



Systematic or Meta-analysis Studies



## Identifying patient values impacting the decision whether to participate in early phase clinical cancer trials: A systematic review

Liza G.G. van Lent<sup>a,\*</sup>, Lea J. Jabbarian<sup>b</sup>, Jelle van Gorp<sup>c</sup>, Jeroen Hasselaar<sup>d</sup>,  
Martijn P. Lolkema<sup>a</sup>, Julia C.M. van Weert<sup>e</sup>, Carin C.D. van der Rijt<sup>a,1</sup>, Maja J.A. de Jonge<sup>a,1</sup>

<sup>a</sup> Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands

<sup>b</sup> Department of Psychiatry, Erasmus MC, Rotterdam, the Netherlands

<sup>c</sup> Department of IQ Healthcare, Radboud University Medical Centre, Nijmegen, the Netherlands

<sup>d</sup> Department of Anaesthesiology, Pain & Palliative Medicine, Radboud University Medical Centre, Nijmegen, the Netherlands

<sup>e</sup> Department of Communication Science, Amsterdam School of Communication Research (ASCoR) and University of Amsterdam, Amsterdam, the Netherlands

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### ABSTRACT

**Background:** For many patients with advanced cancer, the decision whether to participate in early phase clinical trials or not is complex. The decision-making process requires an in-depth discussion of patient values. We therefore aimed to synthesize and describe patient values that may affect early phase clinical trial participation. **Methods:** We conducted a systematic search in seven electronic databases on patient values in relation to patients' decisions to participate in early phase clinical cancer trials.

**Results:** From 3072 retrieved articles, eleven quantitative and five qualitative studies fulfilled our inclusion criteria. We extracted ten patient values that can contribute to patients' decisions. Overall, patients who seek trial participation usually report hope, trust, quantity of life, altruism, perseverance, faith and/or risk tolerance as important values. Quality of life and humanity are main values of patients who refuse trial participation. Autonomy and social adherence can be reported by both trial seekers or refusers, dependent upon how they are manifested in a patient.

**Conclusions:** We identified patient values that frequently play a role in the decision-making process. In the setting of discussing early phase clinical trial participation with patients, healthcare professionals need to be aware of these values. This analysis supports the importance of individual exploration of values. Patients that become aware of their values, e.g. by means of interventions focused on clarifying their values, could feel more empowered to choose. Subsequently, healthcare professionals could improve their support in a patients' decision-making process and reduce the chance of decisional conflict.

### Introduction

In order to develop new, efficacious therapies against cancer, it is necessary to conduct early phase clinical trials: the first step in testing new compounds in humans. These trials are generally conducted in patients with advanced cancer for whom standard treatment is not or no longer an option. The main goal of early phase clinical trials in oncology is to learn as much as possible about the safety, tolerability and mode of action of a new treatment. The focus of these trials is not yet the efficacy of the novel agent. Therefore, they often carry a risk of minor to major side-effects and offer an uncertain chance of clinical benefit. Moreover,

the administration of the new drugs is monitored closely with additional hospital visits, hospitalizations, biopsies, scans and/or blood samples. These procedures make the trial participation more intense compared to most standard therapies or later stage trials. Overall, researchers, together with their patients, have to find a balance between the need for compliance to these procedures and the avoidance of patient duress [1]. An important dimension of this delicately balanced relationship is patients' understanding of the potential risks and obligations in the context of uncertain benefit before deciding whether they actually want to participate in such a trial.

Previous reviews suggest that the decision-making process for

\* Corresponding author.

E-mail address: [l.vanlent@erasmusmc.nl](mailto:l.vanlent@erasmusmc.nl) (L.G.G. van Lent).

<sup>1</sup> Both authors contributed equally.

potential trial candidates calls for the discussion not only of medical-technical information about risks and obligations, but also of patient values and preferences [2,3]. These matters are even more important as decisions regarding early phase clinical trials have to be taken in the absence of evidence regarding their efficacy. A clear discussion of values can help ensure that a treatment plan is attuned to the individual patient's needs and wishes, and consequently better follows a shared decision-making process [4] that builds upon established principles for healthcare ethics [5]. Furthermore, if participating in an early phase clinical trial fits patients' values, they may be better motivated to comply to the specific obligations of a trial. Although previous systematic reviews have examined patients' perception, comprehension and understanding of early phase clinical trials [6,7] and general barriers to participate in clinical trials [8], a systematic overview of relevant patient values in this context does – to the best of our knowledge – not yet exist. Such an overview could help healthcare professionals to anticipate patient values in the consultation and thereby support patients in expressing values in light of their decision-making process. This review thus aims to synthesize and describe which patient values play a role in the decision-making process for early phase clinical trials. We also aim to indicate how these factors relate to the decision to participate or not in early phase clinical trials.

