Annals of Research in Oncology
Vol. 2(1), 76-84, 2022

BRIEF REPORT

ACCESS TO EARLY PHASE CLINICAL TRIALS AT THE TIME OF THE COVID-19 PANDEMIC: AN ITALIAN SURVEY

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Doi: 10.48286/aro.2022.38

History

Received: Jan 27, 2022
Accepted: Feb 16, 2022
Published: Mar 1, 2022

ABSTRACT

Italy was among the first countries hit by the pandemic of coronavirus disease 2019 (COVID-19). The application of strict lockdown measures disproportionately affected both cancer patient care as well as cancer research.

A survey was conducted among Italian oncologists to explore whether and how the COVID-19 outbreak has changed their aptitudes and practice toward early phase studies before and during the COVID-19 outbreak and suggestions to overcome the early phase clinical trial limitation in our country.

A total of 137 physicians completed the survey. In the pre-pandemic period, 103 responders (75.2%) declared a positive aptitude at referring their patients to early phase unit but only 12.6% referred more than 10% of their patients. Of these, 35% declared a reduction in this aptitude during the pandemic period. The majority of responders believe that the COVID-19 pandemic will affect the new oncological drug's marketing (62.3%). Over the COVID-19 pandemic, the majority of participants highlighted the necessity of an "alliance" between leader and satellite centers (59.8%), making the early phase unit distribution's homogeneous on the national territory (37.2%).

Our work provides an overview of the impact of the COVID-19 outbreak on aptitude at referral to early phase clinical studies among Italian oncologists.

KEY WORDS

COVID-19; survey; early phase studies; Italian oncologist; AIOM.

IMPACT STATEMENT

These data offer a snapshot of the aptitude at referral to early phase clinical studies during COVID-19 outbreak.

INTRODUCTION

Since the beginning of 2020, the coronavirus disease 2019 (COVID-19) pandemic has progressively affected millions of people worldwide and has disrupted many aspects of clinical care. According to the World Health Organization (WHO), as of October 20 2021, there were 241.411.380 confirmed cases of COVID-19, including 4.912.112 deaths (1).
Several evidences highlighted a higher risk of death from COVID-19 for cancer patients (2-6). During the first wave of the pandemic, all levels of care (screening, diagnosis, treatment, and follow-up) were disrupted. Moreover, cancer centres started prioritizing care services, cancelling non-urgent appointments, adapting treatment protocols, and shifting to home-based remote care relying on telemedicine consultations (4, 7).
Clinical research was affected by several aspects. Due to the difficulties generated by lockdown conditions, several trials have been interrupted or stopped with a substantial reduction of 74% of patients enrolled in clinical trials in May 2020 compared with the same period in 2019 (8). Concurrently, the reorientation of human and economic resources towards COVID-19 research has further affected clinical trial research. All of these aspects, the disruption and the fast, effective readjustment to address a new challenge, will lengthen the effects of the COVID-19 pandemic on clinical trials research for long after the initial effects have faded (9).
In a communitarian effort, many societies such as the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) published recommendations to provide practical guidance for oncologists and patients. However, this crisis also highlighted the shortcoming of the clinical trial conduction and the need to optimize the bureaucratic system and the use of resources in clinical research (10-12).
Even before the COVID-19 pandemic, important barriers affected the conduct of clinical trials and the changes implemented due to the COVID pandemic were mandatory by the need to ensure the safety of patients, clinical researcher and staff (13, 14).
In this paper, we aim to photograph the aptitude to refer patients at early phase clinical studies among Italian oncologists, the impact of the COVID-19 pandemic on that aptitude and use them as a stimulus to launch a discussion over a framework of broader adaptations needed in the design and implementation of oncology clinical trials in our Country.

