

Factors influencing patients' decisions regarding participation in clinical trials: Review of current literature

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Abstract

Obtaining timely data in clinical trials (CTs) is critical for drug registration. This depends directly on the speed at which patients are recruited. This paper provides an overview of selected scientific works and literature from different countries about patients' motivators and barriers to participating in CTs. From 55 articles retrieved from PubMed, 5 were selected for the analysis. Additionally, 6 publications, including 2 by Polish authors, were reviewed. As a result, we identified 10 factors for further investigation: altruism, hope for personal benefit, access to better care, the role of a doctor, the opinions of close friends or relatives, financial compensation, side effects, the patient's role as a guinea pig, effort and time, and the use of placebo. Regardless of the therapeutic area, health status, study phase, country, geographic area, economic situation, or healthcare system, patients indicated very similar reasons when deciding to participate in a CT. Even if patients as a group had similar motives and concerns, there are individual elements or unusual factors that need to be better understood and evaluated to accelerate the recruitment process in order to avoid certain drugs or therapies being overlooked or underestimated. In this way, investigators can help patients make the best decisions and more effectively support the process of registering a new drug. Future research on factors influencing patients' decisions is still necessary: We do not know how the COVID-19 pandemic may have influenced patient motivation, how new regulations on CTs are changing patients' perceptions of CTs, and what may be important depending on the study, country, therapeutic area and other factors.

Key words: cancer, patient, clinical trial, motivation, altruism

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Background

The critical aspect of every clinical trial (CT) is the recruitment of a planned number of participants. The speed and efficiency of recruitment often determine the success of a study. Understanding the volunteers' motivations for participating in a study has been the subject of numerous investigations and analyses over the years. The diversity of CTs due to different phases, therapeutic areas, criteria, and types, such as platform or basket trials, is not the only complication. There are also cultural, social and ethical differences, as well as the changing awareness and knowledge of societies in different regions of the world over time.^{1,2} Particularly notable is the change in the perception of the significance of CTs in the last 3–5 years, primarily due to the COVID-19 pandemic³ and the rapid progress in developing modern drugs and therapies used in cancer and rare diseases treatment as well as other diseases. In many therapeutic areas like oncology or rare diseases, patient needs are still inadequately met. In 2019, according to data from the report of the National Cancer Registry, over 176,000 new cancer cases and more than 100,000 deaths related to cancer were recorded in Poland, making malignant neoplasms the 2nd leading cause of death in the country (25.7% of male deaths and 23.2% of female deaths in 2019).^{4,5} The issue of potential participants' consent to participate in a study or to decline is of utmost importance from social, economic and healthcare perspectives and directly impacts the wellbeing of each individual.

According to the current state of knowledge, the factors positively influencing patients' decisions regarding participation in CTs include altruism, hope for improvement in health and better medical care related to participation in the study. In turn, the elements that evoke fears and negative reactions include the risks related to the safety of treatment with a new investigational product, requirements regarding the patient's time and effort, and the possibility of being treated as a guinea pig. The studies also paid attention to other factors affecting patients in different ways, such as trust in the doctor, the opinion of relatives and financial compensation. The review of selected works shows that the process of providing information to patients does not raise serious objections and that doctors and patients are appropriately informed, regardless of the country or therapeutic area. In some papers, there are less typical observations depending on the specificity of the examination or the disease. This article provides an overview of selected scientific works and literature from different countries about consent to participate in CTs and related barriers.

Objectives

The aim was to select universal factors influencing patients' decisions and identify variables that may modify them. Finally, it was assumed that a possible way to achieve

this goal would be a selection of publications from different geographic areas, concerning very different therapeutic areas and different types of CTs, including CT phases from 1 to 3. This publication may contribute to the design of further scientific research aimed at better understanding the issues of participation in CTs and lead to the development of tools and methods to enhance recruitment effectiveness in CTs.

Materials and methods

Between May and July 2023, the PubMed database was queried using the following search terms: “patient*” [ti] AND “clinical trial*” [ti] AND (“motivation” OR “determinant*” OR “element*”) AND “decision*”. We excluded articles of the “Review” or “Systematic review” type, and as a result, 550 publications from 1990–2023 were obtained. After the initial elimination of papers whose titles indicated analyses in areas other than those of interest to the authors, the abstracts of 16 publications were reviewed, of which 5 publications were included in the analysis.^{6–10} The main reasons for excluding articles from this review were: analysis of matter not aligned with the primary objective of our publication; specifically focused, tailored or bespoke studies; very specific or narrow patient population represented; and mismatched aspects regarding consent for study participation. In addition, based on reviews of other publications and reports, including references in the previously mentioned articles, another 4 publications were selected.^{11–14} Due to the special interest in the observations resulting from the Polish works, 2 publications in Polish have been added.^{15,16} Works published before 2006 were excluded from the analysis. Finally, 11 papers were selected for analysis and are presented and characterized in Table 1.