## Methods

### Registration of the review

This systematic review was registered online in the PROSPERO database [9], registration number: CRD42020170066.

### Design

We conducted a systematic review of published quantitative, qualitative and mixed-method studies. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10] were used to report and present the information obtained from the different phases of the review.

### Inclusion criteria

Box 1 shows the inclusion criteria. Articles must be original, empirical studies, written in English and concerning adults. We included studies that addressed patient values in the decision-making process for early phase clinical cancer trials. Early phase clinical trials were here considered as phase I or combined phase I/II clinical trials.

### Data collection

A biomedical information specialist of the Erasmus MC Medical Library helped to formulate and conduct a systematic search strategy. The electronic search was performed on December 20, 2019 and updated on December 18, 2020 in the following databases: Embase, Medline (Ovid),

Cochrane, Web of Science, PsycInfo (Ovid), Cinahl (Ebsco) and Google Scholar. Supplementary table 1 provides the search terms per database.

### Study selection

After removing duplicates, two independent reviewers (LL and LJ) used the inclusion criteria in Box 1 to firstly screen titles and abstracts and secondly full-text articles for eligibility. Disagreements were resolved by discussion, if necessary in consultation with other authors (JW, MJ and CR).

### Quality appraisal

The reviewers (LL and LJ) independently appraised the quality of included studies using the QualSyst tool [11]. QualSyst consists of a 14-item checklist for quantitative and a 10-item checklist for qualitative studies (see Supplementary tables 2 and 3), developed to critically appraise the quality of a broad range of study designs. This approach aligns well with the diversity in methods that are included in this review. Each criterion in the checklist was assigned a score of 0 (not met), 1 (partially met) or 2 (sufficiently met). For quantitative studies, N/A was assigned if a criterion was not applicable. Mixed-method studies were appraised by assessing both checklists. Summary scores, reported as percentages, were calculated using the total potential score, minus the number of N/A \* 2. If the QualSyst score was 80% or higher, it was interpreted as strong quality, 60–79% as good quality, 50–59% as adequate quality, and 50% or lower as poor quality. We performed a sensitivity analysis with the strong-quality papers.

### Data extraction and thematic synthesis

A data extraction form was developed to systematically extract data on the study characteristics (e.g. design and population) and results regarding values from the included articles. Derived from previous literature [12,13], values in this review were interpreted as desires, goals or beliefs that people can find important in this context of a life-limiting disease. We applied thematic synthesis [14], a tested method that can be used to translate concepts. Because our aim was to describe patient values in the decision-making process, performing a thematic synthesis enabled us to integrate all findings of studies with qualitative, quantitative and mixed-method designs. First, the reviewers (LL and LJ) meticulously read the articles and filled out the data extraction form. They extracted the data independently, compared their extractions and, if needed, resolved disagreements by discussion. Afterwards, they thematically categorized the extracted data into a list of values based on similarity in meaning. If the included articles did not explicitly name a certain value, the reviewers assigned these themselves after discussion. Oxford Learner's Dictionaries [15] were consulted for existing definitions of the (assigned) values, which were adjusted and/or complemented for the current setting if necessary. All authors critically reviewed the categorizations and descriptions.

#### Box 1

##### Inclusion criteria.

1. Articles must include original empirical studies (i.e. no conference abstracts, reviews).
2. Articles must address:
  - a. patient values;
  - b. regarding (participation in) early-phase (i.e. phase I or phase I/II) clinical cancer trials;
  - c. during the preceding decision-making process (i.e. before actual participation).
3. Articles published in English.
4. Articles concerning adults ( $\geq 18$  years).

## Results

### Study selection

The systematic search identified 3072 articles (Fig. 1). After removing duplicates, 2025 articles were screened on their title and abstract of which 1974 were excluded. Of the 51 articles assessed for eligibility by reading the full text, 16 articles were included in the final analysis. The main reasons for exclusion were not being an original, empirical study (n = 16) and not describing patient values (n = 8).

