New approaches to the implementation of cardiovascular disease prevention
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CHAPTER 8

PARTIAL DISCLOSURE OF STUDY INFORMATION TO PARTICIPATING PATIENTS

EXPERIENCES FROM A RANDOMIZED CLINICAL TRIAL

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Submitted
ABSTRACT

BACKGROUND: When patients and physicians are aware of the fact that their actions are observed and recorded in a trial, this can induce behavioral changes (Hawthorne effect). Furthermore, when evaluating trials where double blinding is not possible due to the nature of the interventions, such as behavioral interventions, contamination can occur. To minimize Hawthorne effects and contamination in the RESPONSE-trial, information about the nature of the intervention (a nurse-coordinated program to reduce cardiovascular risk) was largely withheld from participating patients. After completion of the trial, participants were fully informed of the design of the study and of the reasons for withholding information, and they were interviewed on their perspectives on this approach.

METHODS: The current study was embedded in the RESPONSE trial, a RCT with 754 participants in 11 centers in the Netherlands. Before providing written consent, all patients were required to read the patient information, given time to deliberate, and provided the opportunity to ask any study-related questions. Patients were informed about the subject of the study, i.e. secondary prevention of coronary disease. However, important aspects of the comparison between the two study groups were not disclosed, particularly the fact that patients in the intervention group were referred to a nurse coordinated prevention program, on top of usual care. At the end of the study, complete information was provided, and included a questionnaire on patients’ perspectives on this trial design.

RESULTS: In total, 641 patients completed the end-of-study questionnaire. After full disclosure of the study design, nearly all patients stated that they would still have participated (98% of interventions, 97% of controls), and that they found the reasons for withholding this information to be at least quite adequate (89% of interventions, 90% of controls). Only 6% of intervention and 7% of controls stated that they had identified the design of the other treatment arm. However, more controls would have preferred to have been randomized to the other group (3% interventions vs. 17% controls, p<0.001).

CONCLUSIONS: We found that withholding information about the nature of the interventions and the precise content of the study arms in a large, randomized clinical trial is accepted by patients, and that patients find the motivation for this to be valid. We also found the rate of contamination to be low. In future trials, such strategies may therefore be considered.
INTRODUCTION

Double blind randomized clinical trials are generally considered as the highest level of evidence for clinical research. However, in randomized trials evaluating behavioral interventions, double blinding is frequently not possible, due to the nature of the intervention. When patients and physicians are aware of the fact that their actions are being observed and recorded, this can induce behavioral changes in both interventions and controls, which is known as the Hawthorne effect. Furthermore, in screening and prevention trials where compliance can be difficult to ascertain in advance, ‘contamination’, (i.e. use of the intervention or components thereof in the control arm) may also be difficult to minimize.

In the Randomised Evaluation of Secondary Prevention by Outpatient Nurse SpEcialists (RESPONSE) trial, we compared the effect of implementing a nurse coordinated prevention programme (NCPP) on top of usual care (intervention group) with usual care alone (control group) in reducing cardiovascular risk in patients with coronary artery disease. In this trial, complete knowledge as to receiving or not receiving the nurse’s support could have a marked impact on the outcome parameters in both the intervention group and the control group. To minimize a potential Hawthorne-effect and contamination, we did not disclose the fact that patients were randomized to the NCCP or usual care at the outset of the trial. At the end of the trial, all information about the design of the study was provided to all patients. The institutional committees on human research explicitly approved this process of providing limited trial information to patients.

Withholding information from patients in clinical trials in this manner is generally not acceptable, and there are major ethical implications. Therefore, we sought to evaluate what patients thought of this approach to performing a randomized trial. We hypothesized that patients would not have strong objections provided that the rationale for this approach was solid and clear.

