. For instance, I would not ask participants whether they have trained as healthcare professionals and their primary affiliation. Rather, I would directly ask participants of their views on the authorities' (Cochrane and CONSORT) positions on envelopes. In addition, I would include an open-ended comments field at the end of the survey, in which participants may be able to add information not captured by the survey questions. For instance, it would be interesting to ask participants to share their own anecdotes with envelopes.

Implications

This study found that while the majority of clinical trialists prefer using central randomization instead of envelopes to conceal allocation in RCTs, most trialists also accept that envelopes adequately conceal allocation. Given that anecdotal evidence suggests that envelopes are vulnerable, we feel that the latter finding demonstrates that the dangers of using envelopes are underappreciated in the clinical trials community. However, this finding is

consistent with studies that have assessed the impact of allocation concealment methods on estimates of treatment effects, in which researchers have considered that envelopes are adequate.[14-17] This may be partly because the true prevalence of envelopes' vulnerability remains uncertain; it is certainly possible that envelopes work well most of the time and anecdotal evidence that suggests otherwise represents a small minority of all cases.

Yet, this study also found that when trialists were shown two such anecdotes, they: (1) became less accepting of envelopes, so that fewer accepted that envelopes are adequate later than initially; and (2) shifted their preference away from envelopes, to the extent that more preferred using central randomization later than initially. These results demonstrate that trialists' views on envelopes can be influenced. This is encouraging because it suggests that authorities such as Cochrane and CONSORT may be persuaded to change their positions on envelopes as well. This is important, as unless these groups stop accepting that envelopes are adequate, front-line trialists will continue jeopardizing the integrity of RCTs by using envelopes to conceal allocation.

We suggest that future work focus on improving this study based on the limitations we identified earlier, and assessing whether the results change. We also think it would be worthwhile to compare the results of this study against trialists' expressed views in the published literature. The latter may be accomplished via a systematic survey of methodological literature that focuses on allocation concealment in RCTs.

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TABLES & FIGURES

TABLE 1: SUMMARY OF REGRESSION ANALYSES

Objective	Model (Type)	Dependent Variable	Independent Variable	Hypothesis	Statistics
To understand whether trialists' demographics are associated with (i) their initial acceptability of envelopes; and (ii) their initial preferred method of allocation concealment.	Model #1 (multiple logistic regression)	Participants' initial acceptability of envelopes (accepting that envelopes are adequate vs. not)	Age (30-40 years vs. >60 years, 41-50 vs. >60, 51-60 vs. >60)	N/A (exploratory analyses)	OR and 95% CIs, p-values, and R^2 values
			Gender (male vs. female)		
			Graduate degree (yes vs. no)		
			Training as healthcare professional (yes vs. no)		
			Clinical trials experience (5-10 years vs. >20, 11-15 vs. >20, 16-20 vs. >20)		
			Primary affiliation (academia vs. other)		
	Model #2 (multiple logistic regression)	Participants' initial preferred method of allocation concealment (preferring envelopes vs. not)	Age (30-40 years vs. >60 years, 41-50 vs. >60, 51-60 vs. >60)	N/A (exploratory analyses)	
			Gender (male vs. female)		
			Graduate degree (yes vs. no)		
			Training as healthcare professional (yes vs. no)		
			Clinical trials experience (5-10 years vs. >20, 11-15 vs. >20, 16-20 vs. >20)		
			Primary affiliation (academia vs. other)		
To understand whether trialists' demographics are associated with (i) their change in acceptability of envelopes; and (ii) their change in preferred method of	Model #1 (multiple logistic regression)	Participants' change in acceptability of envelopes (becoming less accepting of envelopes vs. other)	Age (30-40 years vs. >60 years, 41-50 vs. >60, 51-60 vs. >60)	N/A (exploratory analyses)	
			Gender (male vs. female)		
			Graduate degree (yes vs. no)		
			Training as healthcare professional (yes vs. no)		

