

Transparency and public accessibility of clinical trial information in Croatia : how it affects patient participation in clinical trials

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**SVEUČILIŠTE U SPLITU
MEDICINSKI FAKULTET**

IVANA ŠOLIĆ

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INFORMATION IN CROATIA: HOW IT AFFECTS PATIENT PARTICIPATION IN
CLINICAL TRIALS**

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CONTENTS

1. ABSTRACT.....	3
2. INTRODUCTION.....	5
3. METHODS	8
4. RESULTS	11
5. DISCUSSION	15
6. ACKNOWLEDGMENT, AUTHORSHIP CONTRIBUTIONS DECLARATION, FUNDING, CONFLICT OF INTEREST	18
7. ADDITIONAL MATERIAL: TABLE 1-4	20
7. REFERENCES.....	28
8. ŽIVOTOPIS	31

ZAHVALA

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Posebna zahvala roditeljima i bratu koji su lakoćom i sigurnošću svojeg vjerovanja u moj uspjeh bili moja snaga.

1. ABSTRACT

Introduction: Despite increased visibility of clinical trials through international trial registries, patients often remain uninformed of their existence, especially if they do not have access to adequate information about clinical research, including the language of the information. The aim of this study was to describe the context for transparency of clinical trials in Croatia in relation to countries in Central and Eastern Europe, and to assess how informed Croatian patients are about clinical trials and their accessibility.

Participants and Methods: We assessed the transparency of clinical trials from the data available in the public domain. We also conducted an anonymous survey on a convenience sample of 257 patients visiting two family medicine offices or an oncology department in south Croatia, and members of national patients' associations.

Results: Despite legal provisions for transparency of clinical trials in Croatia, they are still not sufficiently visible in the public domain. Among countries from Central and EASE Europe, Croatia has the fewest number of registered trials in the EU Clinical Trials Registry. 66% of the patients in the survey were aware of the existence of clinical trials but only 15% were informed about possibilities of participating in a trial. Although 58% of the respondents were willing to try new treatments, only 6% actually participated in a clinical trial. Only 2% of the respondents were aware of publicly available trial registries.

Conclusions: Our study demonstrates that there is low transparency of clinical trials in Croatia, and that Croatian patients are not fully aware of clinical trials and the possibilities of participating in them, despite reported availability of Internet resources and good communication with their physicians. There is a need for active policy measures to increase the awareness of and access to clinical trials to patients in Croatia, particularly in their own language.

Key words: access to information; awareness; patient participation; clinical trials; registries

2. INTRODUCTION

Transparency is at the heart of health research (1). Transparency and completeness of clinical trial reporting is important not only for unbiased assessment of health interventions and formulation of health practice guidelines (2), but is also an obligation towards altruistic individuals who volunteer for research (3). The increase in the transparency standards for clinical trials that we witness today, from the availability of information about the existence of trials to the availability of trial results and data, is the outcome of joined effort of journal editors, researchers and policy makers to improve the quality of health research and empower the patients and their families to get the best treatment available (3-6).

Despite the increased openness of information of clinical trials, it is still often difficult to successfully enrol participants into trials. Although most patients seem to be aware and willing to participate in clinical trials (7), only a small fraction of patients who meet the requirements actually participate in trials (8). Only 27% of patients discuss clinical trials as an option with their physician (9). There is also evidence of gender imbalance in the awareness about clinical trials, with male patients reporting more often that they are informed about clinical trials (10).

One of the main reasons why patients take part in clinical trials is the possibility to benefit from new treatment (3,11). On the other hand, there are many potential reasons why patients avoid entering a clinical trial. These include the fear of being a “human guinea pig”, trying something no one knows whether it would work, worries that they will be in the control group receiving a placebo and be thus left without help, as well as the feeling that joining a clinical trial means that all hope is lost (12). One of the problems contributing to this distrust is the lack of understanding of the methodology of clinical trials and their purpose, despite the information received during informed consent procedure (11). More active engagement in information translation to patients may be beneficial, as studies show that engagement of special educators, who spend more time talking face to face with participants, improve participants' understanding of specific clinical trial (13). Also, new forms of recruitment strategies may bring down some barriers to patient participation in clinical trial (14). However, there is also evidence that education interventions related to participation in clinical trials may not influence the patients' motivation for trial accrual (15).