METHODS

A specific online questionnaire was sent by e-mail throw the institutional mailing list to all members of the Italian Association of Medical Oncology (AIOM) on May 11, 2021. The survey was open access and was also available to members through the AIOM website and social media channels. Participation was voluntary and anonymous. To deploy the questionnaire rapidly and for very fast data collection, a web-based modality was chosen. The Google Forms platform was chosen to implement the survey, and responses were automatically stored in a database built with Excel (Microsoft Office).
The survey was proposed to physicians involved in clinical oncological activities in both academic and clinical centres. Twenty questions were asked, including multiple-choice, closed- and open-ended questions and were divided into 4 different sections: 1) demographic, medical training and employment information (questions 1-8); 2) aptitudes and practice toward early phase studies before the COVID-19 outbreak (questions 9-11); 3) aptitudes and practice toward early phase studies during the COVID-19 outbreak (questions 12-17); 4) aptitudes and practice toward early phase trials and research activities regardless of the COVID-19 outbreak and suggestions to overcome limits highlighted (questions 18-20). The questionnaire was composed of 20 questions: 65% closed answers with single-choice selection (n = 13) and 35% open

questions with free-text response possibilities (n = 7) (**Supplementary survey**). Responses were described as frequencies and percentages. Statistical analyses were done with SPSS for Windows, version 27.0.

RESULTS

A total of 137 physicians completed the survey. Responses were collected between 11 May and 17 July, with 69% of responses registered in the first 72 hours. The majority were medical oncologists (124/137, 90.5%). Most of the respondents were female (74/137; 54%), aged between 30 and 45 years old (78/137; 57%) and worked in Northern Italy (64/137; 47%). The most common places of work were university hospitals (43/137, 31%) and specialised cancer centres (39/137, 28.5%) (**table I**).

Out of 137 responders, 49 (35.7%) worked in a dedicated Early Phase Unit Trial at the time of survey compilation. The disease of interest was lung cancer for 49 responders (35.8%) followed by gastrointestinal cancer (47/137, 34.3%) and breast cancer (43/137, 31.4%) (**supplementary figure 1**).

Clinicians were asked to compare their aptitude to refer patients at phase I clinical trial Units in the pre-pandemic and pandemic period. One hundred-three responders (75.2%) declared a positive aptitude to refer their patients to early phase Unite in the pre-pandemic period of which only 12.6% (13/103) referred more than 10% of their patients (**figure 1**).

CHARACTERISTICS OF RESPONDERS		
	N = 137	%
Gender		
Male	63	54
Female	74	46
Age		
≤ 30 years old	9	6.6
> 30 - ≤ 45 years old	78	56.9
< 45 years old	50	36.5
Italian geographical area of work		
Northen Italy	64	46.7
Central Italy	60	43.8
Southern Italy	23	9.5
Work setting		
University hospitals	43	31.4
Specialised cancer centres	39	28.5
General hospital	33	24.1
Private centre	9	6.5
Territorial medicine	13	9.5

Table I. *Demographic, Working regions, and Employment Information of the Responding Oncologists.*

This aptitude is widespread among all responders and no difference was observed among different subgroups. In fact, we observed a high aptitude of referral regardless of sex (male 74.6% and female 75.6%), age (≤ 45 years old 75.9% and > 45 years old 74%), geographic work area (78% north, 68% centre, 82.6% south) and place of work (university hospital 79%, specialised cancer centre 82%, general hospital 72.7%, private centre 77.7% and territorial medicine 46.15%). Among those who usually did not refer patients to an early phase clinical trial Unit (34/137, 24.8%), 44.1% (15/34) do not have a nearby centre or do not know how to contact the trial Unit and 38.2% (13/34) declare difficult contact with the early phase units that make it difficult to update which studies are open and with active enrolment.

Out of 103 participants that usually refer patients to the early phase Unit, 35% (36/103) declared a reduction in this aptitude during the pandemic period. Of these responders, 91.7% (33/36) correlate this reduction with the difficulties related to early phase trial conduction during pandemic (*i.e.*, difficult to reach the dedicated centre, the necessity of multiple visits to the hospital or to oncological centres that increase the infection risk and fewer trials available). Moreover, half of the physicians (15/36) declared a difficulty related to pandemic implication and change in professional duties (*i.e.*, increase in care load, involving COVID-19 clinical activities).