### Study characteristics

Table 1 shows that eleven quantitative [16–26], five qualitative [27–31], and no mixed-method studies were included. Most studies were conducted in the USA (n = 12) [16,17,19–21,23,24,26,27,29–31], two in the UK [18,22], one in the Netherlands [25] and one in Japan [28]. Seven studies were conducted between 2000 and 2009 [16,17,20,22,23,26,31], and nine from 2010 onwards [18,19,21,24,25,27–30]. Eleven studies focused only on phase I clinical trials [16,18–21,23,25–29], four studies on phase I/II clinical trials [17,22,30,31] and one study on phase I, II and III clinical trials [24]. For the latter, we only included the results for phase I and II clinical trials.

In terms of population, one study focused specifically on elderly patients with advanced cancer [17], one on patients with pancreatic ductal adenocarcinoma [19], one on patients with advanced breast cancer [29], and one on patients referred for one specific phase I clinical trial [23]. The remaining 12 studies focused on eligible patients with advanced cancer for trial participation in general. Two studies also included oncologists or caregivers [21,27]. With regards to the timing in patients' decision-making process, 10 studies were conducted on patients after they showed interest or decided to participate in a trial, but before (or very shortly) after trial initiation [16,20,22–24,26,28–31]. Three studies were conducted during the period of deliberation, including both acceptors and decliners of early phase clinical trials [18,21,27]. One study concerned potential barriers for eligible seniors (65 + years) to hypothetical participation [17] and two were conducted retrospectively on electronic patient records of both acceptors and

decliners [19,25].

Based on the QualSyst tool (Table 1), two quantitative [20,25] and three qualitative studies [27,29,31] had a good quality, and nine quantitative [16–19,21–24,26] and two qualitative studies [28,30] had a strong quality. Because all included articles were of sufficient quality, we do not indicate their quality in the following paragraphs. Supplementary tables 2 and 3 contain the complete assessment per criterion for the quantitative and qualitative studies.

### Patient values

After scrutinizing the articles for expressions regarding patient values, ten values resulted from categorization based on similarity in meaning. Table 2 provides the complete list of extracted values, with the definitions we used in this review and examples from the articles. In the following paragraphs, we consecutively describe all values.

### Hope [16–18,22–28,30,31]

The value that occurred most often in the included articles was hope for therapeutic benefit. If hope was an important value for patients, this was generally associated with trial acceptance. In four quantitative studies, between 89 and 99% of the patients considered hope a ('very important') supporting factor to participate in a trial, and hope was the main reason for accepting participation in 15–76% of the patients [18,22–24]. Four studies showed that a majority of the patients from the USA and UK, who all recently decided to participate, believed that participating would give them hope (56–99%) [16,18,22,23]. Hope appeared related to higher expectations of (therapeutic) benefit [26]. The possibility of benefit was hypothetically important to almost all senior participants (99%) in another study [17]. Vice versa, a retrospective Dutch study showed that lower expectations of benefit were a reason for trial refusal [25]. Qualitative studies show similar results. In two US studies, patients who had at least shown interest in participation used positive attitudes as justifications for high expectations of benefit [30,31]; and hope for benefit appeared a reason for patients' interest in trial participation in another study [27]. As a Japanese study stated: "Acceptors ultimately lived with the hope of therapeutic benefit, and

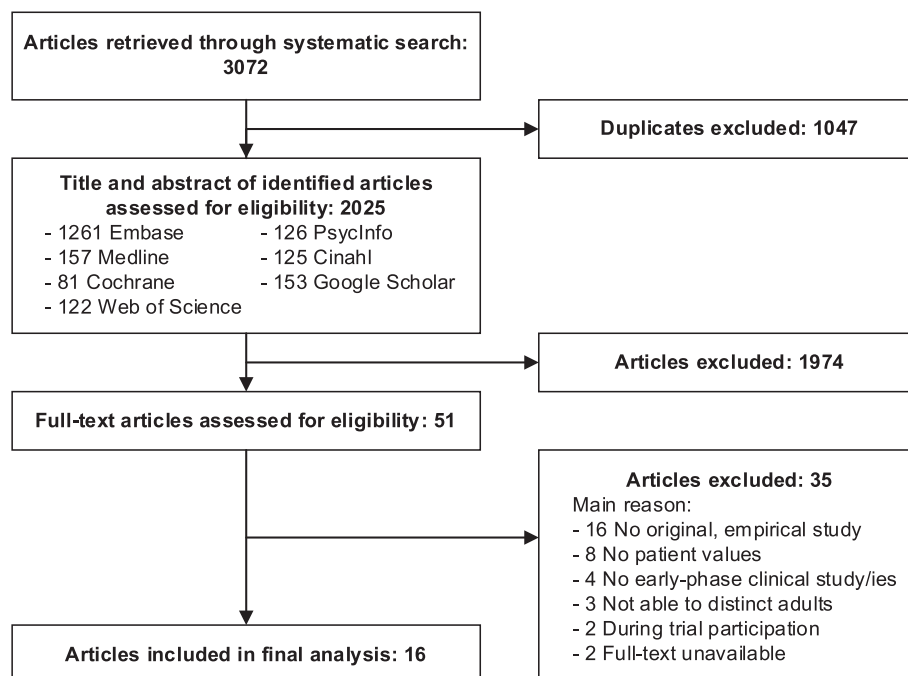


Fig. 1. PRISMA flowchart regarding the process of article inclusion.

