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Reasons given by patients for participating, or not, in Phase 1 cancer trials

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ABSTRACT

Background: Communication with patients contemplating Phase 1 cancer trial participation can be challenging. Controversy exists as to whether they are provided with sufficient information to give genuinely informed consent. We present data examining the reasons patients gave for trial entry.

Method: Following discussions with oncologists about Phase1 trials, participants completed a 19-item study specific 'accept or decline measure' exploring hope, expectations of benefit, altruism, concerns, and general perceptions of the trial information. They also completed 2 standardised questionnaires measuring psychological morbidity and predisposition towards optimism.

Results: Forty patients completed the study questionnaires. Patients were generally optimistic with few concerns about the experimental nature of Phase 1 trials. Most 36/40 (90%) consented to trial entry. Fifty-one percent thought the trial was the only treatment option available. The four main reasons for trial entry were: expectation of some medical benefit (21%); trial the best available option (21%); to maintain hope (15%) and to help with research (13%). Only one patient gave altruism as their main reason for trial participation.

Conclusion: Patients considering Phase 1 trials may be a self-selected group with optimistic expectations of personal benefit driving trial entry rather than altruism. Achieving genuinely informed consent and avoidance of therapeutic misconceptions in such patients may be difficult.

1. Introduction

Phase 1 (P1) clinical trials are crucial in the development of new anti-cancer treatments. New agents that have shown promise in the laboratory are usually tested in patients with advanced disease. The aims of P1 trials are to determine safe dosage range and identify side-effects. These trials convey small prospects of therapeutic benefit and carry varying possibilities of side-effects.[1] It is therefore not surprising that recruiting patients into these studies generates ethical debate[2] and creates challenging communication issues.[3,4]

A systematic review by Todd and colleagues[5] examined the positive and negative attitudes of patients with advanced cancer towards research. In this review 11 studies were identified for evaluation. Most involved hypothetical scenarios and only two were with patients in P1 trials – one qualitative[6] and one quantitative.[7] Common motives for participation were altruism, hope, and for personal benefit. Concerns about negative impact on symptoms and risk of increased hospital admissions emerged as reasons for declining participation. Most patients were positive in general about research despite having advanced disease. Conclusions were that more

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Table 1 – Summary of previous studies examining reasons for P1 cancer trial entry.

Article	Design	*n*	Reasons for clinical trial participation
Rodenhuis et al.[8] (Netherlands)	Open-ended interview	10	Hope of benefit, appease relatives, contribute to research, no other option
Daugherty et al.[9] (USA)	Structured interview	27	Therapeutic benefit (100%), no better option (89%), trust in trial doctor (70%), trust in trial centre (67%), trust in referring doctor (63%), help others (33%), family pressure (30%), contribute to research (22%)
Itoh et al.[10] (Japan)	Questionnaire	32	Trust in doctor (28%), advised by doctor (22%), no other option (9%), altruism (6%)
Yoder et al.[11] (USA)	Structured interview	37	Personal benefit (70%), help others or contribute to research (22%), advised by doctor (8%)
Hutchison[12] (UK)	Structured interview	28	Hope of benefit (top rank), nothing to lose and help others and advised by doctor (equal mid rank), family pressure (bottom rank)
Schutta et al.[13] (USA)	Focus groups	22	Hope of benefit, trust in doctor, positive dissociation with altruism
Tomamichel et al.[14] (Switzerland)	Questionnaire	26	Hope of benefit (59%), trust in doctor (26%), other-unspecified reasons (12%), contribute to research (3%)
Agrawal et al.[7] (USA)	Structured interview	163	Therapeutic benefit-because cancer is growing (75%), family pressure (9%), doctor pressure (7%)

research was still warranted to elicit the experiences and opinions of patients who have either agreed, or declined, to participate in early phase trials.

We found 8 studies where in P1 cancer trials reasons for participation had been recorded and these are summarised in Table 1. Both qualitative and quantitative studies have reached similar conclusions as to why patients participate. Although primarily motivated by hopes for improvements in their condition, other reasons expressed include: appeasing relatives and friends, a desire to contribute to the progress of medicine, trust in the clinician, and a sense that there was 'no other option'. Altruism is commonly quoted as a key driver for trial entry, but these studies show it is infrequently named by patients as a primary motivating factor.