Patients' knowledge and awareness of and participation in clinical trials may be a special problem for smaller research communities such as Croatia. There is little information on how well patients are informed about clinical trials in Croatia (16). Judging from experience of low awareness of and adherence to common medical procedures among

Croatian patients (17,18), high level of information about participation in clinical trials cannot be expected. One of the reasons for the lack of information on clinical trials in Croatia could be because the information is not available in the Croatian language. Most of the information about clinical trials is available only in English, although some countries have followed the recommendations of the World Health Organization (WHO) and established their national registries of clinical trials, with information available in the native language (19).

The aim of our study was to examine the transparency of official information available about clinical trials conducted in Croatia in comparison to other countries in Central and East Europe, and to explore the awareness and opinions of Croatian patients about clinical trials. We targeted general patient population attending family medicine practices as well as patient groups with special interest in clinical trials – cancer patients and patients' associations.

3. METHODS

Study design

Data sources. To identify the availability of information on clinical trials in Croatia, we searched the web-sites of the Ministry of Health (<https://zdravlje.gov.hr/>), which is a regulatory competent authority for the approval of clinical trials, and the Agency for Medicinal Products and Medical Devices (<http://www.halmed.hr/en/O-HALMED-u/>), which hosts the national Central Ethics Committee (CEC). CEC issues opinions in the procedure of granting approvals for clinical trials (20). We compared the legislative framework for the transparency of clinical trials in Croatia to that for other EU countries from Central and Eastern Europe (Bulgaria, Czech Republic, Hungary, Poland, Romania, Slovakia and Slovenia) which had similar social and economic history of transition from socialist to market economy (21), using the information on the ethics review of clinical trial protocols in Europe collected by the European Forum for Good Clinical Practice (20).

The data on the total number of registered clinical trials were collected from two international registers on January 16, 2017: the EU Clinical Trials Register of the European Medicines Agency (<https://www.clinicaltrialsregister.eu/ctr-search/search>), which registers interventional clinical trials on medicines conducted in the European Union (EU) and the European Economic Area (EEA) since 2004, and ClinicalTrials.gov (<https://clinicaltrials.gov/ct2/home>), which is a registry and results database of clinical studies and is hosted by the National Library of Medicine..

Patient survey. The survey was performed on a convenient sample during two months in 2015/2016. Participation was invited from the following patients' populations: 1) patients with chronic diseases visiting two family medicine offices, one in the city of Split and one on the island of Hvar; 2) patients from the Department of Oncology of the University of Split Hospital Centre; 3) members of patients' associations at a national level, via pen-and-paper questionnaire or online social media groups. The survey had a single round of data collection, with no reminders. The survey was voluntary and anonymous, and was approved by the Ethics Committee of University of Split School of Medicine as a part of the research grant "Professionalism in Health Care" funded by the Croatian Science Foundation (Grant No. IP-2014-09-7672). The survey included only adult responders, but they could answer questions for their children.

The survey was constructed as a 20-item questionnaire (**Table 1**) to collect the following information: patients' basic demographic characteristics; predominant

disease/condition and received treatments; relationship with their physician(s); satisfaction with the communication with the physician and the treatment received; interest in their disease and for seeking additional information about it; awareness of clinical trials and participation in them; and willingness to participate in a clinical trial. The questionnaire was piloted with four experts to test its face validity; the pilot resulted in minor language changes but no changes in the questions.