allocation concealment			Clinical trials experience (5-10 years vs. >20, 11-15 vs. >20, 16-20 vs. >20)		
			Primary affiliation (academia vs. other)		
	Model #2 (multiple logistic regression)	Participants' <u>change</u> in preferred method of allocation concealment (shifting preference away from envelopes vs. other)	Age (30-40 years vs. >60 years, 41-50 vs. >60, 51-60 vs. >60)	N/A (exploratory analyses)	
			Gender (male vs. female)		
			Graduate degree (yes vs. no)		
			Training as healthcare professional (yes vs. no)		
			Clinical trials experience (5-10 years vs. >20, 11-15 vs. >20, 16-20 vs. >20)		
			Primary affiliation (academia vs. other)		
To understand whether trialists' views on the two examples are associated with (i) their <u>change</u> in acceptability of envelopes; and (ii) their <u>change</u> in preferred method of allocation concealment	Model #1 (multiple logistic regression)	Participants' <u>change</u> in acceptability of envelopes (becoming less accepting of envelopes vs. other)	Level of agreement that the highlighted differences shown in both examples were due to chance (strongly agree/somewhat agree vs. neutral, somewhat disagree, strongly disagree)	Participants who agree that the highlighted differences shown in both examples were due to a chance will not be less accepting of envelopes.	
			Level of agreement that the highlighted differences shown in both examples were due to a failure to conceal allocation (strongly agree/somewhat agree vs. neutral, somewhat disagree, strongly disagree)	Participants who agree that the highlighted differences shown in both examples were due to a failure to conceal allocation will be less accepting of envelopes.	
	Model #2 (multiple logistic regression)	Participants' <u>change</u> in preferred method of allocation concealment (shifting preference away from envelopes vs. other)	Level of agreement that the highlighted differences shown in both examples were due to chance (strongly agree/somewhat agree vs. neutral, somewhat disagree, strongly disagree)	Participants who agree that the highlighted differences shown in both examples were due to a failure to conceal allocation will not shift their preference away from envelopes.	

			Level of agreement that the highlighted differences shown in both examples were due to a failure to conceal allocation (strongly agree/somewhat agree vs. neutral, somewhat disagree, strongly disagree)	Participants who agree that the highlighted differences shown in both examples were due to a failure to conceal allocation will be shift their preference away from envelopes.	

TABLE 2: CLASSIFIYING PARTICIPANTS' CHANGE IN ACCEPTABILITY OF ENVELOPES

Classification	**Initial acceptability of envelopes** **(Response to question #8 – level of agreement that envelopes are an adequate allocation concealment method)**	**Later acceptability of envelopes** **(Response to question #15 – level of agreement that envelopes are an adequate allocation concealment method)**
Less accepting of envelopes	Strongly agree	Somewhat agree / neutral / somewhat disagree / strongly disagree
	Somewhat agree	Neutral / somewhat disagree / strongly disagree
	Neutral	Somewhat disagree / strongly disagree
	Somewhat disagree	Strongly disagree
Other (more accepting of envelopes or equally accepting of envelopes)	Strongly disagree	Strongly disagree / somewhat disagree / neutral / somewhat agree / strongly agree
	Somewhat disagree	Somewhat disagree / neutral / somewhat agree / strongly agree
	Neutral	Neutral / somewhat agree / strongly agree
	Somewhat agree	Somewhat agree / strongly agree
	Strongly agree	Strongly agree

TABLE 3: CLASSIFIYING PARTICIPANTS' CHANGE IN PREFFERED ALLOCATION CONCEALMENT METHOD

Classification	**Initial preferred allocation concealment method** **(Response to question #12)**	**Later preferred allocation concealment method** **(Response to question #16)**
Shifting preference away from envelopes	Prefer envelopes	No preference / prefer central randomization
	No preference	Prefer central randomization
Other (shifting preference towards envelopes or not shifting preference)	Prefer central randomization	Prefer central randomization / no preference / prefer envelopes
	No preference	No preference / prefer envelopes
	Prefer envelopes	Prefer envelopes