Understanding why patients participate or not in P1 trials could assist the development of communication training courses for specialists working within the area and aid trial recruitment. The difficulties encountered with discussing Phase 3 (P3) cancer clinical trials have been well documented and recommendations made for healthcare professionals communication skills training.[15,16] Subsequently suitable, successful, courses dealing with recruiting patients to P3 trials have been developed and evaluated.[17] Nevertheless, it arguably requires even higher order communication skills to talk to patients about P1 trials.[18–20]

Healthcare professionals are often dealing with vulnerable patients for whom most conventional treatments have failed and who may come to the consultation with unrealistic expectations for benefit. Patient factors contributing to this situation include demography, previous treatment experiences, personality traits and current physical and mental health. Recent meta-analysis[21] confirms that one-third of patients with cancer in acute care suffer mental health problems that warrant appropriate treatment and this prevalence is above that of the general population. The levels of depression and anxiety disorders for patients with advanced cancer in palliative care match or often exceed those in acute care.[22]

Personality traits may also influence health decision-making so are of interest when looking at factors affecting trial recruitment, especially optimism. The benefit of positive thinking is a notion often applied to health/illness and cancer by lay people and some healthcare professionals. In their review Scheier and Carver[23] state the effects of optimism are not limited to making people feel better, it also confers positive influences on what people do and what people are able to achieve in times of adversity. It seems reasonable therefore to pay attention to optimism when trying to understand the decisions patients with advanced cancer make about P1 trial participation.

In this descriptive paper we focus on the reasons patients gave for accepting or declining the invitation to participate in P1 trials, their psychological well-being and predisposition towards optimism.

2. Methods and materials

The data were collected as part of a larger CRUK funded study[20] to improve communication between healthcare

professionals and patients when discussing P1 trials. The study had multi-centre ethical approval (Oxfordshire Research Ethics Committee C Ref: 07/Q1606/20) and all local NHS R&D permissions.

This was a convenience sample. To reduce the risk of introducing selection bias, whenever researchers were present all patients attending clinics for a P1 trial discussion were approached consecutively.

Prior to consultations patients were given an information sheet about the communication study to read and written informed consent was obtained. The consultation was digitally audio recorded, after which the researchers conducted face-to-face study specific semi-structured interviews with patients to determine patients' perspectives on what the consultation had covered. Clinicians also completed a brief questionnaire probing their views on what had been discussed during the consultation. These data have been reported elsewhere.[20] Additionally, patients were given 3 questionnaires to complete at home and return by post after they had made decisions about trial entry.

2.1. Questionnaires

The three questionnaires administered were, (1) clinical trial accept/decline questionnaire, (2) Life Orientation Test-Revised (LOT-R),[24] and (3) General Health Questionnaire-12 item version (GHQ12).[25]

2.1.1. Accept/decline questionnaire

Patients' motivations for trial participation or not, were recorded via a study specific questionnaire (see Appendix A) which was based on a design by Penman and colleagues[26] and from previous research on the reasons patients gave for joining Phase 3 trials.[27] The questionnaire consisted of an initial question ascertaining whether or not the patient had agreed to trial entry. Patients were then asked to rate on a 5-point Likert scale to what extent they agreed or disagreed with a list of 19 reasons that might have influenced the decision to either accept or decline the trial invitation. They indicated the most important reason for their decision and had the opportunity to add further explanations in an additional box (qualitative responses). No formal reliability testing of this questionnaire is available but it has been used in several previous studies.[26,27]

2.1.2. LOT-R

This 10-item self-report scale measures predisposition towards optimism. Validity and reliability have been published and it has been applied in oncology settings.[24] There are six target statements (with an even mix of positive and negative wording), and four filler items. Respondents rate their agreement with items on a 5-point Likert scale ranging from 0 = strongly disagree to 4 = strongly agree. Higher scores represent greater optimism.

2.1.3. GHQ12

This is a well validated self-report measure of general psychological well-being widely used in patient populations.[25] A score above a threshold of $\geqslant 4$ is suggestive of probable psychological morbidity.