**Table 1**  
Study characteristics.

| Ist author (year)                | Study design   | Country         | Target groups                           | Trial phase     | Timing in decision-making process   | Sample size (response rate)   | Quality assurance* |
|----------------------------------|--|-----------------|---|-----------------|---|---|--------------------|
| <b>Quantitative study design</b> |  |                 |   |                 |   |   |                    |
| Agrawal (2006) [16]              | In-person survey   | USA             | ACPs                                    | I               | After deciding to participate, before start of trial                                | 163 patients (ns)   | 82%                |
| Basche (2008) [17]               | In-person survey   | USA             | Elderly ACPs                            | I and II        | Hypothetical - potential barriers to participation                                  | 300 patients (ns)<br>- 154 younger seniors, 65–74<br>- 146 older seniors, 75+ | 86%                |
| Catt (2011) [18]                 | Questionnaire  | UK              | ACPs                                    | I               | After deciding to participate, before start of trial (both acceptors and decliners) | 40 patients (64.5%)   | 89%                |
| Galvin (2020) [19]               | Retrospective chart review   | USA             | ACPs (pancreatic ductal adenocarcinoma) | I               | Before final decision (both acceptors and decliners)                                | 54 patients (N/A)<br>- 28 enrolled in phase I<br>- 26 did not enrol           | 82%                |
| Gordon (2001) [20]               | Encoding answers from semi-structured interviews                         | USA             | ACPs                                    | I               | After deciding to participate, start of trial unclear                               | 144 patients (75%)<br>- 105 referred patients<br>- 39 in-house patients       | 72%                |
| Hlubocky (2018) [21]             | Encoding audio recordings and quantitative analysis of interview answers | USA             | ACPs and oncologists                    | I               | Before final decision (both acceptors and decliners)                                | 100 patients (ns)29 oncologists (ns)  | 80%                |
| Nurgat (2005) [22]               | Questionnaire  | UK              | ACPs                                    | I and II        | After deciding to participate, before start of trial                                | 38 patients (97%)   | 85%                |
| Pentz (2002) [23]                | Questionnaire and media analysis   | USA             | ACPs (referred for one specific trial)  | I               | Before (n = 79) and after (n = 21) informed consent discussion                      | 100 patients (77%)  | 81%                |
| Truong (2011) [24]               | Cross-sectional survey   | USA             | ACPs and parents of paediatric ACPs     | I, II and III** | After deciding to participate, within 3–14 days – start of trial unclear            | 205 patients (71%)<br>- Of whom 50 in phase I<br>48 parents (74%)             | 86%                |
| Van der Biessen (2013) [25]      | Analysis of electronic patient charts                                    | The Netherlands | ACPs                                    | I               | Retrospective - referral source to final decision (both acceptors and decliners)    | 365 patients (N/A)  | 68%                |
| Weinfurt (2003) [26]             | Questionnaire  | USA             | ACPs                                    | I               | After deciding to participate, before start of trial                                | 260 patients (44%)  | 94%                |
| <b>Qualitative study design</b>  |  |                 |   |                 |   |   |                    |
| Garrett (2019) [27]              | Ethnography (observations, interviews and surveys)                       | USA             | ACPs, caregivers and oncologists        | I               | Before final decision, period of deliberation (both acceptors and decliners)        | 96 patients (ns)unknown number of caregivers and clinicians                   | 75%                |
| Kohara (2010) [28]               | Semi-structured interviews and unstructured observations                 | Japan           | ACPs                                    | I               | After deciding to participate, before start of trial                                | 25 patients (81%)<br>- Observations were only possible in 6 patients          | 80%                |
| Reeder-Hayes (2017) [29]         | Semi-structured interviews   | USA             | ACPs (breast cancer)                    | I               | After deciding to participate; on the first day of the trial                        | 18 patients (72%)   | 70%                |
| Sulmasy (2010) [30]              | Semi-structured interviews   | USA             | ACPs                                    | I and II        | After deciding to participate, before start of trial                                | 45 patients (ns)  | 80%                |
| Weinfurt (2008) [31]             | Semi-structured interviews and cognitive interviewing methodology        | USA             | ACPs                                    | I and II        | After deciding to participate, before start of trial                                | 45 patients (63%)   | 60%                |

Abbreviations: ACP = advanced cancer patient; ns = not specified

\* <50%=poor quality; 50–59%=adequate quality; 60–79%=good quality; ≥80%=strong quality

\*\* For this review, only the results for phase I and II clinical trials were included

decliners challenged to live to the end without anticancer treatments” [28].