FIGURE 1: SURVEY WAVES AND RESPONSES

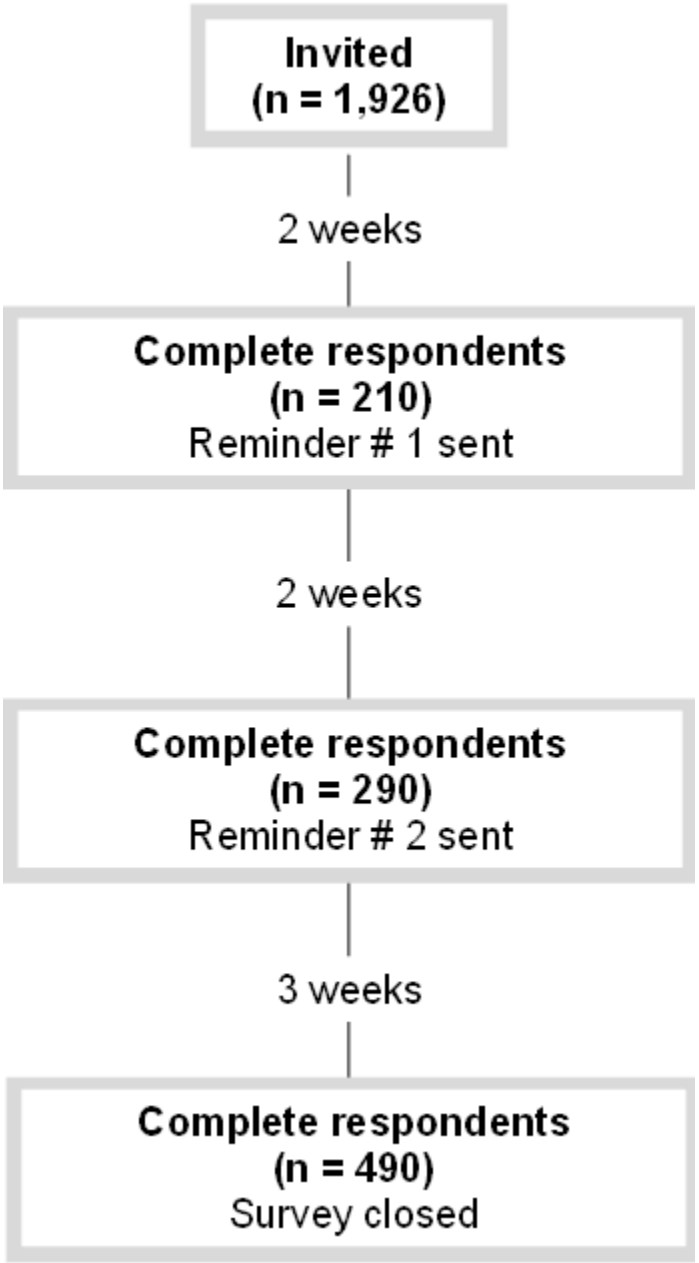

TABLE 3: DEMOGRAPHIC CHARACTERISTICS OF PARTICIPANTS

Characteristic	n (%)
Age (years) (n=542)	
30-40	146 (25.8)
41-50	200 (35.3)
51-60	165 (29.2)
>60	55 (9.7)
Gender (n=574)	
Male	375 (65.3)
Female	199 (34.7)
Research doctorate (n=574)	
Yes	358 (62.4)
No	216 (37.6)
Master's degree (n=571)	
Yes	299 (52.4)
No	272 (47.6)
Clinical trials experience (years) (n=494)	
5-10	172 (34.8)
11-15	131 (26.5)
16-20	79 (16.0)
>20	112 (22.7)

TABLE 4: ASSOCIATION BETWEEN PARTICIPANTS' DEMOGRAPHICS AND THEIR INITIAL ACCEPTABILITY OF ENVELOPES

Independent Variable		OR (95%CI)*	p-value		
Age	>60 vs. 30-40 years	0.60 (0.25, 1.45)	0.26	0.30	R^2 = 0.06
	51-60 vs. 30-40 years	1.03 (0.51, 2.09)	0.93		
	41-50 vs. 30-40 years	0.76 (0.42, 1.39)	0.37		
Gender (male vs. female)		0.79 (0.52, 1.20)	0.27		
Graduate degree (yes vs. no)		0.70 (0.43, 1.14)	0.15		
Training as healthcare professional (yes vs. no)		1.32 (0.66, 2.64)	0.43		
Clinical trials experience	>20 vs. 5-10 years	0.43 (0.21, 0.85)	0.02	0.08	
	16-20 vs. 5-10 years	0.50 (0.26, 0.96)	0.04		
	11-15 vs. 5-10 years	0.72 (0.42, 1.24)	0.23		
Primary affiliation (academia vs. other)		0.82 (0.52, 1.30)	0.40		

*OR>1.0 means that the odds of accepting that envelopes are an adequate allocation concealment method (event) is greater in one group versus the other. OR=1.0 means that the odds of accepting that envelopes are adequate is equal in both groups. OR<1.0 means that the odds of accepting that envelopes are adequate is less in one group versus the other.

TABLE 5: ASSOCIATION BETWEEN PARTICIPANTS' DEMOGRAPHICS AND THEIR INITIAL PREFERRED METHOD OF ALLOCATION CONCEALMENT

Independent Variable		OR (95%CI)*	p-value		
Age	>60 vs. 30-40 years	0.75 (0.22, 2.56)	0.65	0.37	R^2 = 0.06
	51-60 vs. 30-40 years	1.00 (0.43, 2.33)	0.99		
	41-50 vs. 30-40 years	(0.59 (0.28, 1.27)	0.17		
Gender (male vs. female)		0.57 (0.33, 0.97)	0.04		
Graduate degree (yes vs. no)		1.04 (0.54, 2.00)	0.89		
Training as healthcare professional (yes vs. no)		2.94 (0.84, 10.00)	0.09		
Clinical trials experience	>20 vs. 5-10 years	0.83 (0.33, 2.04)	0.68	0.90	
	16-20 vs. 5-10 years	0.71 (0.28, 1.75)	0.46		
	11-15 vs. 5-10 years	0.83 (0.40, 1.69)	0.61		
Primary affiliation (academia vs. other)		0.49 (0.28, 0.85)	0.01		