2.2. Statistical analysis

Using SPSS 16.0 for Windows summary statistics were generated for the data: counts, percentages and averages. A non-parametric correlation, Spearman's rho, was used to test the relationship between psychological well-being and optimism.

Table 2 – Characteristics of the whole study sample.

	(*n* = 40)
Sex	
Male	22 (55%)
Female	18 (45%)
Age	
Mean (S.D.)	58.8 (11.10)
Range (min–max)	29–76 years
Age band	
25–34	3 (8%)
35–44	1 (3%)
45–54	8 (20%)
55–64	15 (38%)
$\geqslant$65	12 (31%)
Missing data	1
Marital status	
Partner	28 (72%)
No partner	11 (28%)
Missing data	1
Employed	
Yes	9 (23%)
No	30 (77%)
Missing data	1
Education	
No school exams	13 (33%)
GCSE/A Level	12 (31%)
University and higher	14 (36%)
Missing data	1
Cancer site	
Colorectal/upper GI	22 (55%)
Breast	6 (15%)
Gynaecological	5 (13%)
Skin	3 (8%)
Other	4 (10%)
Previous treatments	
Surgery (ever)	32 (80%)
- Single intervention	20 (50%)
- Multiple interventions	12 (30%)
Chemotherapy (ever)	38 (95%)
- Single course	7 (17%)
- Multiple courses	31 (78%)
Radiotherapy	12 (30%)
Hormone	2 (5%)
Previous trial experience	
Yes	18 (46%)
Missing data	1
GHQ12	
Above threshold (case)	19 (49%)
Below threshold	20 (51%)
Missing data	1
LOT-R scores	
Mean (S.D.)	15.45 (3.62)
Range (min–max)	8–24

3. Results

3.1. Sample

Recruitment took place from five UK cancer centres (Beatson Oncology Centre, Glasgow; Royal Marsden Hospital, Sutton; Royal Free Hospital, London; Southampton and Oxford CR-UK Medical Oncology Units), between August 2007 and December 2008.

A total of 58 out of 62 patients approached and invited to join the communication study[20] consented. Of these seven did not return questionnaires, five were subsequently ineligible for trials, four only had general trial discussions, one withdrew, and one came for a follow-up visit. Data were therefore available for 40 participants.

Table 2 gives a summary of socio-demographic and other characteristics, and Table 3 specifics of the trials discussed. A Spearman's rho test for the LOT-R scores and GHQ12 cases shows a significant correlation (–0.341 at the 0.05 level, 2-tailed, $n = 39$, one patient did not complete the GHQ12 measure), with lower optimism associated with caseness for probable psychological morbidity.

Table 3 – Trial specifics.

	($n = 40$)
Type of trial discussion	
General discussion	12 (30%)
Dose escalation study	10 (25%)
Targeting/antibody/immunotherapy	11 (27.5%)
Combination (standard chemo plus new agent)	7 (17.5%)
Trial agent	
None discussed (general discussion)	12 (30%)
Cytotoxic and/or antiproliferative	5 (12.5%)
Monoclonal antibody	3 (7.5%)
Tyrosine kinase inhibitor	7 (17.5%)
Angiogenesis inhibitor	4 (10%)
DNA repair inhibitor	5 (12.5%)
Vaccine	2 (5%)
Other	2 (5%)
Route of administration	
None discussed (general discussion)	12 (30%)
Oral only	12 (30%)
Intravenous only	9 (22.5%)
Intramuscular only	2 (5%)
Intravenous and oral	4 (10%)
Unspecified	1 (2.5%)

Overall, 36/40 (90%) patients accepted entry into P1 clinical trials. Only 4/40 (10%) declined, a number too small for any statistical analysis. These decliners' characteristics are displayed in Table 4. Explanations for their decision are presented below as full quotes from the qualitative responses given on the accept/decline questionnaire. The explanations given include quality of life considerations, other treatment options, and time constraints.

3.2. Qualitative responses given by trial decliners

ID 16. Been living on my own. Now back with my husband and moving back to Wales to make the most of whatever time I have left.

ID 20. Quality of life is far more important than quantity of life.