Results

The authors of the selected publications used various methods and techniques for collecting and analyzing information from respondents, e.g., multiple choice questionnaires, closed questions or free text, semi-structured interviews done by trained investigators, self-administered questionnaires, semi-structured telephone interviews, etc. These methods have been classified and compiled in Table 2. Following an exhaustive review of 11 research studies, repeatable factors influencing patients' decisions were identified. These factors are outlined below.

Altruism was the most common factor affecting the patient's consent to participate in a CT; it was mentioned in 10 out of 11 analyzed studies. In some works, altruism appears directly^{3,9,15}; in others, it is presented descriptively. For instance, there is an understanding that the trials will contribute to scientific knowledge,⁶ and the knowledge

Table 1. Publications included in the review of factors influencing patients' decisions regarding participation in CTs

Authors, year of publication, reference	Country	Number of respondents	Age [years], median (range)	Instrument characteristic	Areas addressed in instrument (questionnaire/interview)	Respondent and method	Patient characteristic	Therapeutic area or disease	CT/study characteristic (RCT)	Period of collection responses	Site/s	Phase of CTs
Bleidorn et al., 2015 ⁶	Germany	20 (100% F)	37 (20–65)	Semi-structured telephone interview. Interviews were recorded and transcribed. Data were discussed by team of physician, senior researcher and psychologist	– motivation and influencing factors, – trial decliners' reasons, – barriers for trial participation	an independent interviewer (physician) made interview with patient	CT participants, interview after study follow-up visit	urinary tract infection	urinary tract infection, RCT, 3 phase	November 2012–May 2013 and September–October 2013	Departments of Family Medicine of Hannover Medical School and University Medical Center Göttingen in cooperation with 42 family practices in Lower Saxony and Bremen, Germany	3
Burgess et al., 2009 ⁷	South Africa	250 (52.6% F)	56.3 (±10.9)	18 statements, self-administered questionnaire	– access to services, – emotions and social motivations, – contribution to scientific and learning more about condition, – influence of others	patient	95.6% – currently participating in CT	cardiovascular	cardiovascular: Atherosclerosis, other chronic disease	January 2005–May 2006	TREAD Research, Tygerberg hospital, Parow, South Africa	3
Catania et al., 2008 ⁸	Italy	102 (73.5% F)	58 (21–78)	17-item, multiple choice questions, self-administered questionnaire	– patients' fears, afraid, reticence, prejudices, – patients' expectations towards a clinical experiment, – communication	patient	patients affected with advanced breast or lung cancer, never before participated or discussed the possibility of taking part in CT	malignant tumors, advanced breast (n = 64) or lung cancer (n = 38)	no CT theoretical considerations about participation in CT	September 2006–April 2007	walk-in clinic or day hospital, European Institute of Oncology, Milan, Italy	not specified
Carroll et al., 2012 ⁹	USA	26 (85% F)	56 (41 for 25 th percentile, 61 for 75 th percentile)	semi-structured interviews done by trained investigators and standard prompt questions	Initial thoughts and reactions of patient in case of study proposal to participate. Factors important for patient's decision to participate or not. Factors motivating to participate/not participate. Concerns about participating. Medical benefits, medical risks or harms, nonmedical benefits, nonmedical burdens	patient semi-structured interviews done by trained investigators	patient group I (WHO) with PAH (NYHA I–III)	PAH	Hypothetical 2 RCTs in Pulmonary Arterial Hypertension. The 1 st study with excluded all PAH medications and the 2 nd with placebo or new drug (PAH is a rare disease (6.2%)).	July 2009–August 2009	University of Pennsylvania, Pulmonary Vascular Disease Program, USA	not specified

Table 1. Publications included in the review of factors influencing patients' decisions regarding participation in clinical trials – cont.