METHODS

Design

We conducted the current study embedded in the RESPONSE trial. The study design and results of the RESPONSE trial have been published elsewhere. In brief, RESPONSE was a randomized clinical trial investigating the effect of an NCPP on cardiovascular risk factors in patients who have suffered an acute coronary syndrome (’post-ACS’). Patients were randomized either to 4 visits in the first 6 months post-ACS to the NCPP in addition to usual care (intervention), or to usual care alone (control). Patients attending the NCPP had cardiovascular risk profiling at each visit, including additional blood collection (7 instances in 12 months instead of 3). During each visit, counseling on healthy lifestyles and medication control/titration took place in collaboration with the treating physician. The primary outcome of the trial was the cardiovascular risk profile at 12 months follow-up. The study protocol was approved by the institutional committees on human research of all recruiting hospitals.
Informed consent and patient information

Before providing written confirmed consent, all patients were required to read the patient information, given time to consider participation, and provided the opportunity to ask any study-related questions. Patients were informed about the subject of the study, i.e. secondary prevention of coronary disease, but details about the comparison between the two study groups were not disclosed, in particular the role of the NCPP. As required by regulations applying to scientific research, the patient information contained information about the nature of the study (secondary prevention of coronary disease), and information about randomization, data collection (at baseline, 6 and 12 months follow-up), and extra blood samples. It also stated that some aspects, including a second study observation, would be disclosed but not before completion of the study, but that these aspects conveyed no extra risk and included no experimental treatments:

Participants in this scientific study are randomized to one of two groups. This concerns a second observation included in the study that would, if fully explained, influence the outcomes. There are no disadvantages or extra risks associated with this aspect of the study.

The ‘secondary observation’ in our trial was, in fact, the comparison of the NCPP and the control group. Patients in both the control and the intervention group were not informed about the nature of the intervention, and the NCPP was offered as if it was a part of usual care. We acquired approval from the institutional committees on human research in all participating hospitals, specifically for this part of the study protocol.

Study population

Data from all patients participating or invited to participate in the RESPONSE trial were included in our study. Patients aged 18-80 years were eligible if they had been diagnosed with an acute coronary syndrome (ST-segment myocardial infarction, non-ST-segment elevation myocardial infarction or unstable angina pectoris) within eight weeks prior to entry into the study. Patients were ineligible if they met any of the following exclusion criteria: visits to the nurse coordinated prevention programs not feasible; not available for follow-up; surgery, percutaneous coronary intervention or other interventions expected within 8 weeks after inclusion; life expectancy considered limited (≤2 years); previously enrolled in the nurse coordinated prevention program; New York Heart Association class III or IV heart failure.

Recruitment

Trained research personnel and treating physicians approached eligible patients to request participation in a clinical trial. If interested, patients were provided the patient information and informed consent forms, and given time to consider. Patients who chose not to participate were asked if they were willing to fill in a short questionnaire with their reason for not participating. Consenting patients were included and randomized in the RESPONSE trial.
Follow-up and data collection

Reasons for not participating were grouped as (1) no interest in participating in scientific research, (2) participation in other trial(s), (2) time investment too great, (3) extra blood samples too burdening, (4) no participation due to withheld information in the patient information, and (5) miscellaneous reasons. It was also noted if the patient had read the patient information.

Patients who provided written informed consent were randomized by a web-based protocol, and followed-up for 12 months. After completion of follow-up, all patients were provided an explanatory letter, containing all information that was withheld in the original patient information. The explanatory letter specifically stated which information had not been provided - namely information about the NCPP being compared to usual care, and the reasons for choosing this study design (second study observation). A questionnaire was integrated into the explanatory letter, consisting of questions about (1) how well patients understood the explanatory letter; (2) if the reasons presented for not providing all information were viewed as adequate; (3) if patients could still remember the fact that there was a second study observation; (4) if they would have participated if this information had been available from the start; (5) if they thought to know what the design of the other study arm had been; (6) and if they would have preferred to be in the other group (Box 1). During the trial, we added 3 additional questions to this questionnaire, asking if they found that the care they had received after the ACS was sufficient, if they thought that they had been randomized to the intervention or control group, and how certain they were of this ascertainment (Box 1).

Statistical methods

Patient characteristics were summarized separately for both groups, using numbers and percentages for categorical data, and means and SD for continuous data with a normal distribution. Questionnaire responses were presentenced as number or percentage, as appropriate. Comparisons between groups were summarized as number or percentage, and Fisher’s exact tests were applied. We used SPSS V.23 for all analyses.