ID 44. I decided to become a private patient and have a drug not available on the NHS for a few months. As to whether this was of benefit, I would re-consider a trial if offered at a later date and assuming the drug I am taking is unsuccessful. Time will tell.

ID 60. Decided that this particular trial was very intense and that the travelling would put too great a strain on both myself and my husband. There's another trial in August which is not so intense which hopefully will work in the same way but with fewer visits.

3.3. Reasons for trial entry

Table 5 displays the frequency of agreement to each statement on the accept/decline questionnaire expressed in percentages. The categories 'strongly agree' and 'agree to some extent' were combined. The majority of patients (97%) agreed they had been provided with sufficient trial information, both oral ('the doctor told me what I needed to know') and written ('I was given clear information to read'). Likewise 97% trusted the treating physician and wanted to help with research, and few (16%) felt unable to say no to the trial. A third of the patients were 'worried about being a guinea pig'. A few (16%) were concerned about the burdens associated with the trial. Three quarters thought they would derive some medical

Table 4 – Decliner characteristics.

ID	Sex	Age (years)	Marital status	Employed	Education	Cancer site	Trial type	Previous trial	LOT-R (total)	GHQ12 (*case)
16	F	66	Married	No	No exams	Stomach	Phase 1	Yes	13	11*
20	F	58	Married	Yes	University	Anal	Phase 1	No	21	2
44	M	72	Married	No	GCSE/A level	Lung	Phase 1	No	16	2
60	F	64	Married	No	No exams	Bowel	Phase 1	No	14	8*

* Denotes a case which is a score of $\geqslant 4$ on the GHQ12 and is indicative of probable psychological morbidity.

Table 5 – Frequency of agreement to each statement on the accept/decline questionnaire for all patients ($n = 39^{*}$).

Statement number	Wording	Number agreeing (%) 'strongly agree' or 'agree to some extent'
11	I knew that I could leave the trial at any time	38 (100)***
7	The doctor told me what I needed to know about the trial	38 (97)
8	I trusted the doctor treating me	38 (97)
9	I was given clear information to read about the trial	36 (97)**
15	I wanted to help with the research	38 (97)
4	I felt I had nothing to lose	35 (90)
1	I thought the trial was the best option available	33 (85)
3	I thought joining the trial would give me hope	33 (85)
17	I felt that others with my illness would benefit from the results of the trial	32 (82)
5	I thought the trial offered me some medical benefit	30 (77)
13	I thought the trial offered more intensive follow-up	25 (66)***
6	I was worried about the side-effects of the trial drug(s)	23 (59)
18	The doctor wanted me to join the trial	22 (56)
2	I thought the trial was the *only* option available	20 (51)
19	Others (e.g. family or friends) wanted me to join the trial	20 (51)
16	I was worried about being a 'guinea pig'	13 (33)
12	I did not feel able to say no/refuse	6 (16)***
14	I thought the trial needed too much effort from me	6 (16)***
10	I was not given enough information to read about the trial	5 (14)**

* One decliner did not complete a questionnaire.

** $n = 37$ for statements 9 and 10 due to missing data.

*** $n = 38$ for statements 11, 12, 13 and 14 due to missing data.

Table 6 – The main reason given for joining the trial ($n = 39^{*}$).

Statement number	Wording	Count of reason (%)
5	I thought the trial offered me some medical benefit	8 (21)
1	I thought the trial was the best option available	8 (21)
3	I thought joining the trial would give me hope	6 (15)
15	I wanted to help with the research	5 (13)
2	I thought the trial was the *only* option available	4 (10)
13	I thought the trial offered more intensive follow-up	3 (8)
16	I was worried about being a 'guinea pig'	2 (5)
17	I felt that others with my illness would benefit from the results of the trial	1 (2)
8	I trusted the doctor treating me	1 (2)
11	I knew that I could leave the trial at any time	1 (2)

* One decliner did not complete a questionnaire.

benefit and at least half felt the doctor, and others (family or friends) had wanted them to join the trial.

Table 6 shows the most important reasons given by patients for deciding to accept trial entry. Expectation that the trial offered some medical benefit and that it was the best option available were cited by 21% of patients, and that joining the trial gave hope by 15%. Only one patient said that wanting to help other patients was their primary reason for trial participation, although 13% stated wanting to help with research.