In the last section, we investigated implications for early phase and drug development after the COVID-19 outbreak and suggestions to overcome the limits of an early clinical trial in our Country. Out of 137 responders, thirty-eight (27.7%) believed that the COVID-19 pandemic will not affect the new oncological drug's marketing. The remaining parts believed that there will be a substantial delay due to the fewer patients enrolled and the delay of the early-phase trial (44/137, 32.1%) or fewer studies opened in this period (28/137, 20.4%) or for the use of technical and financial resources to face the pandemic (32/137, 23.4%). Interestingly, a sizable fraction of researchers believed that more than 12 months would be necessary to return to the pre-pandemic levels in terms of clinical research in oncology (55/137, 40.1%) (**supplementary table I**).

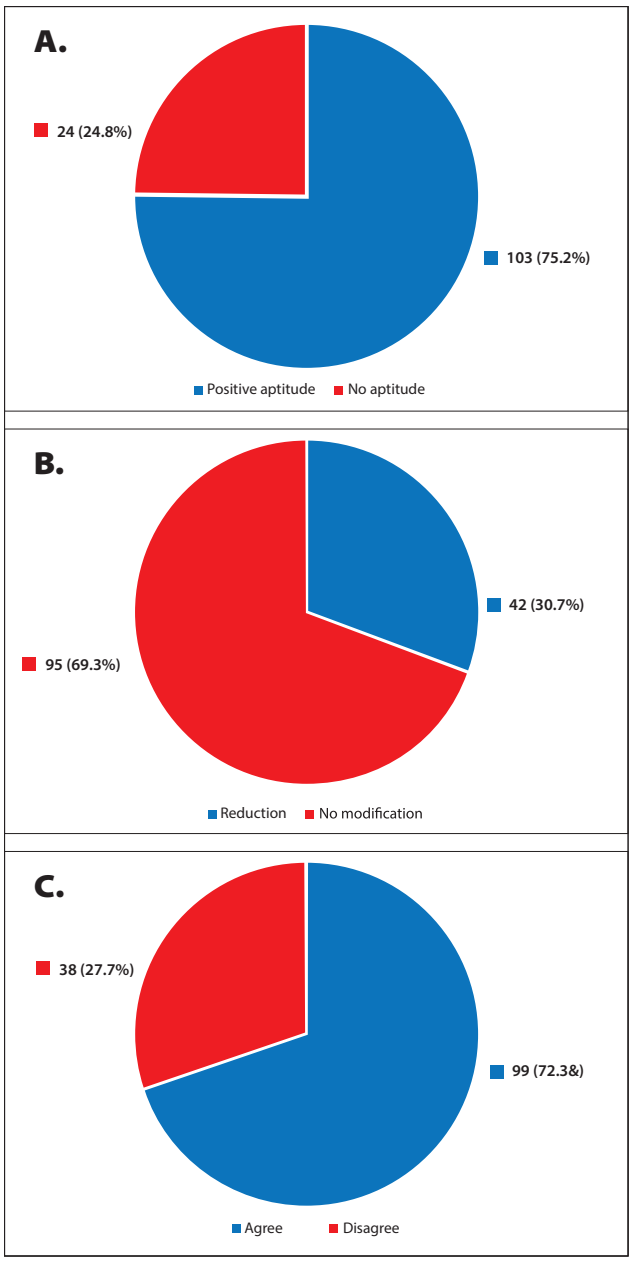

Figure 1. A. *pre-pandemic aptitude at referring patients to early phase clinical trials;* **B.** *modification in the physicians' aptitude at referring during pandemic;* **C.** *Concerned that COVID-19 will negatively affect drug-marketing authorization in the new years.*

The majority of participants highlighted the necessity of an "alliance" between leader and satellite centres (82/137, 59.8%), making the early phase Unit distribution's homogeneous on the national territory (51/137, 37.2%) and improving telemedicine to reduce visits (38/137, 27.7%) (**supplementary table II**).

