Appreciation of the informed consent procedure in a randomised trial of decompressive surgery for space occupying hemispheric infarction

J Hofmeijer, G J Amelink, H M den Hertog, A Algra, L J Kappelle, H B van der Worp, on behalf of the HAMLET and PAIS investigators

See Editorial Commentary, p 1040

J Neurol Neurosurg Psychiatry 2007;78:1124–1128. doi: 10.1136/jnnp.2006.110726

See end of article for authors' affiliations

Correspondence to:
Dr J Hofmeijer, Department
of Neurology, C03.236,
University Medical Centre
Utrecht, PO Box 85500,
3508 GA Utrecht, the
Netherlands; j.hofmeijer@
umcutrecht.nl

Received 7 November 2006

Revised 25 February 2007

Accepted 9 March 2007

Published Online First
30 March 2007

Background and aim: As non-randomised studies have suggested that surgical decompression may reduce mortality in patients with space occupying hemispheric infarction, randomisation may be considered unethical in controlled trials testing this treatment strategy. We studied differences in recall of information and in appreciation of the informed consent procedure between representatives included in the Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial (HAMLET) and representatives of patients participating in the randomised trial of Paracetamol (Acetaminophen) In Stroke (PAIS).

Methods: 1 year after study inclusion, we contacted 30 consecutive representatives who had given informed consent for participation of their relative in HAMLET, and 30 for PAIS. Recall of trial details and appreciation of the informed consent procedure were investigated using standardised questionnaires and compared between the two groups.

Results: All 30 PAIS representatives and 28 HAMLET representatives were interviewed. Participation of their relative in a clinical trial was remembered by 86% of HAMLET and 40% of PAIS representatives ($p < 0.001$). HAMLET representatives remembered more trial details (effect of the treatment under study (61% vs 3%, $p < 0.001$); randomised treatment allocation (71% vs 0%, $p < 0.001$)). With respect to appreciation of the informed consent procedure, we found no differences between the groups: in each trial, four representatives (14% vs 13%) had considered the question of randomisation unacceptable.

Conclusions: Participation of patients in a randomised controlled trial of surgical decompression for space occupying infarction is generally considered acceptable by their representatives, and recall of trial details is better than in a trial in which less vital issues are at stake.

Informed consent from patients or their representatives is considered essential in most clinical trials. In studies of acute stroke,¹ myocardial infarction² or other diseases,^{3–8} the amount of information on the informed consent procedure that study participants could understand and recall has varied. If treatment and thereby study inclusion require urgency because of an acute life threatening situation, it may be difficult to obtain truly informed consent.

The Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial (HAMLET) is an ongoing randomised controlled trial to study the effect of decompressive surgery on functional outcome in patients with middle cerebral artery infarction and life threatening oedema formation.⁹ Non-randomised studies have suggested that this intervention may reduce mortality from 78% to 50% or 16%.^{10–11} An essential inclusion criterion for participation in HAMLET is a reduced level of consciousness. Consequently, informed consent is asked from patients' legal representatives. As patients can deteriorate within hours, there is little time to contemplate participation. It was hypothesised that the life threatening condition and time pressure may compromise the ability of relatives to adequately perceive all relevant details of the trial, and that randomised treatment allocation may be considered unethical and unacceptable by the patients' legal representatives because of the reputed reduction in mortality caused by the treatment under study.

We interviewed legal representatives of patients included in HAMLET to ascertain what information about the trial they could recall and how they had experienced the informed consent procedure. To study the impact of the life threatening

condition and the invasive experimental treatment, we also interviewed legal representatives of patients included in a trial in which less vital issues were at stake, the randomised Paracetamol (Acetaminophen) In Stroke (PAIS) trial,¹² and compared the results.

METHODS

Subjects

We contacted all legal representatives of patients who had given informed consent for participation in HAMLET at the University Medical Centre, Utrecht, or the Academic Medical Centre, Amsterdam, the Netherlands, between 1 September 2002 and 1 August 2005, and those who had given informed consent for patients included in PAIS between 1 January 2005 and 1 January 2006 at the same hospital in Utrecht and the Erasmus Medical Centre, Rotterdam, the Netherlands. In PAIS, informed consent should be obtained from the patient but may also be given by a legal representative in the case of reduced consciousness or aphasia. We interviewed the first 30 representatives who could be contacted from both trials. The interviews took place at different times for each trial, but always approximately 1 year after inclusion. The study protocol was written after the first four patients had been included in HAMLET, when it became clear that the informed consent procedure was often laborious and emotional. The individual