4. Discussion

The results show that most patients offered entry into a P1 trial accepted.

The primary motivations for enrolment were a belief that the trial offered some medical benefit, that it was the best option available, it maintained hope and patients wanted to help with research. Pressure from family and friends was less influential. Concerns about side-effects and burdens were less frequently endorsed, and helping other patients was only given as a primary reason by one patient. Our results therefore show a striking similarity to those reported in previous studies.[7–14]

The low ranking patients gave to altruism (explicitly that others might benefit rather than generally wanting to help with research) as a reason for entering P1 trials in our study is of interest and consistent with previous findings.[9–11,13] In contrast patients entering P3 randomised trials of cancer therapy have cited as their primary motivation: to benefit others in the future (23%), trust in the doctor (21%), and that the trial offered the best option (16%).[27]

It may seem illogical that patients with better chances of gaining personally from trial participation (P3) do so for more altruistic reasons compared to those patients (P1) for whom

therapeutic benefit is a less likely outcome. A number of explanations can be given for these apparent differences. Detailed analyses of the recordings we made of the actual doctor-patient consultations that took place about P1 trials revealed that fundamental components of communication and information sharing about P1 trial participation are often missing.[20] Important omissions included prognostic information and positive discussion about good palliative care. These gaps may lead patients to strongly believe a clinical trial is their 'only option' and encourage over optimism for 'hope of benefit'.

Another possible explanation for differences could be that when a person has better odds of survival and recovery they also have enough resource to think beyond their own situation and outcome and feel they have capacity to be selfless. Conversely, those eligible for a P1 cancer trial often have a much shorter life expectancy and may be driven to try anything they perceive as having even a small chance of personal benefit.

As apparent in our sample (see Table 2) many patients contemplating P1 trials will already have considerable experience of anti-cancer treatments, even with other trials. Moreover, they will report being well informed about the trial they may be about to embark on (see statements 7, 9 and 11 in Table 5) and also hold beliefs that medical benefit for themselves is possible, with 77% of our participants endorsing the statement 'I thought the trial offered me some medical benefit'. These findings concur with the conclusions of Nurgat and colleagues[28] that trialists still need to be aware and take account of the unrealistic expectations for personal benefit that patients may place on new drugs in P1 trials.

The optimism scores for the patients in our study are similar to those published on patients treated for head and neck cancer[29] ($n = 113$, mean 15.48, S.D. 5.351),[c] and also for a sex and age matched normative control group ($n = 114$, mean 14.18, S.D. 4.56). These levels of optimism reflect optimistic personality traits and suggest they held generalised favourable expectations for the future. Optimism is of interest because it has been shown to be associated with psychological well-being, an additional factor that we measured using the GHQ12. Our study reports an association between lower optimism and caseness for probable psychological morbidity which accords with earlier findings. A study by Cohen and colleagues[30] was the first to show that high levels of treatment-specific optimism (i.e. beliefs regarding the treatment working) were associated with better mental health outcomes both before and after participation in a P1 trial. Level of treatment-specific optimism correlated with baseline measures of depressive symptoms, mood disturbance, and symptoms of distress after controlling for age, number of metastases, and time since diagnosis. Importantly treatment-specific optimism was also associated negatively with symptoms of depression at the end of the P1 trial participation.

A recent review[31] discusses the roles optimism might be playing for patients in relation to their health and well-being. Although not referenced in the review, the Cohen study data[30] demonstrates that optimism can play an important part in maintaining psychological well-being in the context of P1 trial participation. Perhaps some people are simply just more cheerful so experience less distress when facing adversity. However, optimism may be related to a proactive, responsive, style of coping (engagement) which in turn is associated with lower distress and better outcomes, including possibly biological ones. Optimism has also been noted to be predictive of resilience against distress.[31] Authors of the review conclude that people who predispositionally hold positive expectations for the future respond to difficulty and adversity in more adaptive ways than those who hold negative expectations and that optimism can confer benefits.[23,31] From this we can understand that optimists will be attracted to engaging in activity that confronts their illness situation. For optimistic patients faced with advanced cancer, P1 trial participation could be viewed as a way of coping with their illness, which for them can have positive effects.