DISCUSSION

This survey provides evidence on a diffuse, positive aptitude of Italian oncologists for referring patients' to early phase clinical trials. This tendency was distributed homogeneous among responders and it was independent of sex, age and working region or setting.

Nevertheless, we noted that, although this aptitude is rather diffuse among physicians, the percentage of patients usually referred to early phase clinical trial units is limited with only 12.6% of responders referring more than 10% of their patients. Numerous reasons could explicate these data, but one of the most important reasons is the asymmetric distribution of Phase I centres on national territories, and the ongoing phases I study concentrated in a few locations (15, 16). Furthermore, in a classification considering the phase I trials conducted worldwide between 1999 and 2020, Italy ranks only 14th position, following other similar European countries (*i.e.*, Germany, France, Spain, and the Netherlands) (17). The low availability of studies in our country and the logistical difficulties associated with an uneven distribution limit the number of patients that could enter an early phase trial. COVID-19 outbreak has disrupted all aspects of health care worldwide with a particular impact on oncological care and clinical trial (2-4). We did not know the long-term implications of this emergency situation but the majority of responders believe that the COVID-19 pandemic will negatively affect the new oncological drug's marketing with a large part of researchers believing that more than 12 months will be necessary to return to the pre-pandemic levels in terms of clinical research in oncology.

Nevertheless, only a minority of physicians declared a reduction in referring aptitude during the pandemic period. In our national context, we may speculate that this correlates with an "a priori" extreme selection whereby only very fit patients that could effort the logistic, economic and social difficulties related to early phase trials were referred, even in the pre-pandemic period. In this type of patient, the major exposition risk derived from a hypothetical inclusion in a phase I/II study (*i.e.*, more visits and travel necessity to other medical centres) could be overcome by the hypothetical benefit derived from these studies.

In our opinion, interesting findings of our survey are enclosed in the fourth questions' group. In this part, responders highlighted the necessity to implement the "early phase system" sharing possible solutions to make it more effective. The vast major-

ity of responders identified the necessity of an "alliance" between the leader and "satellite" centres as a strategy to improve early-phase trial followed by the necessity of a homogeneous distribution of phase I centre on national territory and the suggestion of greater use of telemedicine. These suggestions emphasize the necessity of implementing this system in our country, which can increasingly offer valid therapeutic alternatives (18), making it more efficient even in crisis situations.

Our survey has some limitations. It focused only on the aptitudes and practices of Italian oncologists toward early phase trials, which may explain the relatively low response rate. This could also explain the highest percentage of responders that work in a phase I Unit (35,7%). Moreover, the survey was compiled by oncologists working in different regions with heterogeneous hospital organizations and a different COVID-19 outbreak spread.

Nevertheless, the lack of significant differences in the aptitudes and practice between oncologists' subgroups highlights the global impact of this health care emergency irrespective of the actual burden of the COVID-19 outbreak in each respondent's hospital. Moreover, the necessity to implement early phase trials and some of the proposed solutions are also shared by other researchers (19, 20).

In conclusion, this survey provides evidence of the impact of the COVID-19 outbreak on aptitude at referral to early phase clinical studies among Italian oncologists. We highlighted the necessity to introduce many operational efficiencies in clinical trials some of which were already implemented to face the COVID pandemic. However, this is an opportunity to make permanent improvements in clinical trials, even in early phase clinical trials.

ETHICS

Fundings

There were no institutional or private fundings for this article.