*OR>1.0 means that the odds of preferring envelopes (event) to conceal allocation in RCTs is greater in one group versus the other. OR=1.0 means that the odds of preferring envelopes is equal in both groups. OR<1.0 means that the odds of preferring envelopes is less in one group versus the other.

FIGURE 2: CHANGE IN PARTICIPANTS' ACCEPTABILITY OF ENVELOPES

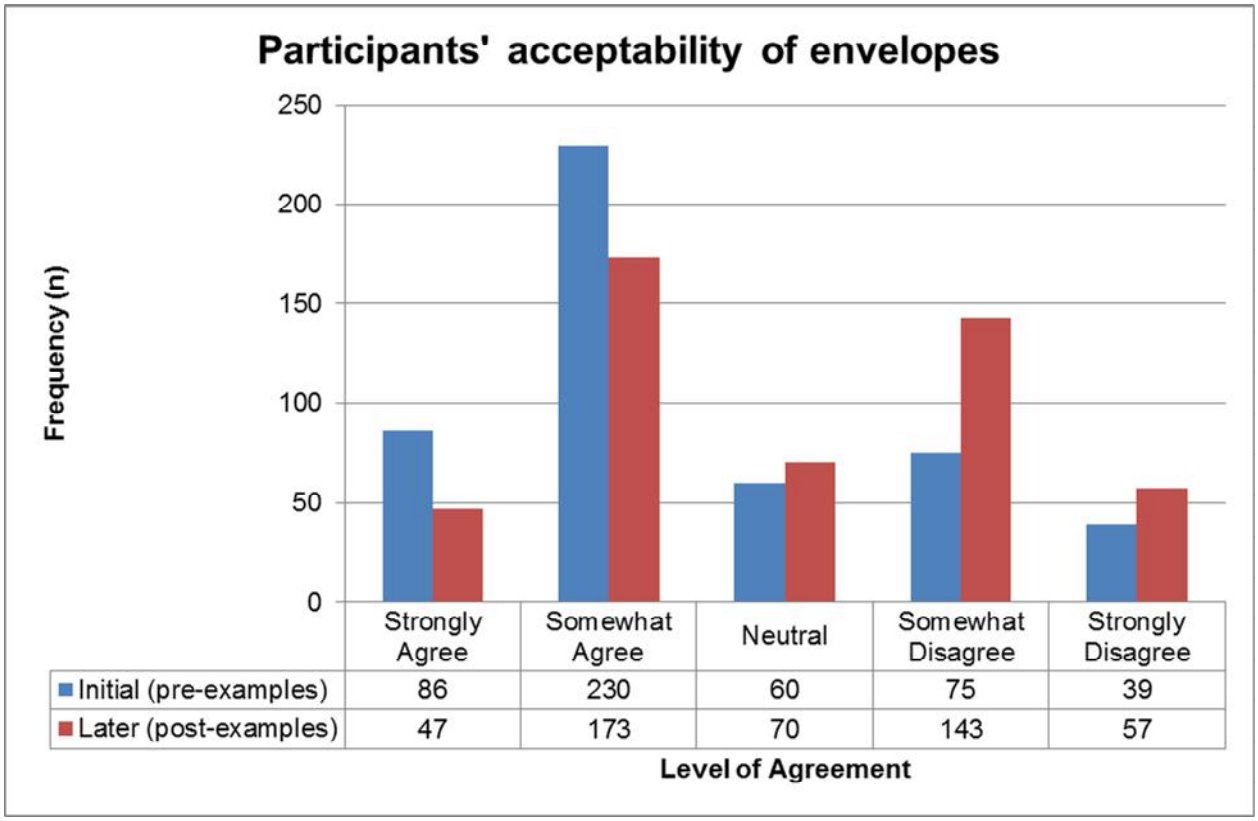

TABLE 6: ASSOCIATION BETWEEN PARTICIPANTS' DEMOGRAPHICS AND THEIR CHANGE IN ACCEPTABILITY OF ENVELOPES

Independent Variable		OR (95%CI)*	p-value		
Age	> 60 vs 30-40 years	2.04 (0.79, 5.26)	0.14	0.20	R^2 = 0.05
	51-60 vs 30-40 years	1.54 (0.76, 3.13)	0.23		
	41-50 vs 30-40 years	0.93 (0.51, 1.69)	0.81		
Gender (male vs. female)		0.65 (0.43, 0.999)	0.049		
Graduate degree (yes vs. no)		0.74 (0.45, 1.22)	0.24		
Training as healthcare professional (yes vs. no)		1.11 (0.53, 2.28)	0.79		
Clinical trials experience	> 20 vs 5-10 years	0.46 (0.22, 0.96)	0.04	0.19	
	16-20 vs 5-10 years	0.57 (0.28, 1.14)	0.11		
	11-15 vs 5-10 years	0.77 (0.44, 1.33)	0.35		
Primary affiliation (academia vs. other)		0.68 (0.43, 1.09)	0.11		

*OR>1.0 means that the odds of becoming less accepting of envelopes (event) is greater in one group versus the other. OR=1.0 means that the odds of becoming less accepting of envelopes is equal in both groups. OR<1.0 means that the odds of becoming less accepting of envelopes is less in one group versus the other.

TABLE 7: ASSOCIATION BETWEEN PARTICIPANTS' VIEWS ON THE EXAMPLES AND THEIR CHANGE IN ACCEPTABILITY OF ENVELOPES

Independent Variable	OR (95%CI)*	p-value	
Agreement that the differences shown in the two examples were due to chance (agree vs. not agree)	0.53 (0.34, 0.81)	0.003	R^2 = 0.08
Agreement that the differences shown in the two examples were due to a failure to conceal allocation (agree vs. not agree)	2.04 (1.37, 3.03)	0.001	

*OR>1.0 means that the odds of becoming less accepting of envelopes (event) is greater in one group versus the other. OR=1.0 means that the odds of becoming less accepting of envelopes is equal in both groups. OR<1.0 means that the odds of becoming less accepting of envelopes is less in one group versus the other.