RESULTS

In total, 1,666 patients were assessed for eligibility in the RESPONSE trial (Figure 1). Of these, 489 did not meet inclusion criteria, and 423 declined to participate. Of those who declined to participate, 134 (32%, mean age 61.4 years, 24% female) completed the questionnaire providing a reason for their non-participation. Most patients who provided a reason found the time-investment too great (50.7%), followed by no interest in participation in scientific research (17.2%) and miscellaneous reasons (17.2%), most of which were psychological reasons (Figure 1). No patient declined because of the withheld information in the patient information. Of all the patients who provided a reason for non-participation, 64% had not read the patient information.

The end-of-study questionnaire was completed by 641 patients, while the additional questions (Box 1, ‘additional questions’) were completed by 146 patients. Patient characteristics are presented in Table 1. The mean age was 57.7 (±9.7) years, and 20.4% were women.
1666 Patients were assessed for eligibility
489 Did not meet inclusion criteria
1177 Patients were asked to participate
754 Provided written informed consent and were randomized
375 Intervention
379 Control
423 Declined to participate
289 Did not provide a reason for non-participation
134 Provided a reason for non-participation
23 Had no interest in participating in scientific research
3 Participated in other trial(s)
68 Found the time investment too great
7 Found the extra blood samples too burdensome
0 No participation due to withheld information in the patient information
23 Miscellaneous reasons for not participating
489 Did not meet inclusion criteria
361 Had complete follow-up
8 Excluded post-randomization due to refusal to participate
1 Randomized in error and were excluded from the study
3 Died
0 Lost to follow-up
2 Had early discontinuation of intervention
321 Completed end-of-study questionnaire
40 Did not complete end-of-study questionnaire
349 Had complete follow-up
9 Excluded post-randomization due to refusal to participate
1 Randomized in error and were excluded from the study
2 Were double randomizations and were excluded from the study
10 Died
1 Lost to follow-up
7 Did not attend 12 months follow-up
320 Completed end-of-study questionnaire
29 Did not complete end-of-study questionnaire
321 Completed end-of-study questionnaire
40 Did not complete end-of-study questionnaire

Figure 1. Trial profile
### Box 1. Summary of questionnaire at completion of study

<table>
<thead>
<tr>
<th>Main questions</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>How understandable do you find the information in this letter?</td>
<td>5-point Likert scale ranging from not understandable at all to completely understandable</td>
</tr>
<tr>
<td>Did you find that the reasons presented for not providing all information at onset of the study adequate?</td>
<td>5-point Likert scale ranging from completely inadequate to completely adequate</td>
</tr>
<tr>
<td>Could you still remember the presence of a second study observation?</td>
<td>Yes, No</td>
</tr>
<tr>
<td>Would you still have participated in this trial if you had had this information beforehand?</td>
<td>Yes, No</td>
</tr>
<tr>
<td>Did you find out yourself what the content in the other study group was?</td>
<td>Yes, No</td>
</tr>
<tr>
<td>You were randomized to one of the two groups. In retrospect, would you rather have been in the other group?</td>
<td>Yes, No</td>
</tr>
</tbody>
</table>

### Additional questions

| Do you find that the care you have received during the last year has been sufficient? | Too much, Sufficient, Too little |
| During the last year, do you have the impressions that you have attended usual care alone, or a nurse coordinated prevention program in addition to usual care? | Usual care alone, Usual care plus nurse coordinated prevention program, Do not know |
| How certain are you that this was, in fact, what you have attended?               | 5-point Likert scale ranging from completely uncertain to completely certain |
Almost all patients found the information in the end-of-study explanatory letter to be at least quite understandable (97% of interventions and 96% of controls with a score of ≥3 on the Likert scale). When asked whether they found the reason for not providing all information to be adequate, 89% of interventions and 90% of controls scored ≥3 on the Likert scale. However, the majority of patients did not recall the existence of the second study observation (62% interventions, 59% controls).