Authors, year of publication, reference	Country	Number of respondents	Age [years], median (range)	Instrument characteristic	Areas addressed in instrument (questionnaire/interview)	Respondent and method	Patient characteristic	Therapeutic area or disease	CT/study characteristic (RCT)	Period of collection responses	Site/s	Phase of CTs
Moorcraft et al., 2016 ¹⁰	UK	276 (32% F)	64 (19–85)	2 questionnaires A and B, both of multiple choice and free text. A – 25 questions for patients who consented, B – 21 questions for patients who declined participation in CT.	1. Reasons for trial participation or not, factors which motivated and influenced patients' decision to participate or not in CT and the main reason of the decision. 2. Patients' views on cancer research and biopsies 3. Patients' understanding of cancer diagnosis. 4. Patients' views on the written trial information, the verbal explanation, trial discussions, and the consent process.	patient	Patient just after decision re: Participation in CT. The questionnaires could be completed in clinic or taken home and returned at the patients' next clinic appointment.	oncology	36 recruiting studies: IMP, palliative and pre-screening in lymphoma and gastrointestinal. Oncology trials: 1 st phase (2), 2 nd phase (10), 2 nd /3 rd phase (2), 3 rd phase (13), not applicable (9), cancers: colorectal, esophagogastric, pancreatic, hepatobiliary, other GI, Hodgkin's lymphoma, non-Hodgkin's lymphoma	August 2013–July 2014	Gastrointestinal and Lymphoma Unit, Royal Marsden Hospital, Sutton, UK	1, 2, 2/3, 3 and N/A
Godskesen et al., 2015 ¹¹	Sweden	88 (60% F)	61 (SD ±9.1), range 39–80)	60 items questionnaire	– decision-making process, – trial information, – understanding and experiences	patient	current CT participant	oncology	9 ongoing RCT, 3 phase (2 breast, 1 prostate, 1 melanoma, 1 gastric, 1 rectal, 1 colorectal, 1 pancreatic, 1 lymphoma)	January–April 2012	Department of Oncology, Uppsala University Hospital, Sweden	3
Kurt et al., 2017 ¹²	USA	1836 (71% F)	3 age categories per each patients' sub-groups	prospective, cross-sectional, self-administered questionnaire-survey	1. Motivational factors: Doctor, research, money, benefit someone in the future. 2. Barriers: Doctors' time, family, beliefs, research, side effects, transport 3. Helpful resources: Additional materials, other patients, language, medical interpreter	patient	active clinic patient, not participating in CT	emergency medicine (n = 523) family medicine (n = 493) infectious disease (n = 435) obstetrics/gynecology (n = 566)	emergency medicine, infectious disease, obstetrics/gynecology no CT theoretical considerations about participation in CT	June 2014–March 2015	Outpatient practices at 3 hospital sites affiliated with a single health network: 2 OB/GYN clinics, 4 FM clinics, 2 ID clinics, 3 separate emergency departments in the USA	not specified
Agrawal et al., 2006 ¹³	USA	163 (44% F)	57.7 (48–68 IQR)	questionnaire of 61 questions in 8 domains	(1) alternative treatment (2) pressure to participate, (3) prognosis, (4) understanding of the protocol, (5) motivations for participation in phase I studies, (6) risk/benefit preferences for cancer treatment, (7) information-gathering behavior about phase I oncology studies (8) sociodemographic characteristics	patient and trained interviewers administered the survey	patient just consented to participate in phase I oncology trial, before receiving any therapy	oncology, advanced cancer	phase 1 oncology trials, advanced cancer patients (had cancer for average 4.8 years)	not specified	5 sites: 1) National Cancer Institute (Bethesda), 2) Institute for Drug Development of the Cancer Therapy and Research Center (San Antonio), 3) Northwestern Cancer Center (Chicago), 4) The University of Texas MD Anderson Cancer Center (Houston), 5) Fox Chase Cancer Center (Philadelphia), USA	1

Table 1. Publications included in the review of factors influencing patients' decisions regarding participation in clinical trials – cont.

Authors, year of publication, reference	Country	Number of respondents	Age [years], median (range)	Instrument characteristic	Areas addressed in instrument (questionnaire/interview)	Respondent and method	Patient characteristic	Therapeutic area or disease	CT/study characteristic (RCT)	Period of collection responses	Site/s	Phase of CTs
Catt et al., 2011 ¹⁴	UK	40 (45% F)	58.8 (29–76, SD $\pm$ 11.1)	Consultation of researcher with patient, semi-structured interview with 3 questionnaires to be completed at home by patient: (1) CT accept/decline questionnaire, (2) Life Orientation Test-Revised (LOT-R), (3) General Health Questionnaire-12 item version (GHQ12).	Questionnaire regarding CT accept/decline consists of 19 items – reasons of decision, for example hope, expectations of benefit, altruism, concerns, general perceptions of the trial information.	patient, researcher consultation and semi-structured interview	Patients attending clinics for phase 1 trial discussion. 46% (n = 18) of patients have earlier experience in CTs.	oncology	colorectal/upper GI (n = 22), breast (n = 6), gynecological (n = 5), skin (n = 3) other (n = 4)	August 2007 – December 2008	5 UK centers: Beatson Oncology Centre, Glasgow; Royal Marsden Hospital, Sutton; Royal Free Hospital, London; Southampton and Oxford CR-UK Medical Oncology Units, UK	1
Kotowski, 2021 ¹⁵	Poland	401 (63.8% F)	5 age categories per 2 patients' sub-groups (cf. Moorcraft et al. ¹⁰)	paper questionnaire including 20 closed questions	1. Knowledge about CT. 2. Level of confidence and associations with CT as opportunities and threats. 3. Readiness to participate in a CT including factors influencing the decision. 4. Expectations re: Future communication and education about CT	patient	Hospitalized patients from oncological and non-oncological clinics, chronic diseases	chronic diseases (oncology and non-oncology)	oncology (n = 211): lung cancer (n = 82), breast cancer (n = 103), colorectal cancer (n = 12), other cancers (n = 18) non-oncology chronic diseases (n = 190): respiratory (n = 149), digestive diseases (n = 20), cardiovascular (n = 12), other chronic diseases (n = 31)	not specified	National Oncology Institute, Military Institute of Medicine – National Research Institute, Institute of Hematology, and Transfusion Medicine, University Clinical Center of the Medical University of Warsaw, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland	N/A
Preus and Preus, 2022 ¹⁶	Poland	2301 (62% F)	3 age categories per 2 patients' sub-groups (cf. Godskesen et al. ¹¹)	questionnaire for patient	knowledge about CT, access to information about CT, attitude towards taking the study drug, factors affecting participation in a CT opinions on healthcare in Poland evaluation of CT informed consent in a CT an opinion on the participants of CTs	patient	patients participated in CT (n = 418), patients not participated in CT (n = 1883)	various diseases and different therapeutic areas	various diseases, e.g., cardiology, oncology, pulmonology, neurology, orthopedics, ophthalmology	not specified	Public hospitals in Poland	N/A