Abbreviations: HAMLET, Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial; PAIS, Paracetamol (Acetaminophen) In Stroke trial

Table 1 Recall of trial details

	HAMLET (n = 28) (n (%))	PAIS (n = 30) (n (%))	p Value
Do you remember your family member having participated in a study?			
Yes	23 (82)	21 (77)	0.22
No	5 (18)	9 (30)	
What was the treatment under study?*			
Correct	24 (86)	12 (40)	0.001
Incorrect	0 (0)	2 (7)	
Don't know	4 (14)	16 (53)	
What were the presumed effects of the treatment under study?*			
Correct	17 (61)	1 (3)	<0.001
Incorrect	5 (18)	10 (33)	
Don't know	6 (21)	19 (64)	
How was treatment allocation achieved?*			
Correct	20 (71)	0 (0)	<0.001
Incorrect	1 (4)	2 (6)	
Don't know	7 (25)	28 (94)	
Was participation voluntary?			
Yes	26 (93)	26 (88)	0.57
No	0 (0)	1 (2)	
Don't know	2 (7)	3 (10)	
Did you receive written information?			
Yes	24 (86)	18 (60)	0.068
No	3 (10)	6 (20)	
Don't know	1 (4)	6 (20)	
Did you read the written information?*			
Yes	21 (75)	12 (40)	0.022
No	2 (7)	3 (10)	
Don't know	5 (18)	15 (50)	
Did you understand the written information?*			
Yes	18 (64)	11 (37)	0.017
No	2 (7)	0 (0)	
Don't know	8 (29)	19 (63)	

HAMLET, Hemispherectomy After Middle cerebral artery infarction with Life-threatening Edema Trial; PAIS, Paracetamol (Acetaminophen) In Stroke trial.

*Statistically significant difference between HAMLET and PAIS.

trials and the present interviews were approved by the ethics committees of the participating hospitals.

Trial physicians had sought written informed consent as soon as possible after a reduction in consciousness caused by oedema formation (HAMLET) or after admission because of acute stroke (PAIS). The time window for inclusion in HAMLET was 96 h after stroke onset whereas this was 12 h in PAIS. However, in both trials, treatment was required to start as soon as possible after neurological deterioration or stroke onset, respectively. The information given about each of the trials included an explanation about the disease and the intervention under study, an explanation of the possible benefits and side effects of the treatment, the controlled design, the voluntary nature of participation, the duration of the trial and the right to withdraw at any time.

Data collection

Legal representatives who had originally given consent were interviewed by telephone by one investigator (JH). The first question was whether the representative could recall having given informed consent for participation of his/her relative in a clinical trial. If not, the interviewer disclosed that the relative had participated in a trial by referring to the meeting with a study physician shortly after clinical deterioration (HAMLET) or admission to hospital (PAIS). Thereafter, recall of trial details and appreciation of the informed consent procedure were investigated using a standardised questionnaire (tables 1

and 2). Finally, representatives were asked whether they would give permission again for participation in a clinical trial under similar circumstances. Legal representatives expressing that they felt that participation was obligatory or had negative feelings were asked for motivation. The answers were categorised as related to (1) the appropriateness of asking for study participation or (2) feelings about the acute and life threatening situation of the patient.

Data analysis

Answers from representatives of patients participating in HAMLET and PAIS are presented as frequencies (n) and proportions (%). A χ^2 test was used for testing differences between groups. Differences in age were tested by means of the Student's t test and differences in initial stroke severity, as expressed by the score on the National Institutes of Health Stroke Scale,¹³ with the Mann-Whitney U test. A p value <0.05 was considered statistically significant.

RESULTS

Of 30 representatives of HAMLET patients contacted, 28 were interviewed; one representative refused to participate and one spoke Dutch insufficiently to communicate by telephone. All 30 representatives of PAIS patients contacted were interviewed. The median time between the informed consent procedure and the interview did not differ between the groups (HAMLET 13 months (range 10–16); PAIS 13 months (range 9–17)). As

