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Knowledge and understanding among cancer patients consenting to participate in clinical trials

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ABSTRACT

The aim of this study was to explore the fulfilment of the requirements of informed consent in patients participating in cancer clinical trials. All patients consenting to a phase II or III clinical trial during one year were included (n = 325, 176 women, 54%). Data were collected by a questionnaire, Quality of Informed Consent. The response rate was 87%. High levels of knowledge (>80%) were found for items concerning voluntariness, randomisation, benefits for future patients, participation in a research trial, and the right to withdraw. Less than 50% responded correctly to items about risks associated with the trial, the unproven nature of the trial and issues about insurances. High levels of perceived understanding were reported. Despite high levels of knowledge and perceived understanding in the majority of elements of informed consent, improvements are warranted regarding knowledge about risks, the unproven nature of the treatment and the duration of treatment.

1. Introduction

Therapeutic development within oncology requires the participation of patients in clinical trials. It is mandatory, according to both international and national guidelines and laws, that every patient who participates in research gives a written informed consent before inclusion. The principles of informed consent are based on the Declaration of Helsinki.[1] The practice of the informed consent has developed from multiple disciplines, such as health professions, the law and moral philosophy.[2] Formal obligations and requirements for informed consent evolved from the standards governing both clinical medicine and human research. In the context of research, informed consent developed in parallel with a informed consent to medical treatment.

Five elements constitute informed consent: voluntarism, capacity, disclosure, understanding and decision.[2–4] Voluntarism requires that the patient is free from coercions and persuasions in decision-making. Capacity refers to the patients' ability in making health care decisions, in terms of ability to make choices, understand relevant information, comprehend the situation and its consequences and to rationally process the information. Competence is an aspect of capacity that refers to the patients' legal status in making decisions. Disclosure involves giving the patient the relevant information concerning the nature and purpose of the treatment, as well as information about the risks, potential benefits and available alternatives. Understanding requires that the patient comprehends the information given and perceive this information as relevant to her situation. Decision refers to the patient accepting the proposed treatment.

Many studies reveal insufficient understanding by patients participating in research studies.[5–8] Research participants may perceive themselves as well informed but nevertheless hold significant misunderstandings.[7,9] Studies also show that investigators/physicians rarely check patients understanding of the information given.[6,8,10]

A clinical trial unit (CTU) has been running at the Department of Oncology, Karolinska University Hospital since 1996. Phase I, II, III and IV trials are conducted at the CTU. The unit

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coordinates between 110 and 120 clinical studies at three clinical sites. In general about 20 studies are in planning phase, 50 studies open for inclusion, 50 studies with patients under treatment or follow-up. The majority of the trials are phase II and III studies. The unit is staffed with 17 research nurses who serve as coordinators for the clinical trial teams and they support the bedside staff in the conduct of the trial by preparing a summary of the study protocol including the definition of tasks and responsibilities of each member of the clinical trial team. Patients usually get their initial information, oral and written, about a clinical trial from their physician at an appointment at the Department of Oncology. It is recommended, but not mandatory, that a research nurse participates on that occasion. Patients are encouraged to discuss the information with friends and/or relatives and to return to the physician and/or the research nurse later with additional questions before making a decision on whether to participate in the trial or not. There is a standard operating procedure (SOP), describing physicians' and research nurses' responsibilities, in accordance with guidelines and laws, including the physician's duty to make sure that the patient understand the implications of participating in the trial.

All patients participating in trials conducted at the CTU sign informed consent forms. The aim this study was to explore the fulfilment of the requirements of informed consent in patients participating in clinical trials at the CTU. Gender and diagnostic groups were also compared with respect to knowledge.

The study was approved by the Regional Ethical Review Board, Stockholm (2005/604-31/3).

2. Patients and methods

2.1. *Subjects*

Patients who had been informed in Swedish about a phase II or a phase III clinical trial at the Department of Oncology, Karolinska University Hospital between September 2005 and September 2006, aged 18 years or older, and had signed a consent form were included.