FIGURE 3: CHANGE IN PARTICIPANTS' PREFERRED METHOD OF ALLOCATION CONCEALMENT

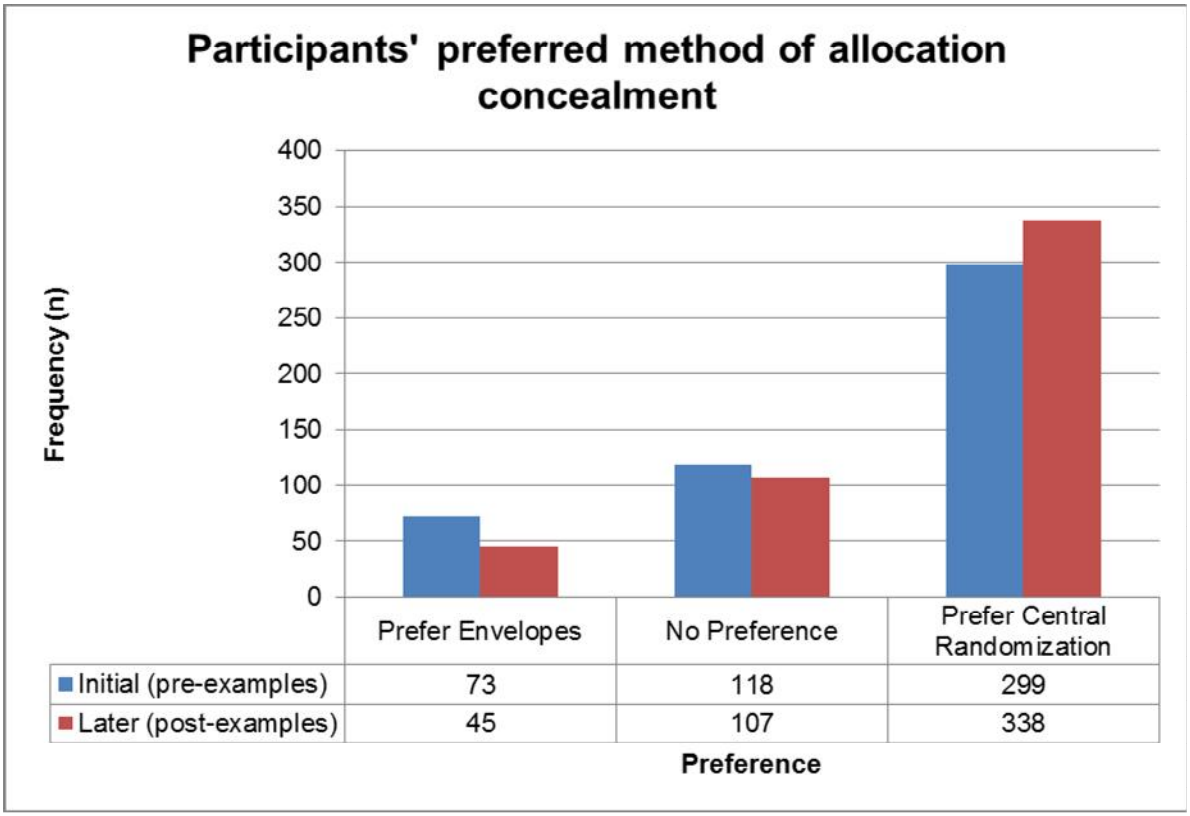

TABLE 8: ASSOCIATION BETWEEN PARTICIPANTS' DEMOGRAPHICS AND THEIR CHANGE IN PREFERRED METHOD OF ALLOCATION CONCEALMENT

Independent Variable		OR (95%CI)*	p-value		
Age	> 60 vs 30-40 years	0.73 (0.15, 3.49)	0.70	0.24	R^2 = 0.05
	51-60 vs 30-40 years	1.51 (0.56, 4.08)	0.42		
	41-50 vs 30-40 years	0.69 (0.28, 1.73)	0.43		
Gender (male vs. female)		0.69 (0.37, 1.31)	0.26		
Graduate degree (yes vs. no)		0.68 (0.32, 1.45)	0.32		
Training as healthcare professional (yes vs. no)		1.10 (0.35, 3.47)	0.88		
Clinical trials experience	> 20 vs 5-10 years	0.61 (0.20, 1.84)	0.38	0.46	
	16-20 vs 5-10 years	0.49 (0.15, 1.59)	0.24		
	11-15 vs 5-10 years	1.09 (0.48, 2.48)	0.83		
Primary affiliation (academia vs. other)		0.63 (0.32, 1.24)	0.18		

*OR>1.0 means that the odds of shifting preference away from envelopes (event) is greater in one group versus the other. OR=1.0 means that the odds of shifting preference away from envelopes is equal in both groups. OR<1.0 means that the odds of shifting preference away from envelopes is less in one group versus the other.

TABLE 9: ASSOCIATION BETWEEN PARTICIPANTS' VIEWS ON THE EXAMPLES AND THEIR CHANGE IN PREFERRED METHOD OF ALLOCATION CONCEALMENT

Independent Variable	OR (95%CI)*	p-value	
Agreement that the differences shown in the two examples were due to chance (Agree vs. not agree)	0.98 (0.52, 1.85)	0.95	R^2 = 0.01
Agreement that the differences shown in the two examples were due to a failure to conceal allocation (agree vs. not agree)	1.70 (0.93, 3.13)	0.09	

*OR>1.0 means that the odds of shifting preference away from envelopes (event) is greater in one group versus the other. OR=1.0 means that the odds of shifting preference away from envelopes is equal in both groups. OR<1.0 means that the odds of shifting preference away from envelopes is less in one group versus the other.