### Trust in the healthcare system or healthcare professional [17,18,20,22–24,28–31]

Although it was hardly ever (2–17%) the main reason for participation according to two studies [18,24], trust was a ‘very important’ supporting factor to participate for patients who were studied in the USA and UK. More specifically, trust in or endorsement by the oncologist contributed to the decision in 66–100% of the patients in five studies [17,20,22–24]. Trust in the nurses (76–93%) [17,22] and trust in the hospital (63–85%) [20,24] were also considered (very) important by most patients. Two qualitative studies showed that (breast cancer) patients considered their oncologist’s recommendation as a reason for their decision to participate [29], sometimes even if their past experiences with anticancer treatments were negative [28]. Patients who decided to participate also used their trust in their healthcare professionals or in medicine as justifications for expected benefit in two

other US studies [30,31].

### Quality or quantity of life [18,22,25,26,28]

In a quantitative and a qualitative study it was stated that trial decliners wanted to make the most of whatever time they have left [18,28]. On the one hand, according to a quantitative study from the Netherlands, both a declining clinical condition and a currently excellent or stable condition were reasons to refuse trial participation [25]. On the other hand, trial acceptors seem to have more ambiguous values as 71% of the patients in an English study agreed that ‘surviving for as long time as possible is the most important thing’, although 60% strongly agreed that they ‘would rather maintain a better QOL for a shorter term than suffer somewhat for longer’ [22]. Only a small correlation coefficient was found for the trade-off between quality and quantity of life with regards to expected benefits from participation in a US study [26]. A Japanese qualitative study elucidated that eventually, “Acceptors recognized that participating in the trial was a chance to live as long as possible” [28].

**Table 2**  
Overview, definitions and examples of the values extracted from the included articles.

| Values*   | Definition in this review  | Examples from included articles  |
|---|--|--|
| Hope (+)  | The desire, belief or feeling that participating in an early phase clinical cancer trial will lead to personal benefit (such as tumour shrinkage or prolongation of life). Hope and optimism are often used as synonyms. [16–18,22–28,30,31]                     | “The possibility of benefit from treatment was important to almost all respondents.” [17]<br>“Some patients say that ‘being positive is the only way to be’, or that ‘being positive improves outcomes’.” [31]   |
| Trust in the healthcare system or healthcare professional (+) | The belief that a healthcare professional or institution (including his/her judgement and endorsement) is good, sincere, and/or honest and that he/she would not willingly trick or harm someone. [17,18,20,22–24,28–31]   | “Trust in the referring physician was a major influencing factor to enter phase I trials for 80% of referred and 95% of in-house patients.” [20]<br>“Most respondents identified the recommendation of their primary oncologist as a reason they participated.” [29]   |
| Quality (–) or quantity (+) of life                           | The preferences someone has regarding the balance and potential trade-off between living as long as possible and maintaining quality of life. [18,22,25,26,28]   | “Both a declining clinical condition and a currently excellent condition were mentioned by individual patients as reasons not to participate.” [25]<br>“Acceptors recognized that participating in the trial was a chance to live as long as possible” [28]<br>“82% strongly agreed or agreed to some extent to the statement “I felt that others with my illness would benefit from the results of the trial.” [18]<br>“(…) One patient explained, “so I’m hoping that the trials turn out better than the already approved procedures. And other people will benefit from what I do.” [27] |
| Altruism (+)  | The desire or willingness to accept or decline participation in an early phase clinical cancer trial motivated by the care for others (including wanting to help research/medicine), even though it does not necessarily lead to personal benefit. [18,23,24,30] | “The decision-making process (..) was influenced by (...) patients’ perceptions of their families’ attitudes toward the trial.” [28]   |
| Social adherence (+/–)  | The desire or willingness to behave according to the expectations, values or attitudes of others (especially family) regarding participation in an early phase clinical cancer trial. [16,23,28–30]  | On the control preferences scale, ranging from 1=“I prefer to make the final selection about which treatment I will receive”, to 5=“I prefer to leave all decisions regarding my treatment to my doctor”, patients on average scored a 1.72. [26]  |
| Autonomy (+/–)  | The desire or ability to act and make decisions without being controlled by and/or dependent on others in the context of a life-limiting disease. [16,17,26]   | “The majority of respondents viewed their religious or spiritual beliefs as important: 64% (63 of 98) very important and 21% (21 of 98) moderately important.” [23]  |
| Faith (+)   | The strong belief in religion or spirituality. [23,26,30,31]   |  |
| Perseverance (+)  |  |  |