N/A – not applicable; F – female; RCT – randomized clinical trial; PAH – pulmonary arterial hypertension; CT – clinical trial; GI – gastrointestinal; OB/GYN – obstetrics/gynecology; FM – family medicine; ID – infectious disease; SD – standard deviation; IQR – interquartile range.

Table 2. Summary of identified factors influencing patients' decisions regarding participation in CTs

Authors, year of publication, reference	Country	Therapeutic area or disease	Number of respondents	Re-spondent status ^A	Altruism	Hope of personal benefit	Access to better care	Role of a doctor	Closest	Financial compensation	Side effect/trial safety	Guinea pig	Time and effort	Selected extra element identified or analyzed in publication	Unique or special observations related to patients' motivation in publication
Bleidorn et al., 2015 ⁶	Germany	urinary tract infection	20 (100% F)	+	yes	yes		yes	–	–	yes	–	yes	spontaneity	Individual treatment preferences of patients: An attractive option was treatment of UTI with no antibiotic.
Burgess et al., 2009 ⁷	South Africa	cardiovascular	250 (53% F)	+	yes	yes	yes	yes	yes	yes	–	–	yes	social outing	Social aspect of participation: Patients appreciated the opportunity to meet other patients with similar problems. Placebo is not a problem for patients.
Catania et al., 2008 ⁸	Italy	malignant tumors, advanced breast or lung cancer	102 (74% F)	–	yes	yes	yes	yes	–	–	yes	yes	yes	Distance to study site is no important.	28% of patients thought that they were being asked to participate in CT, because doctors are interested in advancing their own research.
Caroll et al., 2012 ⁹	USA	PAH	26 (85% F)	–	yes	yes	yes	yes	–	yes	yes	yes	yes	placebo	Patients expressed the heightened concerns regarding the risk in studies with placebo use, without any background therapy.
Moorcraft et al., 2016 ¹⁰	UK	oncology	276 (32% F)	±	yes	yes	yes	yes	yes	–	–	–	–	biopsy	The verbal explanation of the trial was rated as excellent, good, fair or poor by 96.4% of patients; also decliners rated it as excellent/good.
Godskesen et al., 2015 ¹¹	Sweden	oncology	88 (60% F)	+	yes	yes	yes	yes	yes	–	yes	–	–	duty to help	Altruism appeared spontaneously in the pilot test.
Kurt et al., 2017 ¹²	USA	emergency medicine, family medicine, infectious disease, obstetrics/gynecology	1836 (71% F)	+	yes	–	yes	yes	yes	yes	yes	–	yes	beliefs	Impact of the same factor may vary in treatment specialties, for example relationship with doctor is less important in case of emergency medicine patients in comparison to other specialties.

Table 2. Summary of identified factors influencing patients' decisions regarding participation in clinical trials – cont.

