Recall of informed consent information by healthy volunteers in clinical trials

P. FORTUN, J. WEST, L. CHALKLEY, A. SHONDE and C. HAWKEY

From the Department of Gastroenterology, University Hospital Nottingham, Nottingham, UK

Received 5 March 2008 and in revised form 24 April 2008

Summary

Background: Information sheets for clinical research are becoming increasingly complex but the extent to which they are understood is uncertain.

Aims: To assess, as our primary outcome, recall by healthy volunteers of key facts in a patient information sheet in a phase 3 clinical trial. As secondary outcomes, we examined whether there was a difference between medical student and non-medically trained volunteers.

Design: Questionnaire to determine recall by healthy volunteers of informed consent information.

Methods: Eighty-two healthy volunteers participating in a capsule endoscopy study were given a 13 page written information sheet and allowed to ask questions. After indicating they were ready to give consent they were asked to complete a 6-item questionnaire covering the identity and adverse effects of trial treatments and of the procedure, the duration of the trial and value of the inconvenience allowance.

Results: All 82 healthy volunteers were questioned. Of the volunteers, 74 (90%) had university level education and 49 (60%) were clinical medical students. However, only 10 subjects (12%) could name the three trial drugs. The maximum number of risks remembered was 6 (n = 2) of 23. Only 14 (17%) could name three or more potential risks of the medication they might be exposed to, whilst 17 (20%) could identify none. Most subjects (77/82, 90%) identified capsule endoscopy as the trial procedure and impaction/obstruction as its main risk (52/82, 64%). All but one subject (98.8%) could recall the exact value of the inconvenience payment.

Conclusion: A comprehensive information sheet resulted in limited recall of trial risks. Shorter information sheets with a test and feedback session should be trialled so that informed consent becomes valid informed consent.

Background


The current climate of concern about safety of healthy volunteers in clinical trials was highlighted by the serious adverse events (AEs) at Northwick Park Hospital during a phase I trial.1 Our clinical trials unit was conducting a study in healthy volunteers, comparing as a primary endpoint the incidence of small bowel erosions or ulcers in...
subjects randomized to take a COX2 inhibitor, non-steroidal anti-inflammatory (NSAID) plus proton pump inhibitor (PPI) or placebo. Given the topical concerns about safety of COX2 inhibitors and NSAIDs, we conducted a questionnaire-based assessment of the volunteers’ understanding of the study.

**Aim**

To assess, as our primary outcome, recall by healthy volunteers of key facts in a patient information sheet in a phase 3 clinical trial. As secondary outcomes, we examined whether there was a difference between medical student and non-medically trained volunteers.

**Design**

A 6-point questionnaire to determine recall by healthy volunteers of informed consent information.

**Methods**

The subjects were all healthy volunteers taking part in a commercially sponsored trial, comparing the acute effects of a COX2 inhibitor, an NSAID plus PPI and placebo, on small bowel injury using capsule endoscopy. Information about the trial was contained within a 13 page volunteer information sheet, detailing information about trial drugs and their toxicities, trial procedures and potential hazards, duration of the trial, visit schedule and the inconvenience allowance paid for trial participation. In total, 23 drug AEs were mentioned.

We determined the ‘readability’ of the approved information sheet using the Flesch Reading Ease\(^2\) and Flesch-Kincaid tests.\(^3\) The Flesch Reading Ease Score identifies readability based on the average number of syllables per word and the average number of words per sentence. Higher scores signify greater reading eased. The Flesch–Kincaid Grade Level Formula links the 0–100 score to a US grade level, so a score of 8.2 would be understandable by an average student in 8th grade.

The trial and trial documents were approved by COREC and the Hospital Research and Development committee. In addition, we devised a 6 point questionnaire to assess key points about the study. These were based on the suggestions made by six individuals comprising two research nurses and four medical researchers including clinical researchers and statisticians. We agreed on six questions by consensus to evaluate the key areas of which drugs and procedures the volunteers would be exposed to, and their risks. We included details of trial duration and financial reimbursement to assess their recall of practical and motivational aspects of the study. Since our hypothesis was that lengthy trials information is not understood by our volunteers, we deliberately kept the questionnaire short. The questions were as follows:

<table>
<thead>
<tr>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the name of the drug(s) you will be taking?</td>
</tr>
<tr>
<td>What is the name of the main procedure you will undergo to assess the effects of the drug?</td>
</tr>
<tr>
<td>What side-effects can the drugs have?</td>
</tr>
<tr>
<td>What is the possible complication of the small bowel procedure?</td>
</tr>
<tr>
<td>What is the duration of the trial?</td>
</tr>
<tr>
<td>How much is the inconvenience payment?</td>
</tr>
</tbody>
</table>

The questionnaire was piloted on six subjects, prior to being incorporated into the consent procedure. After being screened for eligibility, the volunteers were given the information sheet to read. At least 24 h later they returned and were asked if they had read the information sheet and whether they had any questions about the trial. Once they had indicated readiness to sign the consent form, they were asked the six comprehension questions. Any shortcomings in their understanding of the trial were corrected prior to obtaining written consent to proceed with the trial.