When asked whether they would have participated in the study if all information had been available at baseline, practically all patients, regardless of group (98% of interventions, 97% of controls), stated that they still would have participated. Only 7 patients in the intervention group and 8 in the control group stated that they would not have participated if all information had been available at baseline. When asked whether they had identified what the content was of the other group, only 19 (6%) patients in the intervention group and 21 (7%) in the control group stated that they thought to have identified this. Nine (3%) interventions vs. 49 (17%) controls stated that they would have preferred to be in the other group (p<0.001).

In the added questions (146 respondents), 2 patients in the intervention group found the received care insufficient; in the control group this proportion was slightly higher at 11 patients (3% vs. 14%, p=0.02). In both groups, 66 patients stated that they found the care adequate (96% of interventions, 86% of controls, p=0.051). A single patient in the intervention group found the received care to be too much.

Figure 2 shows how patients identified their treatment group, and how certain they were when identifying their group. When asked into which group they thought to have been randomized, 47 (69%) patients correctly identified their group as the intervention group, and 43 (57%) patients correctly identified their group as the control group (p<0.001). Only 3 (4%) patients in the intervention group and 14 (18%) patients in the control group stated that they were unable to identify their group (p=0.01).

**DISCUSSION**

The main finding of our study is that almost no patients had strong objections to participating in a trial where complete information about the content of the different study groups was not provided. This was in the setting of an implementation trial evaluating the effect of a hospital-based nurse-coordinated prevention programme on cardiovascular risk as compared with usual care alone. Practically all patients (98% of interventions, 97% of controls) would still have chosen to participate after receiving all study information at the end of the trial, and the majority found the reasons for withholding this information to be valid (89% of interventions, 90% of controls).
### Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>No. (%) of Patients*</th>
<th>Intervention (N=366)</th>
<th>Control (N=367)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), mean (SD)</strong></td>
<td>57.5 (9.6)</td>
<td>57.9 (9.8)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>64 (20)</td>
<td>67 (21)</td>
</tr>
<tr>
<td><strong>Diagnostic category at index event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-segment elevation myocardial infarction, n (%)</td>
<td>165 (52)</td>
<td>152 (48)</td>
</tr>
<tr>
<td>Non ST-segment elevation myocardial infarction, n (%)</td>
<td>101 (32)</td>
<td>106 (33)</td>
</tr>
<tr>
<td>Unstable Angina Pectoris, n (%)</td>
<td>54 (17)</td>
<td>61 (19)</td>
</tr>
<tr>
<td><strong>Therapeutic intervention for index event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No revascularisation, n (%)</td>
<td>60 (19)</td>
<td>63 (20)</td>
</tr>
<tr>
<td>Percutaneous coronary intervention, n (%)</td>
<td>250 (78)</td>
<td>238 (75)</td>
</tr>
<tr>
<td>Coronary artery bypass surgery, n (%)</td>
<td>18 (6)</td>
<td>21 (7)</td>
</tr>
<tr>
<td><strong>Previous vascular disease (prior to index event)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>49 (15)</td>
<td>56 (18)</td>
</tr>
<tr>
<td>Percutaneous coronary intervention, n (%)</td>
<td>41 (13)</td>
<td>48 (15)</td>
</tr>
<tr>
<td>Coronary artery bypass surgery, n (%)</td>
<td>16 (5)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>13 (4)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Peripheral artery disease, n (%)</td>
<td>18 (6)</td>
<td>22 (7)</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>3 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>No known previous vascular disease, n (%)</td>
<td>237 (74)</td>
<td>234 (73)</td>
</tr>
<tr>
<td><strong>History of cardiovascular risk factors, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive family history, n (%)</td>
<td>189 (59)</td>
<td>190 (59)</td>
</tr>
<tr>
<td>Diagnosed diabetes mellitus, n (%)</td>
<td>45 (14)</td>
<td>44 (14)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>222 (69)</td>
<td>226 (71)</td>
</tr>
<tr>
<td>Current smoking, n (%)†</td>
<td>149 (46)</td>
<td>133 (42)</td>
</tr>
<tr>
<td>Ex-smoker, n (%)</td>
<td>116 (36)</td>
<td>130 (41)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>132 (41)</td>
<td>109 (34)</td>
</tr>
<tr>
<td><strong>Educational</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fewer than 8 years, n (%)</td>
<td>42 (13)</td>
<td>42 (13)</td>
</tr>
<tr>
<td>College or university, n (%)</td>
<td>73 (23)</td>
<td>65 (20)</td>
</tr>
</tbody>
</table>

Data are n (%), or mean (SD).