2.2. *Procedure*

Data collection started in September 2005 and continued for one year. Research nurses at the Clinical Trial Unit provided the coordinator of this study with data collected on patients included in phase II or III trials at the Department of Oncology. A questionnaire, together with an information letter and a prepaid envelope, was then sent by the study coordinator to the patient's home address, for 75% of the patients within three days after signing the consent form and for 99% within two weeks. In the information letter, patients not accepting to participate in this survey were advised to return the questionnaire without completing it. One reminder was mailed to those who had not returned the questionnaire within two weeks.

2.3. *The questionnaire*

The questionnaire Quality of Informed Consent (QuIC) consists of two parts.[11] The first part (A) measures patients' knowledge on the basic aspects of clinical trials. Part A consists of 20 items with response format 'disagree', 'unsure' and 'agree' out of which 14 items are not phase specific, i.e. the same response alternative is correct irrespective phase of trial. Depending on trial phase, different response categories are corrected for two items. One item is scored for participants in phase II trials only and one item for participants in phase III trials only. Two items applies to patients participating in phase I trials.[11]

The second part (B) comprises 14 questions where patients rate to what extent they perceived that they understood elements of the trial. The response format is a 5-point scale (1 = 'I didn't understand this at all', 5 = 'I understood this very well').[1]

The items cover the eight basic elements, specified in the US federal regulations.[12] Each of the elements is assessed in both part A and B.[11]

The item generation, validation of adequate items and assignment of correct answers included expert review, pilot testing with participants in clinical trials and expert confirmation of the correct responses to part A. Test–retest reliability was performed with good results.[11]

QuIC was translated to Swedish by forward and backward translation followed by pilot testing of the questionnaire in accordance with the guidelines from European Organisation for Research and Treatment of Cancer (EORTC), Quality of Life Group.[13] Ten patients, who had consented to a phase II or III trial, participated in the first pilot testing of the translation of the questionnaire. Three patients reported difficulty with one of the items, which then was amended. The revised questionnaire was thereafter tested on six further patients. No item rendered difficulties for two or more patients.

In addition to QuIC, inquiries about length of consent procedure, previous participation in a clinical trial and time since the initial information when the patient had signed the consent form were posed together with data on education and marital status.

2.4. *Statistical analyses*

Data were categorised in three diagnostic groups, 'breast cancer', 'colorectal cancer' and 'prostate cancer'. A fourth group, 'other', includes data collected from patients with tumour types with fewer than 20 respondents.

Each correct response to the items in part A was assigned a score of 100, incorrect answers and responses in the category 'unsure' were assigned a score of 0. Scores for each of the basic elements were calculated by averaging the scores for that element, e.g. the element 'voluntary nature of participation' was calculated by summarising the scores for items 19 and 20, divided by 2 (number of items). The responses to the items in Part B (range 1–5) were transformed to a 0 to 100 scale (1 = 'I didn't understand this at all' was assigned a score of 0, 2–25, 3–50, 4–75 and 5 = 'I understood this very well' was assigned a score of 100). Scores for each of the elements were calculated in the same way as for part A.

Student's *t*-test was employed to test gender differences and differences in trial phase with respect to 'knowledge' and 'perceived understanding'. Student's *t*-test was also used to analyse differences in age between respondents and non-

respondents. ANOVA was performed to test differences in 'knowledge' and 'perceived understanding' between diagnostic groups. Due to multiple comparisons the level of statistical significance was set to $p \leqslant 0.01$.

3. Results

Questionnaires were mailed to 325 patients, 176 women (54%), who had consented to participate in one of the 35 clinical trials open for inclusion during the study period. A total of 282 patients responded (87%). Demographic characteristics of respondents are shown in Table 1. The number of respondents included in phase II or III trials according to diagnosis are presented in Table 2. Of the non-respondents, 2 questionnaires were returned to sender, 10 patients returned uncompleted questionnaires, and 31 did not reply. Mean age of respondents was 60 years (range 32–82 years). Non-respondents were statistically significantly younger (mean age 56 years, range 28–79 years, $p < 0.01$).