Note was made of the volunteers level of educational attainment, and we documented who were medical students to see if this impacted on their ability to recall the trial information. Results were analysed in STATA 8 with Pearson’s chi-squared test for comparisons of medical student vs. non-medical students’ performance.

**Results**

**Leaflet readability**

The information sheet had a Flesch reading ease of 55.2, and a Flesch Kincaid grade level of 10.

**Volunteer demographics**

All of the 82 subjects who were approached completed the questionnaire. There were 40 females and the mean age was 24 years (range 18–57). Of the volunteers, 74 (90%) had university level education and 49 (60%) were clinical medical students.

The overall performance of the volunteers is shown in Table 1.
Identification of study drugs and their potential side-effects

Seventeen volunteers (21%) were unable to name any class or individual drug that they might be exposed to, whilst 24 (29%) could name the class of the drug only (for example ‘anti-inflammatory’). Only 41 of the 82 subjects (50%) could specifically name a drug rather than naming a class. From these 41 subjects, a total of 71 answers were given. Lumiracoxib was named by 39%, naproxen by 13%, omeprazole (20%) and placebo by 15%. The numbers who could name one, two or all three active drugs were 23 (28%), 8 (9.8%) and 10 (12.2%), respectively.

Twenty three side-effects are identified in the patient information sheet. When asked about potential AEs, 16 subjects (19.5%) were unable to name any. The largest number of AEs that were recalled was six (two subjects). The numbers who could name one, two or all three active drugs were 23 (28%), 8 (9.8%) and 10 (12.2%), respectively.

Understanding of capsule endoscopy and potential AEs

Six subjects (7.3%) could name no intervention or procedure. Two (2.4%) were aware that it involved an endoscopy/monitor of some kind, and 74 (90.2%) could name capsule/pill camera/video capsule. Fifty two (63%) of the subjects were able to name the procedure-related AE mentioned in the information sheet, namely impaction of the capsule. All but three of the volunteers accurately named the duration of the trial (96%). The amount of the inconvenience payment was accurately recalled by all but one of the 82 volunteers.

Medical students compared with non-medical student volunteers

We compared the recall of the 49 (60%) of volunteers who were medical students, and the 33 volunteers who were not medical students. Non-medical student volunteers were significantly less able then those who were medical students to name any study drug (67% vs. 88%, $P=0.048$) or the main risk of the capsule endoscopy procedure (49% vs. 74%, $P=0.021$). Non-medical student volunteers tended to recall less on all parameters regarding drugs, tests and their side-effects (Tables 1 and 2), but not study duration or their payment.

Discussion

This study is the first evaluation of healthy volunteer recall of clinical trial information at the actual time of giving written informed consent, rather than a hypothetical testing scenario, and so reflects the ‘real world’ of clinical trial procedures involving

### Table 1 Recall of trial information by medical students and non-medical students

<table>
<thead>
<tr>
<th>Total correct answers</th>
<th>Medical student volunteers N=49</th>
<th>Non-medical volunteers N=33</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Able to name any study drug</td>
<td>65 (79)</td>
<td>43 (88)</td>
<td>22 (67)</td>
</tr>
<tr>
<td>Able to name all study drugs</td>
<td>10 (12)</td>
<td>8 (16)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Able to name any side effects of the drugs</td>
<td>66 (80)</td>
<td>43 (88)</td>
<td>23 (70)</td>
</tr>
<tr>
<td>Able to name $\geq 3$ side effects of the drugs</td>
<td>14 (17)</td>
<td>10 (20)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Able to name the main study procedure</td>
<td>77 (94)</td>
<td>47 (96)</td>
<td>30 (91)</td>
</tr>
<tr>
<td>Able to name the main risk of the study procedure</td>
<td>52 (64)</td>
<td>37 (74)</td>
<td>16 (49)</td>
</tr>
<tr>
<td>Able to name duration of dosing</td>
<td>79 (97)</td>
<td>47 (97)</td>
<td>32 (97)</td>
</tr>
<tr>
<td>Able to quantify value of inconvenience payment</td>
<td>81 (99)</td>
<td>49 (100)</td>
<td>32 (97)</td>
</tr>
</tbody>
</table>