Statistical analysis

Categorical data were presents as percentages or ratios (when $N < 100$) and continuous data as medians \pm interquartile range. Comparisons were made using chi-square test or Fisher's exact test where expected cell frequency was less than five for categorical data, or Kruskal Wallis test with Mann Whitney U test as a post-hoc test for continuous data. Statistical analysis was performed using the SPSS version 18 (SPSS Inc., Chicago, IL). The significance threshold was set at $P < 0.05$ (for post-hoc tests, Bonferroni adjustment was made and significance threshold was set at $P < 0.01$).

4. RESULTS

Context for trial registration in Croatia

The conduct of clinical trials in Croatia is governed by several laws and regulations (20). Clinical trials, both industry and non-industry sponsored, on drugs and medical devices must be approved by the Minister of Health, after positive approval from the national CEC. Trials involving other interventions, which are outside of the scope of the CEC, must be approved by relevant local ethics committees. There is no national policy on the registration of clinical trials before their inception, but there is legal requirement for a register of all approved clinical trials since 2010 (20). However, the scope of this register is not yet defined and it has not been established, as judged by the information from the web-site of the Ministry (January 2017).

The most recent legal regulation requires that all approved trials should be available not only at the web-site of the Ministry of Health but also in the EU Clinical Trial Register (22). The documentation on approved clinical trials from 2010 onward is available in the form of PDF documents at the Ministry's web-site (23). The information on a trial consists of the official scientific title of the trial in English and Croatian, EU register (EUdraCT) number, name of the tested drug, indication (disease), and trial sites (the name of the institution). The documents list 50 trials in 2016, 59 in 2015, 55 in 2014, 77 in 2013 and 57 in 2012. The lists seem to be have been updated, as some of the trial from earlier years have a notification that they had been closed. According to the database from the European Forum for Good Clinical Practice from 2012 (20), no information is available on the transparency of clinical trials in Bulgaria, Slovakia and Slovenia, while Romania had no policy on the registration of clinical trials. Hungary had no national policy on trial registration but required that all trials are registered in the EU clinical trial register, EudraCT. Poland has a national register, which is not open to the public but permission may be given to interested persons. The Czech Republic has an open national register.

In order to assess the number of past and currently ongoing trials in Croatia and EU countries in Central and Eastern Europe, we searched the EU Clinical Trial Register (EUCTR) and the ClinicalTrials.gov register (Table 2). At the time of the search (16 January 2017), EU Clinical Trials Register had 29502 clinical trials with a EudraCT protocol conducted in the European Union (EU), or the European Economic Area (EEA) after 1 May 2004. ClinicalTrials.gov listed 234467 studies with locations in the USA and 195 other countries. In comparison to other EU countries from Central and Eastern Europe, which joined the EU in 2004 or 2007, Croatia, which joined in 2013, has a smaller number of

registered clinical trials in EUCTR (Table 2). Although the percentage of ongoing registered studies was similar in all countries from our comparison (around 70% or over), the percentage of trials with registered results was the smallest in Croatia: 13% compared to 36-48% in other countries (Table 2). The content analysis of 26 trials with results posted for Croatia demonstrated that 20 had information only in English, and six had the only the scientific title of the trial translated into Croatian, and all other information in English only. In the ClinicalTrials.gov, the percentages of open studies or those with registered results were similar across all countries, with 12-17% of studies still recruiting and with 21-36% of trials having registered results.

Patients' survey

During the sampling time-frame, responses from 257 participants were collected (Table 3). We could not calculate the response rate due to the open nature of the survey, including open call to patients via their respective social media groups. There were 117 men (46%) and 137 women (53%), mostly in the 41-80 age group (67%). Patients were treated for their major chronic disease or cancer in Split (69%), Zagreb (25%) or Osijek (2%). The treatment was mostly received in university hospital centres (67%) and in family medicine practices (40%). Patients reported different chronic conditions, and most common diagnosis were carcinomas (26%), diabetes (13%) and mental illnesses (12%). Members of a patients' association constituted 21% of the respondents.