3.1. *General questions*

Respondents were asked how easy or difficult they found the decision to participate in the clinical trial. A total of 104 patients (37%) responded 'very easy', 88 (32%) 'easy', 64 (23%) 'neither easy nor difficult', 16 (6%) 'difficult', and 6 (2%) 'very difficult'. A total of 76 patients (27%) signed the consent form at the medical visit in connection to the first information about the trial, whereas 204 patients (73%) responded that they signed the consent form later. The patients were asked about the duration of the consent discussion. A total of 39 patients (14%) responded 'less than 15 min', 139 patients (50%) 'between 15 and 30 min', 50 patients (18%) 'between 30 and 45 min', 30 patients (11%) 'between 45 and 60 min', and 18 patients (7%) responded 'more than 60 min'. When asked about other sources of information about the clinical trial, 63 patients (23%) had used written material provided by the hospital staff. A total of 50 patients (18%) reported being given additional information from another physician than the one responsible for inclusion in the trial. Other cancer patients were reported as a source of additional information by 35 patients (13%). The Internet was used by 32 patients (12%), and 13 patients (5%) reported having used textbooks and newspapers for further information. A total of 34 patients (12%) reported that they had previously participated in a clinical trial and 237 (85%) responded 'no' to that question. Seven (3%) responded, 'I don't know'. There were similar proportions of patients previously participating in clinical trials between patients consenting to phase II or III trials (data not shown).

3.2. *Part A knowledge*

Fig. 1 presents the proportions of all patients responding correctly to the 16 items in part A that are applicable to all patients, irrespective of trial phase. Overall, high levels of knowledge (>80%) were found for 7 of the items. These items concerned the voluntary nature of participation, knowledge about randomisation, benefits for future patients, knowledge about the fact of participating in a trial, and the right to withdraw. Five items were responded to correctly by 50–80% of the patients. These items were related to knowledge of no personal benefit of participation, alternatives to trial participation, confidentiality issues, duration of the trial and treatment schedule. Less than 50% responded correctly to four of the items. These items concerned risks associated with the trial, the unproven nature of the trial and issues about insurances in connection to participating in the trial.

Table 3 shows the mean scores, standard deviations and number of respondents for the eight basic elements in part A according to, gender, trial phase and diagnostic group ('breast', 'colorectal', 'prostate' and 'other'). High levels of knowledge were found for two of the basic elements, the 'voluntary nature of participation' (>90%) and 'study contacts' (>80%). Mean

Table 1 – Demographic characteristics

		N	%
Age	$n = 282$ (100%)		
	<45	26	9.21
	45–64	142	50.35
	⩾65	114	40.42
Gender	$n = 282$ (100%)		
	Women	147	52
	Men	135	48
Education	$n = 277$ (98%)		
	Compulsory school (1–9 years)	67	24
	Senior high school (10–12 years)	79	29
	University education (13–16 years)	105	38
	Higher university education (>16 years)	26	9
Marital status	$n = 280$ (99%)		
	Married/living with partner	195	70
	Divorced/separated	42	15
	Never married	26	9
	Widowed	17	6
Language	$n = 280$ (99%)		
	Only Swedish used at home	265	95

Table 2 – Phase II and III trials open for inclusion during the study period and number of patients who consented to participate across cancer diagnosis