### Table 2 Understanding of drug side-effects

<table>
<thead>
<tr>
<th>All volunteers No. (%)</th>
<th>Medical students (N=49) No. (%)</th>
<th>Non-medical students (N=33) No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not know</td>
<td>16 (19.5)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Can name 1 risk</td>
<td>35 (42.7)</td>
<td>22 (45)</td>
</tr>
<tr>
<td>Can name 2 risks</td>
<td>17 (20.7)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Can name $\geq 3$ risks</td>
<td>14 (17.1)</td>
<td>10 (20)</td>
</tr>
</tbody>
</table>
healthy volunteers. We found that understanding of fundamental aspects of the trial following a standard consent process was poor. Despite a comprehensive 13 page information leaflet, one in five subjects had no knowledge of the class or name of the drug that they might be taking, and the same proportion could name no potential adverse effects. Only half were able to name one or more of the drugs. The information sheet warned of 23 potential side effects, yet 20% were unable to recall any side-effects. Forty two percent could only name one side effect, and only 17% could name three or more side effects. Only 14 subjects (12.5%) were aware of any potential cardiovascular effects of the trial drugs, despite the current high level of reporting in medical and lay press about the effects of COX2 inhibitors. The knowledge of the capsule endoscopy procedure was generally good: 90% could name the procedure and 63% were aware of the risk of small bowel impaction.

Are these findings generalizable to the setting of clinical trials involving patients? One obvious difference is the high level of educational attainment of the volunteers, 60% of whom were senior medical students. Without the benefit of a medical background, 33% of non-medically trained volunteers were unable to name any drug they were taking, and only 6% could name all three drugs. A third of non-medical volunteers could name no potential side-effects, and 9 out of 10 could name not more than 2 of the 23 adverse drug reactions listed. These non-medical volunteers might more closely resemble patients in terms of knowledge, and make the findings all the more concerning.

Recall by patients, may be even poorer, as illness, stress or lower educational attainment could affect their understanding. Understanding of consent forms and clinical trial information in patients is similarly lacking, and one study highlighted that 69% of patients admitted to not reading the consent form before signing it. The current standard NHS consent (http://www.dh.gov.uk/en/Publichealth/Scientificdevelopmentgeneticsandbioethics/Consent/Consentgeneralinformation/DH_4015950) has a poor readability score of 45. The UK National Literacy Survey found that 21% of adults have poor literacy skills, so the poor readability of standard consent forms may have wider implications beyond the healthy volunteer trial setting. Bertoli et al. found 51% of patients believed they had a good level of knowledge about a clinical trial, but objective evaluation rated only 14% as having a ‘high’ level of knowledge, trial, suggesting that patients overestimate their level of knowledge.

Our information sheet had a Flesch reading ease of 55.2, between the score of 60 that is regarded as plain English and Time magazine’s score of 52, less that a comic strip score of 90, but much higher than a standard insurance policy score of 15. This suggests that it was not so much the content but the sheer length that may have discouraged subjects from reading the sheet correctly. Recall is just one part of overall reading comprehension, which depends not only on the text (semantic content), but also active integration into the subject’s previous knowledge or situational experience. An interesting finding in this study was that the medical student volunteers (who might be expected to bring more situational experience) only performed better that the non-medical volunteers in two of the six domains.

It would be useful to examine what forces driving the production of complex trial information, which has increased in length and complexity over time, even though it has long been established that comprehension is inversely proportional to length. This suggests that increasingly complexity will fail to secure any improvement in safety for subjects taking part in research. Others have taken an ecological view of the organizational factors that are responsible for the creation of problematic patient information, and the influence of external stakeholders to guarantee ‘legal defensibility’ for example.

A systematic review of interventions to improve patients’ understanding in informed consent showed generally poor results with multimedia and ‘enhanced’ consent forms, for example by modifying the content, writing style, format or length. Two trials of the 30 reviewed that did show significant gains involved increased person-to-person interaction and increased discussion time. Trials which give a short test of comprehension, with feedback of incorrect answers do statistically improve understanding scores compared with controls in elderly volunteers. A small study in psychiatric patients and healthy controls suggested that the feedback of correct answers was superior to improving the structure of the consent form. However, the techniques trialled lack practical application, involving multiple choice questions or two or three repeated tests until the subjects answer correctly. Therefore, they may simply demonstrated rote learning rather than real understanding. One study had a 31-item questionnaire A representative sample of key points seems requisite. Another concern is that test and feedback tends to produce greater increases in understanding in the better educated. Overall, Flory’s review suggests a benefit from personal interaction in conveying...
trial information, and possibly test and feedback. We have not yet had the opportunity to test any intervention that might improve comprehension.

The Association of American Medical Colleges has suggested three strategies to improving the informed consent process: short and simple information, dividing the information into essential and supplemental information and verification of comprehension.5 We propose a two part information sheet. The first would be a key points summary outlining essential patient information, restricted to two pages. The second longer part would document the relevant trial information in full. Subjects could then be tested on key points prior to consent to verify understanding, and corrected if necessary. Inherent in this process would be increased interaction between the trial participant and the researcher. This carries the potential risk of adding a further tier of bureaucracy and forms; however, the current questionnaire only took a few minutes to conduct. Verification of informed consent is essential for ethical research conduct, since ‘subjects who do not understand the potential risks of a trial cannot be said to have chosen freely to face those risks’.19 Given the paucity of understanding in the current trial, it may provide a safety check to ensure that valid informed consent is truly obtained.

References