**Table 2 (continued)**

| Values*            | Definition in this review  | Examples from included articles   |
|--------------------|--|---|
|                    | The desire to keep fighting/ battling (or to keep living), despite having little treatment options or a bad prognosis. [16,17,23,30] | “Our respondents’ clear communication that research offers hope substantiates a general perception that the elusive chance of cure and the opportunity to keep fighting draw patients to seek investigational approaches to treat their diseases, even among patients who correctly understand the low probability of personal benefit from a phase I trial.” [23]<br>“Even should the prognosis be grim, many viewed their expressions of high expected therapeutic benefit as signs they were not quitters, would always continue battle, would never “lose hope.” [30] |
| Risk tolerance (+) | The willingness or ability someone has to accept risks or take gambles. [18,25,26,28]  | “I can abandon living. But it is also a terrible experience if I abandon living. So I take a gamble of having the possibility of living because I will suffer whether I am living or abandoning living.” [28]   |
| Humanity (–)       | The desire to be, feel, or be treated as a person rather than a god, an animal or a machine. [18,29]                                 | “A third of the patients were ‘worried about being a guinea pig’.” [18]   |

\*General direction: + = motivating for trial acceptance; +/- = motivating for trial acceptance or refusal; – = motivating for trial refusal

**Altruism [18,23,24,30]**

Quantitative studies from the USA and UK show that between 82 and 93% of the patients in three studies considered altruistic motivations such as helping future patients to be supporting [18,23] and 30% as ‘very important’ [24] in their decision to participate, but only for 2–16% of the patients altruism was the main motivating factor [18,23]. This aligns well with a qualitative study, according to which patients who decided to participate often spontaneously expressed altruistic motivations when they were asked about their beliefs regarding a trial [30]. However, it was rarely patients’ primary reason for accepting trial participation.

**Social adherence [16,23,28–30]**

For some patients it can be important to make a decision in line with the expectations, values or attitudes of others. In two quantitative studies from the USA [16,23], patients generally did not feel pressured to participate by their families (80–86%). Instead, they felt supported by their family for joining a trial (71%) [23]. Nevertheless, two qualitative studies implied that social support or patients’ perceptions of their families’ attitude influenced the decision to participate in a trial [28,29]. More specifically, no patients accepted or declined participation against their families’ will in a Japanese study [28]. Some patients in a US study tried to behave as ‘model patients’ in adhering to social behavioural expectations, or even reported a sense of duty to reassure their loved ones with expressing positive expectations [30].

**Autonomy** [16,17,26]

The desire or ability to act and make decisions independently can support both the acceptance and refusal of trial participation. The impact of a treatment on patients' own functioning was considered an important factor in assessing a trial's acceptability in a (hypothetical) quantitative study [17]. According to a US study, if a trial impaired their ability to think (and thus their ability to act independently), 24% of patients who recently signed consent would not participate in it [16]. On the other hand, 44% of the patients reported that participating in a trial would give them a sense of control [16] (and thus strengthen their sense of autonomy). A US study, which controlled for patients' preferences with regards to shared decision-making, showed that patients in general preferred to make the final decision for trial participation themselves, or with little involvement of their doctor [26].

**Faith** [23,26,30,31]

Most patients (85%) in a quantitative study from the USA saw their own religious or spiritual beliefs as moderately or very important for their decision [23]. Furthermore, patients with higher levels of faith or patients who considered faith 'very important', estimated their chance of benefit higher [26] and specified personal benefit more often as their main reason for trial participation [23]. Two qualitative studies confirmed that faith was indeed used as a justification for expectations of benefit by patients who decided to participate in a trial, although their results differed [30,31]. One study stated that it was not often mentioned as potential justification [31], whereas the other found it one of the main justifications for expected benefit [30]. The latter however also included faith in medicine and science, which was mentioned more often than religious faith. The role of (religious/spiritual) faith thus appears to be limited to a supporting factor for participation.