Although 82% participants reported that they felt free to ask their physicians about their treatment, 69% of those were actually interested in asking their physician and/or did ask (Table 4). Even when they asked, 20% did not understand or did not fully understand the information they got from their physician. Although patients reported good communication with their physicians, a half of the respondents searched for more information, mostly from friends (33%) or the Internet (41%), predominantly using general internet searches rather than specialized health sites. Only 2% of the respondents were aware of publicly available trial registries, such as ClinicalTrials.gov.

Although 66% of the respondents were aware of clinical trials, only 15% were informed about possibilities of participating in a trial (Table 5). Furthermore, 58% of the respondents were willing to try new treatments but only 6% actually participated in a clinical trial. Men significantly more often reported being informed about clinical trials than women

(63% vs. 37%, $P=0.017$).

Survey respondents coming from different patients' groups significantly differed in their answers (Table 6). As expected, patients attending the hospital oncology department reported having significantly more annual appointments with the physician(s) than other respondent groups ($P<0.001$). Respondents from the online survey and those from patients' associations reported more often that they were aware of clinical trials in comparison to other groups ($P<0.001$). Online survey respondents also more often reported the willingness to try new treatments than the other groups, except the respondents from patients' organizations ($P=0.014$).

5. DISCUSSION

Our study showed that Croatian patients were not well informed about possibilities of participating in a clinical trial. Although they were reportedly aware of existence of trials, they did not take the opportunity to participate in them. Only 12% of the patients reported to be informed about clinical trials by their physicians, which is much lower than current percentages reported elsewhere in EU, such as 27% in England and Scotland (9). Men in our study, similar to the study in the UK (9) more often reported knowledge of clinical trials, although women significantly more often used the Internet to search for health information, as has been shown for other patient populations (24).

The results of our survey should be interpreted with caution because of the methodological constraints of the convenient survey sample and self-reported nature of the answers. The survey was performed in a single university hospital centre and two family medicine practices in South Croatia, as well as on a national, albeit small sample of members from patients' organizations, and cannot be fully representative of the whole Croatia. The sample may have been biased towards patients treated in larger cities in Croatia, as over 90% of the respondents were treated in two largest hospital settings – Zagreb and Split. However, this means that the observed low level of engagement in or information on clinical trials in such a sample may be an underestimation of the situation at the national level, and may be even lower in rural areas. Our study is, to the best of our knowledge, the first published survey of patients' awareness and participation in clinical trials in Croatia, and should be taken as the baseline and evidence for any future actions and interventions to increase the knowledge and participation in clinical trials.

The low awareness and participation of patients in clinical trials observed in our study may be linked to low transparency of clinical trials in Croatia. Although Croatia has good legal provisions for increasing trial transparency, with the requirement for listing of the approved trials and the national register (22), neither the listing of approved trial nor the register have been fully implemented: the register does not exist and the listings lack sufficient information for someone who may be eligible for a trial. For example, only the institutions where the trial is performed are listed, without contact details for responsible person(s) that could be contacted about trial participation. In contrast, major trial registers, like the ClinicalTrials.gov in the USA, have been developed to help individuals with serious or life-threatening diseases or conditions and their families to find trials testing new interventions, as well as to help researcher identify most suitable participants for the trials (25). The lack of sufficient information on approved trials at the Ministry site is also against

the standards of the WHO in regard to the minimum amount of information needed for trial registration (26): 1. Primary Registry and Trial Identifying Number, 2. Date of Registration in Primary Registry, 3. Secondary Identifying Numbers, 4. Source(s) of Monetary or Material Support, 5. Primary Sponsor, 6. Secondary Sponsor(s), 7. Contact for Public Queries, 8. Contact for Scientific Queries, 9. Public Title, 10. Scientific Title, 11. Countries of Recruitment, 12. Health Condition(s) or Problem(s) Studied, 13. Intervention(s), 14. Key Inclusion and Exclusion Criteria, 15. Study Type, 16. Date of First Enrollment, 17. Target Sample Size, 18. Recruitment Status, 19. Primary Outcome(s) and 20. Key Secondary Outcomes.