Authors, year of publication, reference	Country	Therapeutic area or disease	Number of respondents	Respondent status ^A	Altruism	Hope of personal benefit	Access to better care	Role of a doctor	Closest	Financial compensation	Side effect/trial safety	Guinea pig	Time and effort	Selected extra element identified or analyzed in publication	Unique or special observations related to patients' motivation in publication
Agrawal et al., 2006 ¹³	USA	oncology, advanced cancer	163 (44% F)	±	–	yes	yes	yes	yes	yes	yes	–	–	The information patients found most useful is that “drug kills cancer cells”.	Side effects like nausea, fatigue, a bone marrow biopsy, spending a night in the hospital; even a 10% chance of dying would not deter 90% of patients from enrolling in a phase 1 research study.
Catt et al., 2011 ¹⁴	UK	oncology	40 (45% F)	±	yes	yes	–	yes	yes	–	yes	yes	yes	Patients' personalities and their tendency to be optimistic: More optimistic patients may be more likely to participate in studies.	According to authors, patients of phase 1 studies comparing to phase 3 gave lower ranking to altruism as a primary motivation for study participating in comparison to patients of phase 3. Possible explanation is that participants of 3 phase studies have enough resources to think beyond their own situation and outcome and feel they have capacity to be selfless. Another explanation was using some components in communication with patients of phase 1.
Kotowski, 2021 ¹⁵	Poland	oncology and non-oncology chronic disease	401 (64% F)	–	yes	yes	yes	yes	yes	–	yes	yes	–	Possibility to withdraw from the study at any time	For patient's undecided to participate in the study, their decisions would ultimately be influenced by: The terminal phase of the disease or the lack of other options of treatment.
Preus and Preus, 2022 ¹⁶	Poland	various diseases and different therapeutic areas	2,301 (62% F)	±	yes	yes	yes	yes	–	yes	–	–	–	Access to information about CT	no comment

Respondent status: + participant of CT; – not participated in CT; ± mixed group of patients: Participants and non-participants. F – female; UTI – urinary tract infection; CT – clinical trial; PAH – pulmonary arterial hypertension; GI – gastrointestinal.

gained will help others in the future¹² or benefit others directly.¹⁰ Of patients participating in palliative studies (lymphoma and gastrointestinal), 25–62% indicated altruism as the main reason for their consent to participate, and 84–96% noted that it was a factor that influenced their decision positively.¹⁰ Godsken et al. reported similar findings: although altruism is mentioned as the most important decision factor by 28% of the respondents, it is also highly expressed as the median for agreement, reaching the value of 9.7 on a 10-point scale. Altruism as a motivator appears in every study, independently of the therapeutic area, phase, population, or country. Sometimes, altruism appeared spontaneously as a motive for trial participation in the pilot test.¹¹

Hope for personal benefit was another common motivation for respondents. This category includes hope itself, medical benefits, hope for a cure, and the desire for the best available treatment or access to medical care. Hope is usually ranked high in terms of frequency and it also stands out when the question concerns the most important motivator. For example, in a study by Catt et al., 21% of people indicated that their primary motivation for participating in the study was that “the trial offered me some medical benefit.” Furthermore, 15% said that “joining the trial would give me hope.” The frequency of agreement reached 77% for the 1st statement and 85% for the 2nd.¹⁴ The same inseparable link between participation in the trial and hope is mentioned in the study from the USA, where the use of a new chemotherapeutic drug had a positive effect on patients' outlook.¹³

Personal benefit was also mentioned in the study among German patients with urinary tract infections (UTI); they perceived the benefit as being able to handle future UTI treatment themselves without doctor consultation and avoiding “harmful” antibiotic treatment.⁶ In the Kotowski's study, hope was defined as “an opportunity for a new drug” and was indicated as the reason for consent to join a CT by 78.6% of non-oncological and 67.0% of oncological patients.¹⁵ Another analysis from Poland showed that “access to innovative therapies” was a motivator for 50% of patients previously participating in CTs and 74.6% with no such experience.¹⁶ This factor is, therefore, extremely important regardless of the therapeutic area, patient experience, health condition, or geographic location.

Access to better care covers access to better or extra examinations, investigations or medication. Compared to hope for personal benefit, this motivation is distinguished by a more measurable and real, material nature, e.g., more tests or access to a test that the patient would not have had if he had not participated in the study. This factor also includes access to certain drugs.

This motivation was expressed by patients from different countries and different care systems, including those from Sweden,¹¹ Italy,⁸ Poland,^{15,16} USA,¹³ UK,¹⁰ and South Africa.⁷ Discussing this factor, the authors point to various grounds for justifying such a choice. In South Africa,

“access to medication” was mentioned by 81% of respondents (“agree” or “strongly agree”) and “access to investigations” by 80%. The study drugs used in trials in South Africa are often already registered in the USA or Western European countries yet are still not available for patients in South Africa.⁷ The high rate (mean = 8.7 on a 10-point scale) of Swedish respondents (n = 86) agreed that “access to extra exams” was the reason they had decided to participate in randomized CTs.¹¹ A Polish study showed that both oncological (76%) and non-oncological (63.3%) patients indicated easier access to additional tests.¹⁵