APPENDIX 1: LIST OF 119 CORE CLINICAL JOURNALS

1. Academic medicine: journal of the Association of American Medical Colleges
2. AJR. American journal of roentgenology
3. American family physician
4. American heart journal
5. The American journal of cardiology
6. The American journal of clinical nutrition
7. American journal of clinical pathology
8. The American journal of medicine
9. The American journal of nursing
10. American journal of obstetrics and gynecology
11. American journal of ophthalmology
12. American journal of pathology
13. American journal of physical medicine & rehabilitation / Association of Academic Physiatrists
14. The American journal of psychiatry
15. American journal of public health
16. American journal of respiratory and critical care medicine
17. American journal of surgery
18. The American journal of the medical sciences
19. The American journal of tropical medicine and hygiene
20. Anaesthesia

21. Anesthesia and analgesia
22. Anesthesiology
23. Annals of emergency medicine
24. Annals of internal medicine
25. The Annals of otology, rhinology, and laryngology
26. Annals of surgery
27. The Annals of thoracic surgery
28. Archives of dermatology
29. Archives of disease in childhood
30. Archives of disease in childhood. Fetal and neonatal edition
31. Archives of environmental & occupational health
32. Archives of general psychiatry
33. Archives of internal medicine
34. Archives of neurology
35. Archives of ophthalmology
36. Archives of otolaryngology--head & neck surgery
37. Archives of pathology & laboratory medicine
38. Archives of pediatrics & adolescent medicine
39. Archives of physical medicine and rehabilitation
40. Archives of surgery (Chicago, Ill : 1960)
41. Arthritis and rheumatism
42. BJOG : an international journal of obstetrics and gynaecology
43. Blood