According to our analysis of information on trials available in major international registries, Croatian patients can learn most about potentially relevant clinical trial from ClinicalTrials.gov then from any other, including the EUCTR. In general, ClinicalTrials.gov has more registered studies from the countries analysed in our study than the EUCTR mostly because the scope of the two registers is different and the US register is older than the EUCTR (5,6). EUCTR, which Croatia officially joined in 2013, still has the fewest number of registered trials from Croatia, especially those with already available results. Unfortunately, almost all of the information in EUCTR is not in Croatian, and all information in the ClinicalTrials.gov is in English.

In conclusion, despite increased transparency of clinical trials worldwide, Croatian patients still have limited access to full information about clinical trials performed in Croatia, particularly in their own language and have low awareness about clinical trials and the possibilities of participating in them is rather low, despite reported availability of Internet resources and good communication with their physicians. The first step in increasing this transparency for the benefit of the patients would be to fully implement legal provisions that have existed for more than five years (20). Only when the basic information about clinical trials is full, transparent and easily accessible, preferably in native language, efforts could be focused on managing the communication with patients (14), with physicians and other health workers to support participation in clinical trials and clear insecurities with participants (27).

**6. ACKNOWLEDGMENT, AUTHORSHIP CONTRIBUTIONS DECLARATION,
FUNDING, CONFLICT OF INTEREST**

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AUTHORSHIP CONTRIBUTIONS DECLARATION

AM conceived the study; all authors designed the study protocol. All authors collected that data, AS performed statistical analysis, and all authors contributed to the interpretation of data. IS and AS wrote the first draft and AM and IP revised the manuscript for intellectual content. All authors approved the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

7. ADDITIONAL MATERIAL: TABLE 1-4

Table 1. Survey questionnaire

1.	General information: Age (number)*: _____ Gender <input type="checkbox"/> female <input type="checkbox"/> male
2.	The main disease you are suffering from:
3.	Are you a member of any patients' association (mark the answer)? If the answer is yes, which one? NO YES Patients' association:
4.	City where you are seeing the specialist physician who treats you from your main disease (you can mark multiple answers): a) Zagreb b) Split c) Rijeka d) Osijek e) Other (which one):
5.	Type of institution where you are getting your treatment (you can mark multiple answers): a) University hospital centre b) Hospital c) Health centre d) Family medicine offices e) Private specialist physician f) Other (what type):
6.	How often do you see your specialist physician who treats you from your main disease (the average number of visits per year)?
7.	Does your specialist physician discuss your therapy with you? No Yes Yes, but not clearly If you are not satisfied with communication with your physician, please describe a problem:
8.	Does your specialist physician answers clearly to your questions? No Yes Yes, but not clearly If you are not satisfied with communication with your physician, please describe a problem:
9.	Do you feel free to ask your specialist physician if there is any therapy that would be better for you and your treatment? YES NO Write any comments, if you wish.
10.	Do you ever seek information about your diagnosis or treatment elsewhere? YES NO
11.	If you do seek information on your diagnosis or treatment, what do you use? You can mark multiple answers. a) books b) friends (including friends who are health professionals) c) research articles d) pharmaceutical promotional materials e) Internet f) medical lay journals g) other source of information:
12.	Are you willing to try some new, potentially better, types of therapy for your disease that are current or being investigated? YES NO
13.	Have you ever been informed about possibility to participate in a trials that are investigating new ways of treating your disease? YES NO
14.	If the answer to previous question is yes, who informed you (you can mark multiple answers)? a) physician b) pharmacist c) family member/friend d) patients' association where you are the member e) Someone else (who?):
15.	Have you ever heard of clinical trials or experiments? YES NO
16.	If you have heard of clinical trials, please describe what they mean for you.
17.	Do you have Internet access (at home, at work or any other place)? YES NO

18.	<p>If you are searching online for possibilities to participate in a clinical trial, which sources of information do you use (you can mark multiple answers)?</p> <p>a) internet search engine (Google and similar)</p> <p>b) www.zdravlje.hr</p> <p>c) www.clinicaltrials.gov</p> <p>d) www.trialscentral.org</p> <p>e) something else (which one):</p>
19.	<p>Have you ever participated in a clinical trial? YES NO</p>
20.	<p>If you have participated in a clinical trial, please describe your experience:</p>

*The online version of the survey had categories for age: 0-17, 18-40, 41-65, 66-80, and >80 years.