An additional motivation was the role of a doctor, which included trust in the doctor, the relationship, the doctor's advice, any pressure from the doctor, and the doctor's reputation. In various studies, this element always refers to the doctor who is the investigator; it can be a specialist like an oncologist working at a university hospital or a general practitioner, as in the study from Germany. In one study, 97% of patients from the UK confirmed that they trusted the doctor who treated them; for 1%, it was even the most important factor in the decision to join a CT.¹⁴ In a separate study, authors from South Africa asked patients about being under pressure from the staff, and 94% of participants confirmed they did not feel any. In the same study, 67% of participants strongly agreed or agreed that they had received advice from the doctor to take part in the study.⁷ In the Swedish study, 70% reported that they did not sense the doctors' expectation that they would agree to participate in the trial. The mean value for the opinion that patient participation was based on the doctor's expectation (expressed by the statement “my doctor thought so”) was 4.1 on a 10-point scale. According to the authors, half of the respondents preferred to share the responsibility for making the decision by seeking consultations with a doctor or relatives.¹¹

A similarly important and positive role of a doctor is the trust the doctor builds with patients. In the study from the USA related to an active drug, trust was the motivation for 60% (one of the top 3 most often indicated factors), while in the palliative study, it was the motivation for 49% (also in the top 3).¹⁰ In another American study from 2006, the authors reported that only 7% felt moderate or significant pressure from the study's clinical researchers.¹³

A different scenario was observed within the subgroup of emergency medicine patients in the study by Kurt et al. They were less likely to be influenced by the doctor's reputation or their relationship with the investigator, but these patients, due to the emergency, may have lacked the opportunity to establish a relationship or learn about the investigator's reputation.¹² Overall, studies showed that the doctor's role is crucial, and investigators should appropriately balance positive communication about the study without exerting pressure in order to recruit patients. However, there are situations where the doctor's significance might not be as pronounced.

Several studies also analyzed the influence of close individuals on a patient's decisions.^{7,10–15} In the case of close relatives, their influence on decisions was primarily examined in terms of what level of pressure they exerted on the patient; however, according to results, patients did not generally feel pressure from their loved ones. In a Swedish study, the opinion that “those close to me thought I should agree to participate” only reached a mean of 2.4 on a 10-point scale. These results were too low to conclude that the patient was under the pressure or significant influence of close relatives.¹¹

Almost half of all patients from South Africa claimed that they were influenced by their family or friends, and the remaining 50% confirmed that the opinion of friends or relatives was significant for them.⁷ In a paper from the UK, a questionnaire revealed that 51% of patients agreed with the statement “Others (e.g., family or friends) wanted me to join the trial”; however, there was nothing included about the strength of such an influence.¹⁴ This suggests that not only in Scandinavia, where autonomy is a fundamental ethical principle, patients do not perceive pressure from their families or friends as a primary motivating factor. Additionally, in an American study from 2006, the authors explained that only 9% of patients in phase 1 oncological study felt a moderate or significant amount of pressure from their families.¹³

The study by Kurt et al. identified family concerns as a significant barrier to agreeing to participate in a CT for patients in the emergency medicine group (mean response = 2.4). The authors explain that this is a result of difficulties associated with involving loved ones in the patient's decision-making process during emergencies. Often, they are not present or near the patient, or they may also be under significant stress.¹² This example shows that the specificity of the trial should always be taken into consideration.

Financial compensation as a motivation was analyzed in 5 studies.^{7,9,12,13,15} Investigators, bioethicists and ethics committees usually regard this as essential information. Based on the included studies, this factor does not appear to be particularly significant in patients' decision-making process. In a study from South Africa, 80% stated that money had little importance in their decision to participate in a CT. On the other hand data showed that almost 5.5% strongly agreed, 8% agreed and 7% partly agreed with the statement that trial was an “easy way to obtain money.”⁷

In a Polish study, reimbursement of travel costs ranked 7th out of 8 factors determining respondents' potential participation in clinical study.¹⁶ This element was mentioned by 22.2% of previous CT participants and 23% of those who had not participated yet. In a study from the USA, motivation for all patient subgroups (emergency medicine, family medicine, infectious diseases, obstetrics/gynecology) seemed to be minimally influenced by the money offered for participation.¹² The mean response for financial compensation (value: 1.77–2.17) was low, but not as low as for the category “the doctor conducting the research is the same race/ethnicity as me” (value: 1.02–1.56).

In another study from the USA, the financial costs of participation were deemed unimportant in patients' opinions: information about participation costs was most useful for only 1% of patients.¹³

In yet another American study, the compensation or reimbursement was somewhat relevant to the patient's decision.⁹ Based on quoted patient statements, the attitude towards reimbursement seemed pragmatic: “Compensation would help, but if I would not be compensated, that would not prevent me from doing it.” Thus, while the financial aspect was slightly important, it did not play a decisive role in the decision-making process. The lack of cost reimbursement did not seem to significantly alter the percentage of patients agreeing to participate in the study. In most cases, a pragmatic approach was observed among patients.