44. BMJ (Clinical research ed)
45. Brain: a journal of neurology
46. The British journal of radiology
47. The British journal of surgery
48. CA: a cancer journal for clinicians
49. Cancer
50. Chest
51. Circulation
52. Clinical orthopaedics and related research
53. Clinical paediatrics
54. Clinical pharmacology and therapeutics
55. Clinical toxicology : the official journal of the American Academy of Clinical Toxicology and European Association of Poisons Centres and Clinical Toxicologists
56. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne
57. Critical care medicine
58. Current problems in surgery
59. Diabetes
60. Digestive diseases and sciences
61. Disease-a-month : DM
62. Endocrinology
63. Gastroenterology

64. Gut
65. Heart & lung : the journal of critical care
66. Heart (British Cardiac Society)
67. Hospital practice (1995)
68. Hospitals & health networks / AHA
69. JAMA : the journal of the American Medical Association
70. The Journal of allergy and clinical immunology
71. The Journal of bone and joint surgery. American volume
72. The Journal of bone and joint surgery. British volume
73. The Journal of clinical endocrinology and metabolism
74. The Journal of clinical investigation
75. Journal of clinical pathology
76. The Journal of family practice
77. Journal of immunology (Baltimore, Md : 1950)
78. The Journal of infectious diseases
79. The Journal of laryngology and otology
80. The Journal of nervous and mental disease
81. Journal of neurosurgery
82. The Journal of nursing administration
83. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons
84. The Journal of paediatrics
85. Journal of the Academy of Nutrition and Dietetics

86. Journal of the American College of Cardiology
87. Journal of the American College of Surgeons
88. The Journal of thoracic and cardiovascular surgery
89. The Journal of trauma and acute care surgery
90. The Journal of urology
91. The journals of gerontology. Series A, Biological sciences and medical sciences
92. The journals of gerontology. Series B, Psychological sciences and social sciences
93. Lancet
94. Mayo Clinic proceedings. Mayo Clinic
95. The Medical clinics of North America
96. The Medical letter on drugs and therapeutics
97. Medicine
98. Neurology
99. The New England journal of medicine
100. The Nursing clinics of North America
101. Nursing outlook
102. Nursing research
103. Obstetrics and gynecology
104. The Orthopedic clinics of North America
105. Pediatric clinics of North America
106. Pediatrics
107. Physical therapy

108. Plastic and reconstructive surgery
109. Postgraduate medicine
110. Progress in cardiovascular diseases
111. Public health reports (Washington, D.C. : 1974)
112. Radiologic clinics of North America
113. Radiology
114. Rheumatology (Oxford, England)
115. Southern medical journal
116. Surgery
117. The Surgical clinics of North America
118. Translational research : the journal of laboratory and clinical medicine
119. The Urologic clinics of North America

APPENDIX 2: SURVEY

Domain 1: Demographics

1) What is your age (years)?
    - <30
    - 30-40
    - 41-50
    - 51-60
    - >60

2) What is your gender?
    - Female
    - Male

3) If you hold a Doctorate degree (Ph.D., D.Phil., Sc.D., etc.), please indicate in what discipline:
    - Health research methodology
    - Epidemiology/clinical epidemiology
    - Statistics/biostatistics
    - Clinical medicine
    - Clinical research
    - Public health

- Other (please specify): _____
- Not applicable; I do not hold a Doctorate degree

4) If you hold a Master's degree (M.Sc., M.P.H., etc.), please indicate in what discipline:
   - Health research methodology
   - Epidemiology/clinical epidemiology
   - Statistics/biostatistics
   - Clinical medicine
   - Clinical research
   - Public health
   - Other (please specify): _____
   - Not applicable; I do not hold a Master's degree

5) If you are a healthcare professional, please indicate in what discipline:
   - Medicine
   - Dentistry
   - Nursing
   - Allied healthcare (pharmacy, physical therapy, occupational therapy, etc.)
   - Other (please specify): _____
   - Not applicable; I am not a healthcare professional

6) How many years of experience do you have in conducting clinical trials research?
    - <5
    - 5-10
    - 11-15
    - 16-20
    - >20

7) What is your primary place of affiliation?
    - Government
    - Industry
    - Academia
    - Other (please specify): _____

Domain 2: Mode of Allocation Concealment

Domain 2A: Envelopes (sequentially numbered, sealed, opaque)

1) Please rate your agreement with the following statement:

    Such envelopes are an adequate method of concealing allocation in randomized controlled trials.