Table 2 Trial appreciation

	HAMLET (n = 28) (n (%))	PAIS (n = 30) (n (%))	p Value
Was the information provided clear to you?*			
Yes	27 (96)	14 (47)	<0.001
No	0 (0)	1 (3)	
Don't know	1 (4)	15 (50)	
Did you perceive the outcome of treatment allocation as a matter of life or death?*			
Yes	23 (82)	10 (33)	0.001
No	4 (14)	16 (54)	
Don't know	1 (4)	4 (13)	
Do you have negative feelings about the informed consent procedure?*			
Yes	9 (32)	1 (3)	0.014
No	18 (64)	28 (94)	
Don't know	1 (4)	2 (3)	
Do you feel that the question for participation and randomisation was acceptable at that moment?			
Yes	19 (68)	16 (54)	0.40
No	4 (14)	4 (13)	
Don't know	5 (18)	10 (33)	
Were you capable of deciding about participation?*			
Yes	17 (61)	13 (43)	0.018
No	8 (29)	4 (14)	
Don't know	3 (10)	13 (43)	
Did you feel participation was voluntary?			
Yes	18 (65)	23 (77)	0.18
No	8 (28)	3 (10)	
Don't know	2 (7)	4 (13)	
Do you regret having given permission?			
Yes	3 (11)	0 (0)	0.12
No	23 (82)	25 (83)	
Don't know	2 (7)	5 (17)	
Are you glad with the treatment your relative received?			
Yes	14 (50)	19 (63)	0.17
No	5 (18)	7 (23)	
Don't know	9 (32)	4 (13)	
Would you have preferred the doctor having taken the responsibility for treatment choices?			
Yes	11 (39)	6 (20)	0.12
No	15 (54)	17 (57)	
Don't know	2 (7)	7 (23)	
Would you have preferred the doctor having taken the responsibility for study participation?			
Yes	3 (11)	0 (0)	0.063
No	21 (75)	20 (67)	
Don't know	4 (14)	10 (33)	
Would you approve participation again under similar circumstances?			
Yes	17 (61)	20 (67)	0.78
No	2 (7)	1 (3)	
Don't know	9 (32)	9 (30)	
How do you feel about being interviewed again?			
Positive	23 (82)	23 (77)	0.49
Negative	3 (11)	2 (7)	
Neutral	2 (7)	5 (17)	

HAMLET, Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial; PAIS, Paracetamol (Acetaminophen) In Stroke trial.

*Statistically significant difference between HAMLET and PAIS.

expected, because of the maximum age limit of 60 years in HAMLET, mean age of the patients at study inclusion was significantly lower in HAMLET (48 (8) years) than in PAIS (69 (13) years; mean difference 22, 95% CI 16–27). In both trials, informed consent was most frequently given by the patient's partner. In PAIS, informed consent was given more frequently by the patient's (grand) children (n = 10) than in HAMLET (n = 3, p = 0.046).

Mean stroke severity, as assessed by the score on the National Institutes of Health Stroke Scale, was significantly

higher in patients included in HAMLET (median 23; range 20–31) than in PAIS (median 14; range 3–26; p = 0.02), and in HAMLET, the survival rate at follow-up (n = 18, 60%) was significantly lower than in PAIS (n = 26, 87%, p = 0.03). The results of the interviews on recall of the details of the trial are summarised in table 1 and the results of the interviews on appreciation of the informed consent procedure are summarised in table 2.

Relatives of HAMLET participants remembered significantly more trial details. With respect to appreciation of the informed

consent procedure, we found fewer differences between the groups. Of the representatives of HAMLET participants, 8 (27%) felt participation to be obligatory compared with 3 (10%) of those in PAIS ($P = 0.1$). On inquiry, it appeared that these representatives felt this obligation only with respect to their relatives because of the reputed reduction in mortality. Of the representatives of HAMLET participants, 9 (30%) had negative feelings about the informed consent procedure compared with 1 (3%) of those in PAIS ($p = 0.01$). On inquiry, these negative feelings concerned the acute and emotional situation and not the question of study participation in all but one representative. With regard to these negative feelings in representatives of HAMLET patients, there were no differences between representatives of patients who received surgical or best medical treatment ($n = 4$ (27%) and $n = 5$ (36%), respectively ($p = 0.4$)) or between representatives of patients who died or survived ($n = 3$ (27% of all deaths) and $n = 6$ (33% of all survivors), respectively; $p = 0.6$).

DISCUSSION

Despite the reputed large impact on survival of decompressive surgery, representatives of patients included in HAMLET were equally satisfied with the informed consent procedure as those in a study assessing the effect of paracetamol on stroke outcome. In both trials, most representatives considered trial participation and randomisation acceptable, despite the serious illness of their relatives. The majority would give informed consent again in similar circumstances. HAMLET representatives remembered significantly more trial details.

Several factors have been put forward to explain the poor recall of the study details of patients and representatives participating in clinical trials.¹⁻¹⁴ Being admitted with an acute and life threatening disease has been proposed as a major factor compromising the ability to retain information.¹ It has been suggested that knowledge of details of a clinical trial may be better in relatives than in the patients themselves, not only when the relative had given consent, but also when the patient had done so.¹ However, in some countries, obtaining consent by relatives is not possible. The present study implies that recall of information may be better in life threatening situations than in other neurological emergencies. The impact of the treatment under study undoubtedly plays an important role.