**Perseverance** [16,17,23,30]

A US qualitative and a quantitative study illustrated that trial participation offered patients the opportunity to keep fighting against their cancer [23,30]. Even among patients who correctly understood the low chance of benefit, this could be a reason that patients decide to participate [23]. Additionally, entering a trial as part of a 'battle with cancer' was one of the main reasons for expected benefit [30]. Another US study showed that the majority of patients who decided to participate (91%) would still not be persuaded to refuse trial participation if there was a 10% chance of death by the experimental drug [16]. One of the studies showed that older seniors were less willing to accept moderate to severe toxicity than younger seniors [17].

**Risk tolerance** [18,25,26,28]

A quantitative study from the USA showed that monetary risk-seeking preferences – in other words, patients who considered (monetary) certainty to be less important – were correlated with higher expectations of benefit [26]. In a Japanese study, patients realized that their decision would have to be made under uncertainty and that they would take a gamble by participating in a trial [28]. In a quantitative study from the UK, patients worried (strongly) about side effects [18]. According to a Dutch study, these concerns were a reason to refuse trial participation [25]. Likewise, in a US study, fear of adverse effects was a reason for patients who met all eligibility criteria to refuse trial participation (8%) [19]. On the other hand, in a study from the UK, 'better standard of care and closer follow-up' was a supporting factor for 61% of the patients who decided to participate in a trial, and 'closer monitoring of patients in trials' for 58% [22]. This is in line with the finding from another US study that 78% of the patients received (moderate to a lot of) comfort from having regular diagnostic tests and physician visits, and 74% felt (somewhat or very) anxious if they were not receiving some

sort of anticancer treatment [16].

**Humanity** [18,29]

In a quantitative study from the UK, 33% of the patients worried (strongly) about 'being a guinea pig' [18]. Additionally, a few of the respondents in a qualitative study (n = 2) who had recently decided to participate in a trial, still mentioned a general dislike for the idea of 'feeling like a guinea pig' [29].

**Sensitivity analysis**

When the analysis was repeated with only the strong-quality papers, the same values as mentioned above were found.

**Discussion**

Our aim was to synthesize and describe which patient values play a role in the decision-making process for early phase clinical trials and to indicate how these factors may be related to the decision to participate or not. By identifying ten patient values that are relevant to patients with advanced cancer facing the decision whether to participate in an early phase clinical trial or not, we may enable caregivers to be more sensitive to patients' values and to support shared decision-making that is in accordance with these values. This review shows that patient values indeed contribute to patients' decisions. Overall, patients who seek trial participation usually report a combination of hope, trust, quantity of life, altruism, perseverance, faith, and/or risk tolerance as their (most) important values. Patients who refuse trial participation mainly reported the values quality of life and/or humanity. Other values, such as social adherence and autonomy, can be reported by both trial seekers and/or refusers, dependent upon how these values are manifested in a patient.

It is important to realize that these values do not carry the same weight for all patients, and sometimes have different meanings. Therefore, it remains essential to assess, interpret and weigh all values in the context of each individual patient and to be aware of the role that other stakeholders can play in the decision-making process. For example, patient values could partially depend upon country or culture: following families' wishes may be more important or decisive in countries with collectivist cultures, such as Japan [28], compared to countries where individual values are more central. Moreover, even if two patients consider the same value important, that does not necessarily lead to the same decision. For instance with regards to autonomy, if a treatment would negatively impact patients' own cognitive functioning, this could decrease the preference for participation in a respective trial [16,17], but participating in a trial could also give patients a sense of control [16]. Additionally, some values may be interconnected. For instance, similar needs or assumptions may underlie faith (in a religion) and trust (in healthcare); and some patients who consider perseverance important may also not want to give up hope and value their quantity of life. Vice versa, some patients may struggle while weighing several values, for instance between making an autonomous decision and incorporating their family's wishes or doctor's endorsement, or between trusting their healthcare professional and not wanting to 'feel like a guinea pig' (humanity).

A major part of patients' considerations revolves around quality and quantity of life. Although some of the included studies presented these as two sides of a scale or trade-off [22,26], we would like to argue that this is in fact a debatable point of view. Quality and quantity of life are not as mutually exclusive as it may seem. This is supported by the finding that some trial acceptors mainly valued quantity of life, but simultaneously preferred to live for a shorter term with better quality of life [22]. How quality and quantity of life are being approached and interpreted, seems to differ between individual patients. Especially quality of life has different meanings for various patients. It can be argued that for patients

who value quantity of life, this actually represents their personal quality of life. If a decision is in line with what patients value (most), this can add to their quality of life, even if their main value is quantity of life. Part of the dilemma behind this decision is that, usually, there is no clear 'right' or 'wrong'; not only regarding the available options and participating in early phase clinical trials or not, but also regarding patient values.