Diagnosis	Number of trials in phase II	Number of patients in phase II	Number of trials in phase III	Number of patients in phase III	Total number of trials	Total number of patients
Breast cancer	2	23	6	73	8	96
Colorectal cancer	2	7	3	47	5	54
Prostate cancer	2	17	2	33	4	50
Pancreatic cancer	0	0	2	19	2	19
Ovarian cancer	0	0	3	17	3	17
Lung cancer	1	9	4	5	5	14
Malignant melanoma	2	13	0	0	2	13
Kidney cancer	1	10	0	0	1	10
Stomach cancer	1	4	0	0	1	4
Head and neck	0	0	2	3	2	3
Sarcoma	0	0	1	1	1	1
Thyroid cancer	1	1	0	0	1	1
Total	12	84	23	198	35	282

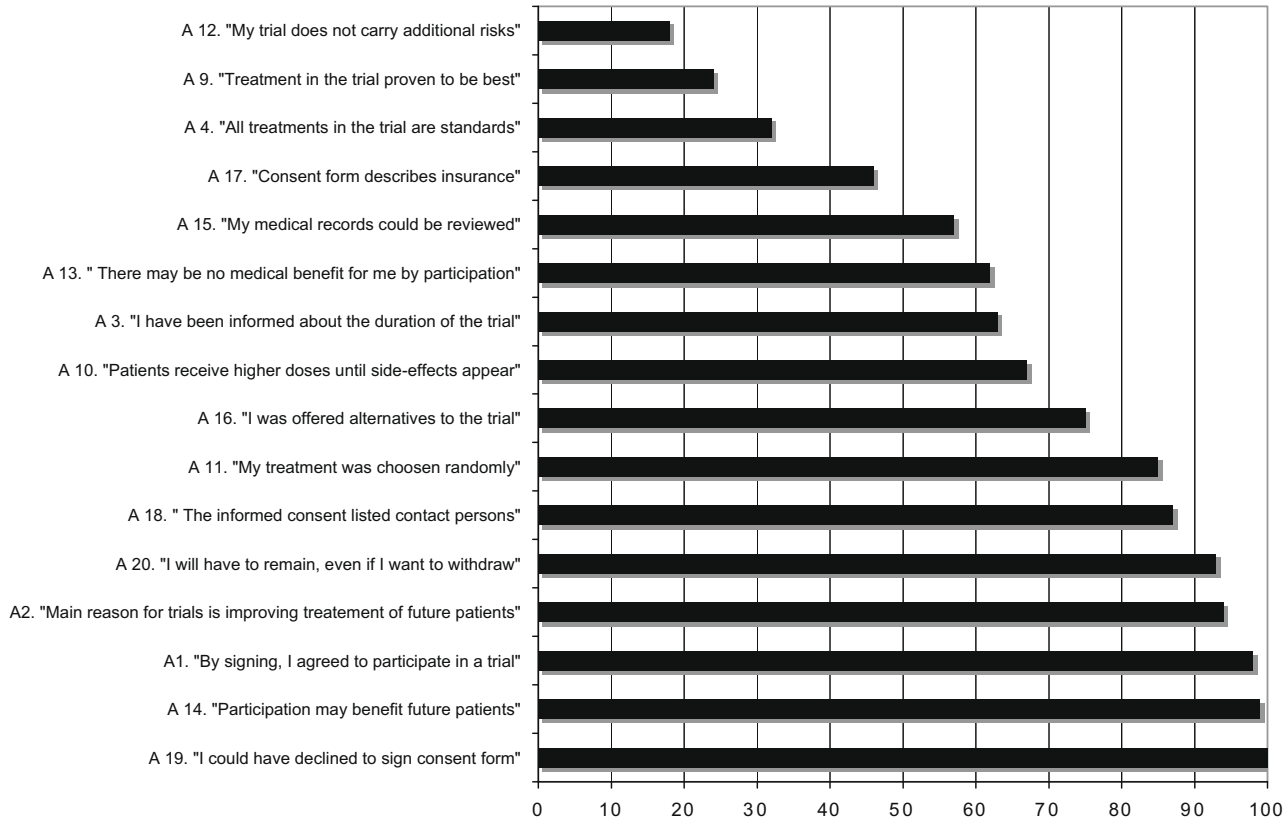

Fig. 1 – Proportion of correct responses to the 16 items applicable to all patients.