*Unless otherwise indicated. Percentages may not sum to 100 because of rounding.
†Smoking status prior to index event
SD=standard deviation
These findings should be viewed in the context that a considerable percentage of patients (17%) in the control group would - in retrospect - have preferred to be randomized to the intervention group. Furthermore, a small percentage in both groups found the provided care to be insufficient (3% of interventions, 14% of controls). Only a single patient in the intervention group found the care provided in our trial to be too intensive.

Potentially, those patients most opposed to our trial design may have chosen not to participate at all. We attempted to quantify this by asking all patients who declined to document their reasons for non-participation. However, only 32% were willing to provide such a reason. Due to the ethical limitations inherent to any trial (i.e. no consent to use patient data), we are unable to provide more data about these patients. It should however be taken into consideration that of those who did provide a reason, only 36% read the patient information at all, and no-one specified the withheld information as a reason for non-participation.

The main reason for withholding information in our trial was to prevent a Hawthorne-effect and contamination. While the majority of patients were able to correctly identify their treatment group (69% of interventions and 57% of controls), only a small percentage (6% of interventions and 7% of controls) thought to have identified the design of the other group. While we did not test patients' knowledge of the design of the other study group, this finding emphasizes that while double blinding in implementation trials such as ours is impossible, it is possible to successfully blind patients with regards to the content of other treatment arms, potentially reducing contamination.

Some previous trials have adopted comparable strategies. Similar to our trial, Little et al. performed an “open randomized trial” where patients gave written consent to a “study looking at how quickly sore throats settle.” To minimize contamination between the groups, physicians were asked not to discuss certain aspects of the trial (the efficacy of antibiotics) before randomization, and during the consultation physicians opened a sealed envelope containing one of three randomized advice sheets based around different prescribing strategies. However, this trial was performed in primary care in patients with a self-limiting disease, while our trial was performed in a population with a recent coronary event who required long-term secondary prevention.

In a randomized trial evaluating smoking cessation interventions using nicotine replacement therapy and behavioral therapy, patients were similarly not informed about the behavioral intervention in order to avoid a Hawthorne effect. However, patient perspectives were not reported in this study.

In a cluster randomized trial evaluation an intervention to reduce salt intake in West Africa villages, blind recruitment was used in an effort to reduce selection bias and ensure comparability of the intervention groups. While similar to our patient level blinded recruitment, patients in this trial were informed about their group directly after the completion of the inclusion, and data on patient perspectives were not presented.

Strengths and limitations

There are several strengths to our study. First, our analysis was a pre-specified analysis in a large randomized clinical trial, in which the majority of patients completed the end-of-study questionnaire. Second, comprehensive baseline data and follow-up until 1 year were available, with a low number of dropouts and patients lost to follow-up.
Some limitations of our study should be considered. First, the end-of-study questionnaire consisted of a limited number of questions, which could be answered with 2-5 options. While a qualitative analysis might have provided more information about patient perspectives on our trial design, this was beyond the scope of our trial. Second, the added questions were answered by a smaller number of patients than the initial questionnaire. Third, ideally we would have objectively tested patients’ knowledge of the content of the other group at the end of the trial, before all trial information was provided. However, even after this information was provided, only a small percentage reported to have identified the content of the other group.

**CONCLUSION**

We found that withholding information about the nature of the interventions and the design of the study arms in a large, randomized clinical trial is accepted by patients, and that patients find the motivation for this (to minimize a Hawthorne-effect and contamination) to be valid. In future trials, such strategies can be considered.
REFERENCES