Table 2. Clinical trials from EU countries in Eastern and Central Europe registered in international trial registries*

Country	EU Clinical Trials Register			ClinicalTrials.gov		
	Total	Opened (%)†	With registered results (%)	Total	Opened (%)†	With registered results (%)
Bulgaria	1289	868 (67)	610 (47)	1430	240 (17)	424 (30)
Croatia	196	174 (89)	26 (13)	772	130 (17)	225 (29)
Czech Rep.	3340	2421 (72)	1606 (48)	3304	545 (16)	969 (29)
Hungary	3414	2473 (72)	1612 (47)	3028	506 (17)	929 (31)
Poland	1771	1258 (71)	630 (36)	4794	766 (16)	1367 (29)
Romania	195	168 (86)	70 (36)	1969	294 (15)	681 (35)
Slovakia	885	625 (71)	398 (45)	1362	167 (12)	495 (36)
Slovenia	293	223 (76)	137 (47)	482	84 (17)	101 (21)

*Search performed on 16 January 2017.

†EU Clinical Trials Register: filtered as “Ongoing” for Trial Status in Advanced Search; ClinicalTrials.gov: filtered as “Open Studies” for Recruitment in Advanced Search.

Table 3. Descriptive statistics of the study sample (N=257)

Characteristics	No. (%) [*]
Gender (N, %)	
Female	137 (53)
Age group in years (N, %) [†] :	
0-17	10 (4)
18-40	49 (19)
41-65	92 (36)
66-80	81 (32)
≥81	9 (4)
Main disease (N, %) [‡] :	
Cancer/tumour	66 (26)
Mental illness	31 (12)
Diabetes	33 (13)
Hypertension	18 (7)
Heart conditions	16 (6)
Pulmonary diseases	7 (3)
Spine and bones diseases	16 (6)
Other diseases	46 (18)
Patients' association membership (N, %)	53 (21)
Place of treatment (N, %):	
Zagreb	64 (25)
Split	177 (69)
Osijek	6 (2)
Institution of treatment (N, %) [‡] :	
University Hospital Centre	173 (67)
Hospital	36 (14)
Health centre	12 (5)
Family medicine offices	103 (40)
Private specialist physician	22 (9)

^{*}Percentages are to the total sample, to indicate missing responses.

[†]Children were not recruited for the study, but parents could answer the survey about the experiences in the treatment of their children.

[‡]Percentages do not add up because multiple choices were possible.

Table 4. Patient's satisfaction and interest about their disease and treatment*

	Total (No., %) (N=257)	Men (No., %) (N=117)	Women (No., %) (N=137)	P†
Feels free to ask physician about the treatment	211 (82)	100 (48)	110 (52)	0.190
Discusses therapy with physician:				
Yes	177 (69)	77 (44)	100 (57)	0.519
Yes, but not clearly	37 (14)	18 (50)	18 (50)	
No	29 (11)	15 (54)	13 (4)	
Physician answers to patient's question:				
Yes	195 (76)	90 (46)	105 (54)	0.414
Yes, but not clearly	35 (14)	13 (39)	20 (61)	
No	15 (6)	9 (60)	6 (40)	
Seeks for information about disease and treatment elsewhere:	133 (52)	60 (46)	71 (54)	0.538
Source of information seeked elsewhere (multiple responses allowed):				
In books	53 (21)	22 (42)	30 (58)	0.147
Friends (including friends who are health professionals)	84 (33)	39 (48)	43 (52)	0.377
Research articles	36 (14)	13 (36)	23 (64)	0.055
Pharmaceutical promotional materials	12 (5)	4 (33)	8 (67)	0.372‡
Online	105 (41)	43 (41)	61 (59)	0.010
Medical lay journals	19 (7)	6 (32)	13 (68)	0.080
Online searching tools used:				
Internet search engine (Google or similar)	107 (42)	44 (42)	62 (59)	0.251
<i>www.zdravlje.hr</i>	24 (9)	12 (50)	12 (50)	0.317
<i>www.clinicaltrials.gov</i>	6 (2)	1 (17)	5 (83)	0.232‡