### Limitations

The finding that some of the values were extracted more often than others does not necessarily mean that these also play a more important role in the decision-making process – possibly, they could be the only values that have received attention thus far. For instance, because nearly all included studies were conducted in Western countries, mostly the USA, the extracted values and their relation with trial acceptance or refusal may be prone towards countries with similar cultures, while relevant values or interpretations for countries with other, especially non-Western, cultures could still be missing from our overview. Furthermore, a certain (manually extracted) matter was often not explicitly indicated as being a patient value in the included studies. Most studies asked patients to what extent a certain pre-defined reason was motivating or decisive in their considerations. This makes it difficult to interpret the intrinsic value for patients behind statements such as 'feeling like a guinea pig'. Studies rarely asked patients openly about their values or their general motives in the decision-making process. Additionally, only a few studies included patients who eventually refused trial participation, and most studies were conducted after patients had decided to participate in a trial. Following the theory of cognitive dissonance [32], people eventually may discard the arguments against their decision. It thus remains unclear whether other relevant values in the decision-making process, especially those associated with patients who decide to refuse trial participation, have been sufficiently explored or whether they are simply less relevant in this context.

With regards to phase I clinical trials, the success rate in terms of tumour response has improved over the years [33], especially as a result of the development of targeted therapy and the selection of patients based on molecular and genomic tumour analyses. This development makes it difficult to compare trials between different time frames. Furthermore, changing success rates may affect patients' decisions regarding participation in early phase clinical trials. A previous study showed that patients who thought they would live for at least 6 months were more likely to favour life-extending treatment compared to those who estimated this chance lower [34]. In this review, expectations of benefit were mentioned in association with several important values for trial seekers (hope [26,30,31], trust [30,31], faith [30,31], perseverance [30] and risk tolerance [26]). Although patient values indeed seemed important in the decision-making process for early phase clinical trials, their exact roles remain to be determined. Other factors, such as practical or logistical considerations, could also play a role in this process. The endpoint in the reviewed studies was trial participation, but that is a medical approach. The patient-centred approach would be to (prospectively) look at a variety of relevant endpoints, such as decisional conflict, decisional regret or patient duress. These areas offer a number of opportunities for future research, in particular to investigate more openly which (other) values play a role in this context and how they relate to other endpoints or factors.

### Practical implications

In the context of early phase clinical trials, some kind of shared decision-making process is very important since there is no clear 'right' or 'wrong' option. Especially because their endorsement or recommendation can be decisive [18,24], healthcare professionals should be (made) aware of their responsibility in this process. Compared to standard treatment decisions, supporting the decision-making process is

more difficult. A shared decision is often based on the best available clinical evidence, healthcare professional's experiences and patients' preferences [35]. With regards to the first two, caregivers can only inform patients that these are not available yet in the context of early phase clinical trials. We still believe it to be a shared decision-making process, because it is a reciprocal process of informing, exploring what is important for patients, and using these combined insights to weigh all available options with each patient. Most patients seem to want to make the final decision themselves or with little involvement of their healthcare professional [26]. However, we believe that it is the responsibility of the healthcare professional to make the patient (more) aware of his values, thereby supporting patient's decision-making.

Given that different values prevail in each patient, we recommend healthcare professionals to consider an (open) assessment to support every patient's decision. Asking open questions to explore patient values, for instance about what patients still want to do or achieve or what their wishes are in the last phase of their lives, could provide more clarity into the individual patient's wishes and thereby enable a more patient-centred approach towards discussing trial participation and refusal. Since not all patients might be equally aware of their values, this approach may also support patients in composing/explicating their set of relevant values for this decision. Moreover, preparatory interventions specifically aimed at the clarification of patient values could empower patients to discuss these matters more openly as well. The main goal however should never be to 'check boxes' by discussing all possible values with all patients, nor to steer patients towards a certain decision by only focusing on values that fit that decision. We propose to have a discussion about which values are relevant for the individual patient and thus for the decision to participate in an early phase clinical trial or not. This may ultimately improve the decision-making process (resulting in e.g. less decisional conflict, decisional regret, or patient duress) every patient has to go through.

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### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctrv.2021.102217>.

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