scores higher than 70% were found for the basic elements 'research purpose and procedures, duration, experimental procedures' and 'alternatives to participation'. There was a statistically significant difference in knowledge about 'Procedures in the event of research injury' between the diagnostic groups ($p = 0.008$). Higher mean scores were found for respondents with breast cancer (56.2) compared to respondents with colorectal cancer (35.2, $p = 0.001$) and respondents in the group 'other' (35.0, $p = 0.005$). Mean scores for 'benefits for self and other' ranged between 56.7 and 68.0 and for 'confidentiality' between 48.0 and 65.5. The lowest mean scores (range 7.7–21.9) were found for 'potential risks or discomforts' (Table 3).

Table 3 – Knowledge – number of respondents (n) mean scores and standard deviations (SD) for the eight basic elements according to, gender, trial phase and diagnostic group

Element[a]	Total n = 272–281 mean (SD)	Women n = 140–147 mean (SD)	Men n = 128–134 mean (SD)	Phase II n = 82–84 mean (SD)	Phase III n = 185–197 mean (SD)	Breast n = 93–96 mean (SD)	Colorectal n = 49–54 mean(SD)	Prostate n = 49–50 mean (SD)	Other n = 77–81 mean (SD)
Research purpose and procedures, duration, experimental procedures	76.0 (14.7)	76.0 (15.0)	76.0 (14.4)	77.1 (16.7)	75.5 (13.8)	76.2 (15.7)	72.3 (10.7)	77.3 (12.3)	77.4 (16.9)
Potential risks or discomforts	17.6 (38.2)	19.3 (39.6)	15.8 (36.6)	21.4 (41.3)	16.0 (36.7)	21.9 (41.6)	7.7 (26.9)	14.0 (35.0)	21.3 (41.2)
Benefits to self and other	61.9 (23.7)	60.8 (23.9)	63.1 (23.6)	60.2 (24.3)	62.6 (23.5)	58.9 (22.6)	68.0 (24.9)	56.7 (20.5)	64.9 (25.3)
Alternatives to participation	75.4 (43.2)	79.6 (40.4)	70.7 (45.7)	76.2 (42.8)	75.0 (43.4)	82.3 (38.4)	73.6 (44.5)	68.0 (47.1)	72.8 (44.8)
Confidentiality	56.6 (49.7)	55.8 (49.8)	57.5 (49.6)	65.5 (47.8)	52.8 (50.0)	60.4 (49.1)	59.3 (49.6)	48.0 (50.5)	55.6 (50.0)
Procedures in the event of research injury[b]	45.7 (49.9)	50.0 (50.2)	41.0 (49.4)	55.9 (49.9)	41.3 (49.4)	56.2 (49.9)	35.2 (48.2)	54.0 (50.3)	35.0 (48.0)
Study contacts	86.7 (34.0)	85.0 (35.8)	88.6 (32.0)	84.4 (36.6)	87.7 (32.9)	86.5 (34.4)	78.8 (41.2)	87.8 (33.1)	91.4 (28.3)
Voluntary nature of participation	96.2 (13.2)	95.9 (13.8)	96.6 (12.6)	96.4 (13.0)	96.2 (13.3)	97.4 (11.2)	93.4 (17.1)	98.0 (9.9)	95.7 (14.1)

a Range for each of the eight elements was 0 to 100, higher values indicating better knowledge.
b Statistically significant difference between the diagnostic groups, $F(3,276) = 4.044$, $p = 0.008$ breast/colorectal $p = 0.01$, breast/other $p = 0.005$.