Previous studies have shown low recall rates of complex information, such as randomisation¹⁵ and other methodological details.¹⁶ None of the representatives of PAIS participants could recall the process of random treatment allocation, whereas this was recalled by two-thirds of the representatives in HAMLET. As treatment allocation in HAMLET is not blinded, the concepts of drawing lots and probability are much more explicit and probably easier to retain.

HAMLET differs from other acute neurological emergencies in terms of the high case fatality rate of the disease and the presumed large effect on the death rate of the treatment under study. Three-quarters of the representatives indeed considered the outcome of randomisation a matter of life or death. However, about two-thirds considered participation in a clinical trial and randomisation acceptable. One-third expressed negative feelings about the first conversation with the study physician, but these negative feelings concerned the acute and emotional situation and not the request for study participation in all but one representative. It has been suggested that positive answers with regard to appreciation of trials may be biased by the hospital connection of the interviewer.¹ However, the results of the present interviews show that even in a study like HAMLET, in which the clinical situation is perceived as life threatening, asking permission for study inclusion is generally considered acceptable.

In some countries, obtaining informed consent from relatives is not possible. In other countries, authorities allow deferred consent in life threatening situations when proxy decision makers may be influenced by anxiety and stress and are consequently presumed to be unable to give full informed consent.¹⁷ In the present study, the majority of HAMLET representatives considered themselves in retrospect capable of deciding about participation. In addition, only a minority would have preferred the doctor to have taken the responsibility for study participation. Deferred consent or consent waiver would therefore have been unnecessary and inappropriate in HAMLET.

Recall rates of trial information were low among representatives of PAIS patients. These results suggest that even in a relatively simple and straightforward trial such as PAIS, obtaining truly informed consent may be difficult.

The present study has limitations. Firstly, differences between the answers of representatives from either study may have been influenced by inherent differences in the emotional experiences between the groups. However, finding no differences between the groups of legal representatives with regard to the experience of the informed consent procedure and finding even better recall rates of trial details among HAMLET representatives dispelled some of the concerns about the appropriateness of asking for informed consent in a trial such as HAMLET. Secondly, bias may have been introduced by not interviewing representatives of patients who had refused to participate in either of the trials. However, of the 56 representatives asked for participation of a relative in HAMLET up to 1 August 2006, only three refused, in all cases to avoid survival with severe disability. Thirdly, patients included in HAMLET were younger than those included in PAIS. In PAIS, informed consent was more frequently given by the patient's children than in HAMLET. This may suggest a possible effect of age of the representatives. Fourthly, we do not have data on understanding of the trial information at the time of inclusion, so it is impossible to ascertain whether the information was initially understood and then forgotten. Finally, differences between the groups may have failed to reach statistical significance as a result of the small populations—for example, with regard to the question of feeling participation obligatory.

We conclude that perception of information about a clinical trial by representatives of patients with a neurological emergency is probably better if the condition is more severe and if the reputed effect of the treatment under study is larger. Participation of patients in a randomised controlled trial of surgical decompression for space occupying infarction is generally considered acceptable by their legal representatives.

ACKNOWLEDGEMENTS

The HAMLET investigators are: *Executive Committee*: A Algra, GJ Amelink, J van Gijn, J Hofmeijer (trial coordinator), LJ Kappelle, MR Macleod (UK national coordinator) and HB van der Worp (principal investigator). The *Steering Committee* comprised the principal investigators of each actively randomising centre (S de Bruijn, GJ Luijckx, R van Oostenbrugge, J Stam and JThJ Tans) and the members of the Executive Committee. *Data Monitoring Committee*: Y van der Graaf (chair), PJ Koudstaal and AIR Maas. *Advisory Committee*: GW van Dijk, W Hacke (chair), CJ Kalkman, CAF Tulleken and CAC Wijman.

The PAIS investigators are: *Executive Committee*: DWJ Dippel (principal investigator), MH den Hertog (trial coordinator), HB van der Worp (co-principal investigator) and HMA van Gemert. *Steering Committee*: A Algra, LJ Kappelle, J van Gijn, PJ Koudstaal and the members of the Executive Committee. *Data Monitoring Committee*: M Correia, M Vermeulen, PAG Sandercock (chair) and EW Steyerberg.