In addition to the aforementioned factors that positively impacted study participation, some factors exerted negative influence, referred to as barriers.

First, several studies examined the potential side effects of the trials, including trial safety and drug toxicity. In 1 study, 53% of Italian patients expressed concerns about potential and lesser-known side effects.⁸ Similarly, in the UK study, 59% of respondents claimed, “I was worried about the side-effects of the study drug/s.”¹⁴ In addition, 65% of those in an American study expressed concerns about side effects.⁹ The risk of unknown side effects emerged as the primary barrier across all patient subgroups from the study (mean values: 2.59–3.25).¹² In the German study on UTI treatment, many interviewees held the opinion that a UTI is not a serious condition, and thus they were willing to participate in the study. Conversely, had the condition been more severe, they might have declined participation.⁶ A Polish study reported that patients were afraid of higher toxicity of the experimental treatment, with rates of 64.7% for oncology and 48% in case of non-oncology patients.¹⁵

In summary, the potential for adverse effects significantly impacted patient decisions, acting as a notable barrier to participation. Concerns about potential and lesser-known side effects were widespread, influencing willingness to engage in CTs. The perceived risk associated with unknown side effects was a primary deterrent for various patient subgroups.

Patient concern about being guinea pigs appeared in 4 of the analyzed studies.^{8,9,14,15} The fear of being a “guinea pig” emerged as a significant barrier. This concept has not been precisely defined, but it can refer to the perceived objectification of the patient in the study. In the study by Catania et al., this concern was expressed by 36% of patients,⁸ and a similar result was observed in the study from the UK (33%).¹⁴ In a study by Carroll et al., 15% of the participants communicated their fears about being a guinea pig.⁹ The same factor was noted in the Polish study; of the patients who would not agree to participate in the study ($n = 59$, 14.9% of respondents), 59.3% ($n = 35$) stated that they did not agree to be an experimental “guinea pig.”¹⁵

Effort and time were 2 factors considered together. They were considered in 5 studies.^{6,8,9,12,14} In the German patients with UTI, the authors noted that trial-related time and effort may have kept patients from participating, which is particularly true for employed patients.⁶ Patients expressed that visits and phone calls were always difficult to reconcile with work. Based on a study from the USA involving pulmonary arterial disease (PAH) patients, it is evident that the time demand of the trials could be challenging for some patients and may have hindered enrollment.⁹ Patients were afraid of missing work or having to travel to sites. Of those who were asked to participate in 8 visits within 16 weeks, 65% of participants claimed that this was a burden or inconvenience related to the time demands. In the same study, 23% identified "duration of trial" as an issue. Another American study showed that time commitment was more visible as a barrier for those who graduated college or had a higher degree in comparison to those with less than a high school education.¹²

Contrary to the above examples, patients from South Africa expressed that time was not a huge issue. Only 7% of patients felt that they did not have the time required to participate in a CT; 81% of them "strongly agreed" or "agreed" with the statement "I have the time." However, this response could be related to the fact that 66.5% of the respondents from the South Africa trial were unemployed.⁷

In an Italian study, 55% of patients were afraid of wasting time, but the reason was completely different: They were afraid of using inefficient drugs.⁸ In a study from the UK, 16% of patients agreed with the questionnaire statement "I thought the trial needed too much effort from me"; however, this percentage included only 6 patients and is therefore not a representative sample for conclusive findings. In summary, it should be noted that the time commitment necessary to participate in CTs can be a barrier for professionally active people.

In CTs, the issue of placebo usage can often create misunderstandings. In the case of 1 study, the potential issue of a placebo was analyzed.⁹ The authors presented 2 hypothetical randomized CTs to the patients: One with the continuation of background therapy and another without any treatment in which only a placebo was allowed. Based on the responses, it is evident that patients were not interested in studies where they did not receive any treatment. Concern about placebo was expressed by 38% of the potential participants in a hypothetical study. This finding may indicate that more clarification is necessary for randomized placebo-controlled trials, emphasizing that patients are never left without treatment.

Discussion

A review of publications shows that regardless of the therapeutic area, health status, phase of the study, country, geographic area, economic situation, or healthcare system,

patients point to the same or very similar factors when deciding to participate in a CT. This area is researched in different ways, using various methods and techniques of data collection and analysis, but regardless of the methods, similar results were obtained.

In most cases, motivations include altruism, hope for personal benefit and access to better care. In addition, barriers include concerns about safety, potential side effects, and the fear of being treated as a guinea pig. These patterns are independent of the size of the study group or the patient's previous experience with CTs.