Discussions are challenging with patients who have a predisposition towards optimism and who seek personal medical benefit from P1 trial entry. A recent publication showed that P1 clinicians frequently omit to check understanding about prognosis and fail to discuss supportive care in a positive light.[20] Equally patients can misinterpret what is said especially if communication is ambiguous about likely benefit. Lack of clarity about trial aims leads to disturbing misinterpretations and hopeful elaborations from patients. Nevertheless patient-centred interventions have been shown to benefit patient understanding of P1 trials at both the informed consent stage[32] and at trial end.[33] Data from the study reported here and elsewhere[20] have contributed to the development of a comprehensive educational programme. This comprises facilitated discussions using DVDs with illustrative early-phase trial scenarios, didactic evidence-based presentations, and communication exercises. A paper showing the evaluation of the efficacy and acceptability of these materials will be published shortly and facilitators trained to deliver the programme.

Although larger than many previous publications, the relatively modest numbers in our study could be a limitation. Lack of patients declining entry made it impossible to explore differences between those accepting and declining trial entry. However, patients coming for P1 trial consultations may be a self-selected group as our data are an honest reflection of the types of patient coming forward for trial discussions. Furthermore, the five key UK centres involved in the study afforded a mix of trials and serve populations of widely varying socio-economic backgrounds which ensured a representative mix of patients.

In conclusion, a better understanding of why patients may or may not participate in P1 clinical trials is useful when developing educational materials aimed at ensuring communication achieves ethical and informed consent.

Conflict of interest statement

None declared.

[c] Llewellyn et al.[29] – to allow for comparison the data were kindly supplied by the authors for re-scoring using the 0–4 Likert scale as a 1–5 scale was used in publication.

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Appendix A. Accept and decline questionnaire

CONFIDENTIAL **ID:**

Accept or Decline Phase 1 Clinical Trial Questionnaire

We are interested in the reasons why patients **accept** or **decline** to take part in phase 1 clinical trials. We would be grateful if you would fill in this questionnaire at home **after you have made a decision**. It will not be shown to your doctor or any of the staff at the hospital. A pre-paid envelope is provided for the return of the form.

	Yes	No
First, we would like to know if you are taking part in the trial?	☐	☐

Below are some reasons that may have influenced your decision to **accept** or **decline** to take part in this clinical trial. Please answer each question and tick the box that shows most clearly how you feel.

	Strongly agree	Agree to some extent	Unsure	Disagree to some extent	Strongly disagree
1) I thought the trial was the best option available	☐	☐	☐	☐	☐
2) I thought the trial was the **only** option available	☐	☐	☐	☐	☐
3) I thought joining the trial would give me hope	☐	☐	☐	☐	☐
4) I felt I had nothing to lose	☐	☐	☐	☐	☐
5) I thought the trial offered me some medical benefit	☐	☐	☐	☐	☐
6) I was worried about the side effects of the trial drug/s	☐	☐	☐	☐	☐
7) The doctor told me what I needed to know about the trial	☐	☐	☐	☐	☐
8) I trusted the doctor treating me	☐	☐	☐	☐	☐
9) I was given clear information to read about the trial	☐	☐	☐	☐	☐
10) I was not given enough information to read about the trial	☐	☐	☐	☐	☐
11) I knew that I could leave the trial at any time	☐	☐	☐	☐	☐
12) I did not feel able to say no/refuse	☐	☐	☐	☐	☐
13) I thought the trial offered more intensive follow-up	☐	☐	☐	☐	☐
14) I thought the trial needed too much effort from me	☐	☐	☐	☐	☐
15) I wanted to help with the research	☐	☐	☐	☐	☐
16) I was worried about being a 'guinea pig'	☐	☐	☐	☐	☐
17) I felt that others with my illness would benefit from the results of the trial	☐	☐	☐	☐	☐
18) The doctor wanted me to join the trial	☐	☐	☐	☐	☐
19) Others (e.g. family or friends) wanted me to join the trial	☐	☐	☐	☐	☐

Which of the above was the most important reason for you out of the list? (Please give number) _ _____

Are there any other reasons for your decision? Please list them below:

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