*The numbers for men and women do not always add because of missing data. The numbers in brackets for man and women are row percentages, and numbers in brackets for the Total are the percentage of all respondents.

†Chi-square test.

‡Fisher's exact test.

Table 5. Patient's awareness of clinical trials*

	Total (No., %) (N=257)	Men (No., %) (N=117)	Women (No., %) (N=137)	P†
Aware of clinical trials	169 (66)	80 (48)	88 (52)	0.425
Informed about possible participation in clinical trials	38 (15)	24 (63)	14 (37)	0.017
Informed about possible participation in clinical trials by:				
Physician	31 (12)	20 (65)	11 (36)	0.316
Pharmacist	6 (2)	3 (50)	3 (50)	0.669‡
Family member/friend	10 (4)	4 (40)	6 (60)	0.156‡
Patients' association	6 (2)	5 (83)	1 (17)	0.378‡
Willingness to try new treatments	149 (58)	74 (50)	74 (50)	0.147
Participated in clinical trials	15 (6)	8 (53)	7 (47)	0.338

*The numbers for men and women do not always add because of missing data. The numbers in brackets for man and women are row percentages, and numbers in brackets for the Total are percentage of all respondents.

†Chi-square test.

‡Fisher's exact test.

Table 6. Patients' responses according to the place of survey*

	City family medicine office (N=87)	Island family medicine office (N=31)	Hospital oncology department (N=52)	Patients' associations (N=55)	On- line patient survey (N=32)	P†
Gender (No.)						
Male	42/87	14/30	22/52	23/55	16/30	0.825
Female	45/87	16/30	30/52	32/55	14/30	
No. of appointments with physician per year (median, IQR)	2 (3)	2 (2)	13.5 (20)	3 (3)	3.5 (3)	<0.001‡
Seeks for information about disease and treatment elsewhere (No.)	38/81	19/31	26/51	30/54	20/29	0.272
Willingness to try new treatments (No.)	46/79	13/29	32/46	33/55	25/29	0.014§
Awareness of clinical trials (No.)	43/85	17/30	35/48	46/53	28/29	<0.001#
Informed about possible participation in clinical trials (No.)	13/81	3/29	7/50	12/54	3/29	0.598
Participated in clinical trials (No.)	5/82	1/31	0/50	7/53	2/29	0.060

*Data as presented as the number of responses/total responses for the question.

†Chi-square test or Fisher's exact test for comparisons including cell frequencies less than five. Bonferroni adjustment for all post hoc analysis was set to the significance threshold of $P=0.01$.

‡Kruskal-Wallis test and post-hoc analysis (Mann Whitney U test): Hospital oncology department group vs all other survey places ($P<0.001$).

§Post-hoc analysis: Online-patient survey group vs Island family practice group ($P=0.001$), City family medicine office group ($P=0.007$) and Patients' association group ($P=0.014$).

Post-hoc analysis: City family medicine office group vs Patients' association group ($P<0.001$); Hospital oncology department group ($P=0.012$) and On-line patient survey group ($P<0.001$); Island family medicine office vs Patients' association group ($P=0.002$) and On-line patient survey group ($P<0.001$); Hospital oncology department group vs On-line patient survey group ($P=0.009$).

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