In some studies, patients indicate factors that do not appear in other analyses, which are most often determined by the specifics of the study or possibly by local factors due to socioeconomic or cultural circumstances. An example is a study from South Africa, in which social motivation, i.e., the desire to interact and meet other patients, was highlighted.⁷ In contrast, for studies conducted on diseases that are not directly life-threatening (e.g., UTIs), patients were willing to take more risks by their own choice and were guided by individual therapeutic preferences.⁶ Overall, patients as a group or community were driven by similar motives and concerns.

Analyzing the statements of individual patients cited in the papers, there were clear differences on the individual level in the rationale for justifying the patient's decision. The individual patient's decision to participate in the study was multifaceted and motivated by very different individual factors and circumstances. Examples of these factors would be the severity of the disease, the level of anxiety or concern about side effects, and the risk of losing one's job due to the study length and participation required.

Repeated factors in the analyzed works, which, although they influenced patients' decisions to a lesser extent, were important for patients, include doctor's advice and opinions of relatives. At the same time, the data presented showed that patients were not subjected to pressure from the environment. A factor that turned out to be appreciated by patients but did not have a decisive influence on their attitude or decision was financial compensation.

Based on a review of the literature mentioned above, the determinants of consent can be divided according to several categories, regardless of the phase of the study, therapeutic area, patient population, etc. The following are 3 classifications of motivators developed based on selected literature.

1) All factors influencing patients' decisions to participate in the study can be assigned to 1 of the following 2 categories:

1. Factors motivated by personal benefit, satisfying the individual needs of the patient as an individual, such as hope for improvement in health, absence of the occurrence of adverse symptoms, financial compensation, and the sense of belonging to a group.

2. Factors based on benefit and good for the community such as altruism, acting for the world, science, and medical progress.

2) Motivators for participation in a CT can also be arranged using the criterion of frequency and universality:

1. Common, standard factors: e.g., hope for personal benefit, better medical care, altruism, willingness to support science, fear of side effects, burdensome procedures, medical risk, and safety

2. Atypical and unique factors that depend on the project and the specifics of the study. These factors could include project-specific requirements such as procedures required in the study (e.g., number of biopsies), treatment preferences (antibiotic compared to non-antibiotic treatment), patient's situation (e.g., employment or lack of work), time commitment and effort required (e.g., missing work as addressed in a study from the USA compared to the opportunity for unemployed patients in the South African study), and the investigator's gender in gynecology studies.

The factors mentioned in the first point appear in every study regardless of the therapeutic area, phase or research method (interview, questionnaire, others). They play a role in each patient's decision regardless of previous study experience or knowledge of the study, and they affect the patient's final decision. Atypical factors should be kept in mind when analyzing study specificity, cultural differences and unique study procedures. Often, these factors are less studied due to their rarer occurrence in studies, and it is easier to overlook them or underestimate their role.

3) Criterion of importance/significance:

1. Critical: Primary factors or direct motivations/barriers, e.g., personal benefit, lack of other treatment options, individual treatment preference, prior experience, and altruism.

2. Major: Secondary factors or supporting motivations/barriers, e.g., opinion of loved ones, doctor's advice, faith, and fear of side effects.

3. Minor: Other factors, e.g., sense of belonging to the community, reputation of the center or trust in the institution, financial compensation, and race of investigator.

In the case of these factors, their assignment to different groups may overlap; in other words, the same motivator may appear in different categories, transitioning among adjacent groups rather than transitioning from extreme minor to critical categories. For example, doctor's advice might appear in both the minor and critical categories, although it is generally assigned to the major category. In contrast, a sense of belonging to the community (minor) will not be observed in the critical category.

Limitations

Limitations of this review are due to methodological differences and different sizes of patient groups, as well as various therapeutic areas and phases of trials. In some publications, the respondents were participants in CTs, while in others, they were not. In addition, papers that addressed patient participation in hypothetical, non-existent CTs were included in the analysis.^{8,9,15} The data presented

in this review were collected by authors from 2005 to 2015 (note: There was a lack of information in Polish papers about collection time). Thus, all of these studies were performed before the outbreak of the COVID-19 pandemic. This period may have significantly affected the level of knowledge about and attitudes towards CTs, and thus, the factors motivating patients to participate may have altered. Additionally, in recent years, 2 extremely important regulations have appeared in European Union countries, affecting the way CTs are conducted.^{17,18} Therefore, it is necessary to analyze and determine the motivations and barriers to patient agreement to participate in a CT.

Conclusions

Based on the conducted review, it is evident that there are various correlations between the examined factors and the patient's decision to participate in a CT. It is recommended to examine which dependencies exist between the type of clinical study, the characteristics of the study participant candidate, and the final decision of the patient regarding their participation in the CT. Future studies on factors influencing patients' decisions regarding participation in CTs should include more diverse groups of patients examined using similar methods. It would also be worthwhile to conduct such studies to see how the COVID-19 pandemic may have affected patient motivation.

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