- Strongly agree
- Somewhat agree
- Neutral
- Somewhat disagree
- Strongly disagree

Domain 2B: Central or "third-party" randomization (telephone, fax, web-based; pharmacy or randomization centre)

1) Please rate your agreement with the following statement:

   Central or "third-party" randomization is an adequate method of concealing allocation in randomized controlled trials.

   - Strongly agree
   - Somewhat agree
   - Neutral
   - Somewhat disagree
   - Strongly disagree

Domain 3: Comparison of Allocation Concealment Methods

1) Which of the following statements best represents your current view on the two formerly mentioned allocation concealment methods?

   - Envelopes are preferable to central or “third-party” randomization for allocation concealment in randomized controlled trials

   - Central or “third-party” randomization is preferable to envelopes for allocation concealment in randomized controlled trials

   - Envelopes and central or “third-party” randomization are equally good choices for allocation concealment in randomized controlled trials

Domain 4: Evidence from the Literature (Example 1)

Please consider the following study comparing angiotensin-converting-enzyme (ACE) inhibition versus conventional therapy (diuretics, beta-blockers, or both) on cardiovascular morbidity and mortality in patients with hypertension:
Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet*. 1999;353(9153):611-6.

The following is an adapted portion of Table 1 from the above study:

Medical history	ACE inhibition treatment (n=5492)	Conventional treatment (n=5493)
Myocardial infarction	40	55
Ischaemic heart disease	64	81
Stroke	50	39
Transient ischaemic attacks	43	35
Atrial fibrillation	36	34
Congestive heart failure	19	10
Cardiovascular complications	219	213
Diabetes mellitus	309	263

Consider that, at the time, evidence suggested, and people believed, that beta blockers (conventional treatment, in this study) were better for people with heart disease. The table above indicates that significantly more people with heart disease (medical history of myocardial infarction and ischaemic heart disease) were assigned to the standard treatment group in which patients received beta blockers (p=0.037).

Now consider that ACE inhibitors were better for renal disease (of which diabetes mellitus is a leading cause). Again, the table indicates that significantly more diabetic participants were assigned to ACE inhibition (p=0.048).

The authors describe the allocation concealment method as follows:

"The randomisation sequence was generated by computer and conveyed to the investigators by means of sealed numbered envelopes, one for each patient, with instructions to use the envelopes in numerical order." (Hansson et al., 1999).

Domain 5: Evidence from the Literature (Example 2)

Please consider the following study comparing the rate of cesarean delivery in women given regional epidural versus systemic analgesia in labour.

Wong CA, Scavone BM, Peaceman AM, et al. The risk of cesarean delivery with neuraxial analgesia given early versus late in labor. *N Engl J Med*. 2005;352(7):655-65.

The following is an adapted portion of Table 1 from the above study:

Characteristic	**Regional epidural (n=366)**	**Systemic analgesia (n=362)**
Cervical dilation at first request for analgesia		
≤1.5 cm	113	152
>1.5 to <3.0 cm	130	111
≥3.0 cm	123	99

Consider that, at the time, professional associations recommended to not give regional epidural early in labour because of concerns about delaying labour and the requirement of a caesarian section if epidural was given early. The table above indicates that, of those women who were early in labour (cervical dilation of ≤1.5 cm), a greater proportion were randomized to receive systemic analgesia at their first request (p=0.0017).

The authors describe the allocation concealment method as follows:

"Group assignments were sealed in sequentially numbered, opaque envelopes that were opened only after cervical dilatation was determined to be less than 4.0 cm." (Wong et al., 2005)

Domain 5: Re-assessment of Envelopes

1) Please rate your agreement with the following statement:

   The imbalances in baseline characteristics shown in both examples are due to chance.

   - Strongly agree
   - Somewhat agree

- Neutral
- Somewhat disagree
- Strongly disagree

2) Please rate your agreement with the following statement:

The imbalances in baseline characteristics shown in both examples are due to a failure to conceal allocation.

- Strongly agree
- Somewhat agree
- Neutral
- Somewhat disagree
- Strongly disagree

3) Please rate your agreement with the following statement:

Envelopes are an adequate method of concealing allocation in randomized controlled trials.

- Strongly agree
- Somewhat agree
- Neutral

- Somewhat disagree
- Strongly disagree

2) Which of the following statements best represents your current view on the two formerly mentioned allocation concealment methods?

   - Envelopes are preferable to central or “third-party” randomization for allocation concealment in randomized controlled trials

   - Central or “third-party” randomization is preferable to envelopes for allocation concealment in randomized controlled trials

   - Envelopes and central or “third-party” randomization are equally good choices for allocation concealment in randomized controlled trials