3.3. *Part B perceived understanding*

Mean scores, standard deviations and number of respondents for the eight basic elements in Part B according to, gender, trial phase and diagnostic group are shown in Table 4. High levels of perceived understanding were found for six of the basic elements, the 'voluntary nature of participation', 'study contacts' (>90%), 'research purpose and procedures, duration, experimental procedures', 'alternatives to participation', 'confidentiality' and 'benefits to self and other' (>80%). Mean scores for perceived understanding of 'potential risks and discomfort' ranged between 74.2 and 80.4. There was a statistically significant difference in perceived understanding concerning 'procedures in the event of research injury' between trials phases ($p = 0.002$) and diagnostic groups ($p = 0.003$). Higher mean scores were found for respondents with breast cancer (65.8) compared to the respondents with colorectal cancer (43.7, $p = 0.001$) and between respondents with colorectal cancer and prostate cancer (67.5, $p = 0.002$). The basic element 'potential risks or discomforts' got the lowest mean scores of perceived understanding (range 43.7–9.6) (Table 4). The mean score for the overall perceived understanding of the implications of participating in the clinical trial was 86.3, range 85.4 (breast cancer) to 88.5 (prostate cancer).

If the basic elements are placed in rank order according to mean scores, the 'voluntary nature of participation' and 'study contacts' consistently gets the highest rank, both in part A (knowledge) and part B (perceived understanding), irrespective of gender, trial phase or diagnostic group. The same concordance between part A (knowledge) and part B (perceived understanding) is true for the basic elements that gets the lowest rank 'potential risks and discomforts' and 'procedures in the event of research injury' (Tables 3 and 4).

4. Discussion

In this study, the majority of the participants perceived themselves as well informed. High levels of knowledge were found for some items while our results revealed a lack of knowledge with respect to other items required for informed consent.

The proportion of patients responding correctly to the items about knowledge in part A varied. Most patients were aware that they were participating in research and that participation was voluntary. Surprisingly, over 90% responded correctly that the main reason for the trial was to improve treatment for future patients. It could be expected that the patients in this vulnerable situation would have their own best in mind. Studies have found that some research participants do not comprehend differences between research and treatment, a phenomenon called 'therapeutic misconception'.[14,15] This phenomenon has been found to be associated with overestimations of clinical benefit as well as with underestimation of risks. Although a high proportion was found to respond correctly concerning the main reason for the trial, only 24% correctly responded to the items stating 'The treatment being researched in my clinical trial has been proven to be the best treatment for my cancer' and as few as 18% responded correctly to the item stating: 'Compared to standard

Table 4 – Perceived understanding – number of respondents (n) mean scores and standard deviations (SD) for the eight basic elements according to, gender, trial phase and diagnostic group

Element[a]	Total n = 278–282 mean (SD)	Women n = 146–147 mean (SD)	Men n = 132–134 mean (SD)	Phase II n = 82–84 mean (SD)	Phase III n = 195–198 mean (SD)	Breast n = 95–96 mean (SD)	Colorectal n = 52–54 mean (SD)	Prostate n = 50 mean (SD)	Other n = 80–82 mean (SD)
Research purpose and procedures, duration, experimental procedures	85.7 (16.0)	86.6 (15.0)	84.6 (16.9)	88.2 (16.0)	84.6 (15.9)	87.7 (13.7)	81.5 (15.9)	88.1 (17.4)	84.6 (17.2)
Potential risks or discomforts	76.7 (28.2)	77.2 (27.1)	76.1 (29.4)	80.4 (26.3)	75.1 (28.8)	74.2 (27.3)	74.5 (28.9)	77.5 (32.4)	80.4 (25.8)
Benefits to self and other	83.4 (18.6)	84.6 (18.4)	82.1 (18.8)	85.6 (17.9)	82.5 (18.8)	84.2 (18.4)	84.7 (15.3)	80.5 (22.5)	83.4 (18.3)
Alternatives to participation	85.4 (26.4)	88.5 (22.6)	82.0 (29.7)	83.6 (28.6)	86.1 (25.4)	88.4 (23.0)	88.0 (21.3)	80.5 (32.8)	83.2 (28.3)
Confidentiality	84.3 (26.2)	84.2 (25.9)	84.3 (26.7)	89.3 (20.6)	82.1 (28.1)	82.9 (27.6)	82.9 (23.7)	87.5 (26.4)	84.9 (26.4)
Procedures in the event of research injury[b,c]	58.5 (39.9)	59.9 (41.1)	56.8 (38.6)	69.6 (36.8)	53.7 (40.2)	65.8 (37.0)	43.7 (39.9)	67.5 (37.9)	53.7 (41.5)
Study contacts	93.1 (17.8)	92.3 (19.4)	94.0 (16.0)	92.0 (21.0)	93.6 (16.3)	90.8 (21.0)	92.4 (18.1)	95.0 (13.4)	95.1 (15.9)
Voluntary nature of participation	98.9 (6.6)	98.8 (6.1)	99.1 (7.1)	98.8 (8.6)	99.0 (5.5)	98.7 (6.7)	99.5 (3.4)	98.5 (10.6)	99.1 (4.7)