HAMLET and PAIS are supported by grants from the Netherlands Heart Foundation (grant Nos 2002B138 and 2002B148, respectively). Marrit van Buuren and Naziha el Ghannouti are greatly acknowledged for their efforts, especially in data management.

Authors' affiliations

J Hofmeijer, L J Kappelle, H B van der Worp, Department of Neurology, University Medical Centre Utrecht, Utrecht, the Netherlands

G J Amelink, Department of Neurosurgery, University Medical Centre Utrecht, Utrecht, the Netherlands

A Algra, Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, the Netherlands

H M den Hertog, Department of Neurology, Erasmus Medical Centre, Rotterdam, the Netherlands

Competing interests: None.

REFERENCES

- 1 Schats R, Brilstra EH, Rinkel GJ, *et al*. Informed consent in trials for neurological emergencies: the example of subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry* 2003;**74**:988–91.
- 2 Williams BF, French JK, White HD. Informed consent during the clinical emergency of acute myocardial infarction (HERO-2 consent substudy): a prospective observational study. *Lancet* 2003;**361**:918–22.
- 3 Griffin JM, Struve JK, Collins D, *et al*. Long term clinical trials: How much information do participants retain from the informed consent process? *Contemp Clin Trials* 2006;**27**:441–8.
- 4 Sugarman J, McCrory DC, Hubal RC. Getting meaningful informed consent from older adults: a structured literature review of empirical research. *J Am Geriatr Soc* 1998;**46**:517–24.
- 5 Joffe S, Cook EF, Cleary PD, *et al*. Quality of informed consent in cancer clinical trials: a cross-sectional survey. *Lancet* 2001;**358**:1772–7.
- 6 Cassileth BR, Zupkis RV, Sutton-Smith K, *et al*. Informed consent—why are its goals imperfectly realized? *N Engl J Med* 1980;**302**:896–900.
- 7 Harrison K, Vlahov D, Jones K, *et al*. Medical eligibility, comprehension of the consent process, and retention of injection drug users recruited for an HIV vaccine trial. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995;**10**:386–90.
- 8 Howard JM, DeMets D. How informed is informed consent? The BHAT experience. *Control Clin Trials* 1981;**2**:287–303.
- 9 Hofmeijer J, Amelink GJ, Algra A, *et al*. Hemispherectomy After Middle cerebral artery infarction with Life-threatening Edema Trial (HAMLET). Protocol for a randomised controlled trial of decompressive surgery in space-occupying hemispheric infarction. *Trials* 2006;**7**:29.
- 10 Rieke K, Schwab S, Krieger D, *et al*. Decompressive surgery in space-occupying hemispheric infarction: results of an open, prospective trial. *Crit Care Med* 1995;**23**:1576–87.
- 11 Schwab S, Steiner T, Aschoff A, *et al*. Early hemispherectomy in patients with complete middle cerebral artery infarction. *Stroke* 1998;**29**:1888–93.
- 12 van Breda EJ, van der Worp HB, van Gemert HM, *et al*. PAIS investigators. PAIS: paracetamol (acetaminophen) in stroke; protocol for a randomised, double blind clinical trial [ISRCTN 74418480]. *BMC Cardiovasc Disord* 2005;**5**:24.
- 13 Brott T, Adams HP Jr, Olinger CP. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989;**20**:864–70.
- 14 Oddens BJ, Algra A, van Gijn J. Informing patients about clinical trials. *Clin Invest* 1993;**71**:572–3.
- 15 Ross S, Grant A, Counsell C, *et al*. Barriers to participate in randomised controlled trials: a systematic review. *J Clin Epidemiol* 1999;**52**:1143–56.
- 16 Miller C, Searight H, Grable D, *et al*. Comprehension and recall of the informational content of the informed consent document: an evaluation of 168 patients in a controlled clinical trial. *J Clin Res Drug Dev* 1994;**8**:237–48.
- 17 Alves WA, Macciocchi SN. Ethical considerations in clinical neuroscience. Current concepts in neuroclinical trials. *Stroke* 1996;**27**:1903–9.

bmjupdates+

bmjupdates+ is a unique and free alerting service, designed to keep you up to date with the medical literature that is truly important to your practice.

bmjupdates+ will alert you to important new research and will provide you with the best new evidence concerning important advances in health care, tailored to your medical interests and time demands.

Where does the information come from?

bmjupdates+ applies an expert critical appraisal filter to over 100 top medical journals. A panel of over 2000 physicians find the few 'must read' studies for each area of clinical interest.

Sign up to receive your tailored email alerts, searching access and more...

www.bmjupdates.com