a Range for each of the eight elements was 0–100, higher values indicating better perceived understanding.
b Statistically significant difference between the trial phases, $t(276) = 3.082$, $p = 0.002$.
c Statistically significant difference between the diagnostic groups, $F(3,274) = 4.868$, $p = 0.003$ breast/colorectal $p = 0.001$, colorectal/prostate $p = 0.002$.

treatments for my type of cancer, my clinical trial does not carry any additional risks or discomforts'. Thus, although aware of being included in research, the patients in our study tended to overestimate the benefits and to play down the risks associated with participation. The mean values for perceived understanding on these items were overall high. An explanation could be that, after having consented to participate, the risks are minimized, and that the patients focus on the possible benefits of participation.

The overall relative high mean scores on perceived understanding underline the importance of checking patients' knowledge. Patients might think they have understood the information and consequently report high mean scores on perceived understanding, but this is based on inaccurate or incomplete understanding. However, a concordance in the rank order, based on mean scores, of the basic elements between knowledge (part A) and perceived understanding (Part B) was found. The 'voluntary nature of participation' and 'study contacts', consistently got the highest rank. On the other hand, the elements 'potential risks and discomforts' and 'procedures in the event of research injury' were assigned the lowest rank in all groups. Despite low mean scores in knowledge and relative high mean scores in perceived understanding, the ranking order shows the basic elements that respondents perceive themselves least informed about.

One difference in knowledge was found between diagnostic groups. Patients with breast cancer had a higher level of knowledge about the basic element 'procedures in the event of research injury' compared to the patients with colorectal cancer and patients in the group 'other'. This difference could not be explained by gender differences, since no difference between men and women was found with respect to knowledge. There is, however, a possibility that the procedures differ between the diagnostic groups in informing patients when recruiting them to clinical trials.

The study has a number of strengths. All patients were included in trials conducted at one department and the trials were run by the CTU. Consecutive patients were included during one year and the response rate was high. The patients were asked to participate in this study closely to having consented. Thus, the risk of recall bias was limited. A number of different diagnoses were included as well as both women and men in various ages. The results can therefore be generalised to all the participants in clinical trials at the CTU irrespective of age, phase II or III, gender and diagnosis.

This study also has a number of limitations. The questionnaire used was developed in English but translated to Swedish using a forward and backward translation procedure. The translation was tested on 16 patients and revised during this process. However, the Swedish version has not been formally validated or reliability tested. The questionnaire is intended for assessments in phase I to III clinical trials. Due to the low number of participants in phase I trials, less than 20 during year 2005, this study was restricted to participants in phase II or III trials.

In conclusion, the results show that most patients have high knowledge and high levels of perceived understanding in the majority of the elements of informed consent. However, there are some areas where knowledge is limited and where improvements are warranted. Risks and discomforts

are underestimated and the unproven nature of the treatment is less well known and understood.

Conflict of interest statement

None declared.

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