Conflict of interests

AP worked at AstraZeneca Medical Affair Division from March 2015 to December 2018 and received personal fee from GSK. SD worked at AbbVie Medical Affair Di-vision from July 2017 to March 2020. GS has served on advisory boards for TESARO Bio Italy S.r.l, Johnson & Johnson, Clovis Oncology Italy S.r.l. He received support for travel or accommodation from MSD Italy S.r.l and Clovis Oncology Italy S.r.l, and institutional research funding from MSD Italy. S.r.l. GD has served on advisory board of Beigene and received sup-port for travel and accommodation from Roche. PL, RF, MF, VA, RG and FPS indicated no conflicts of interests.

Availability of data and materials

Available just before a reasonable request.

Authors' contribution

Conceptualization, PL, RF and MF; methodology, GD; formal analysis, PL; writing original draft preparation, PL, RF, MF and VA; writing review and editing, all authors. All authors have read and agreed to the published version of the manuscript.

Ethical approval

N/A.

Consent to participate

N/A.

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SUPPLEMENTARY MATERIALS

Supplementary survey. Impact of the COVID-19 pandemic on early stage clinical trials

Early phase clinical trials (phase I and II) represent one of the most critical moments in the development of new drugs, requiring intensive clinical monitoring in the face of an uncertain benefit for the patient. With this survey we would like to evaluate the impact of the COVID-19 pandemic in the propensity to refer patients to centers that conduct early phase clinical trials and how this may affect future clinical practice.

1. How old are you?
- ☐ < 30 years
- ☐ between 30 and 45 years
- ☐ > 45 years old

2. Gender
- ☐ Man
- ☐ Woman
- ☐ Not binary
- ☐ I'd rather not answer

3. In which center do you work?
- ☐ Local Health Service
- ☐ General Hospital
- ☐ Private Clinic
- ☐ Scientific Institute for Research, Hospitalization and Healthcare (IRCCS)
- ☐ University Hospital

4. In which territorial area of Italy do you work?
- ☐ North
- ☐ Center
- ☐ South

5. Specify the region:
- ☐ Valle d'Aosta
- ☐ Piedmont
- ☐ Liguria
- ☐ Lombardy
- ☐ Trentino Alto Adige
- ☐ Veneto
- ☐ Friuli Venezia Giulia
- ☐ Emilia Romagna
- ☐ Tuscany
- ☐ Umbria
- ☐ Lazio
- ☐ Marche
- ☐ Abruzzo
- ☐ Molise
- ☐ Campania
- ☐ Basilicata
- ☐ Puglia
- ☐ Calabria
- ☐ Sicily
- ☐ Sardinia

6. What is your medical specialization?
- ☐ Oncology
- ☐ Radiotherapy
- ☐ Gynecology
- ☐ Pulmonology
- ☐ Pediatrics
- ☐ Endocrinology
- ☐ Gastroenterology
- ☐ Other:

7. Do you have a focus on a particular cancer type? (multiple choice possible)
- ☐ Breast
- ☐ Lung
- ☐ Gastro-intestinal
- ☐ Genitourinary
- ☐ Melanomas and other skin cancers
- ☐ Gynecological
- ☐ Head-neck
- ☐ Endocrinological tumors
- ☐ Rare tumors
- ☐ Pediatric tumors
- ☐ I have not a specific a specific focus

8. Do you work in an early stage clinical trials unit?
- ☐ Yes
- ☐ No

9. Before the COVID-19 pandemic, did you generally refer your patients to early stage clinical trials?
- ☐ Yes
- ☐ No

10. If "YES", to what extent?
- ☐ < 1%
- ☐ between 1% and 5%

- ☐ between 5% and 10%
- ☐ more than 10%

11. If "NO", why? (multiple choice possible)
- ☐ I am not updated on the status of early phase clinical trials
- ☐ I have no reference centers nearby
- ☐ I don't have contacts with the reference center
- ☐ I think that early phase studies have not clinically significant benefit
- ☐ Other:

12. Has the pandemic changed your attitude to referring patients to early stage clinical trials?
- ☐ Yes, I refer less patients
- ☐ Yes, I refer more patients
- ☐ No

13. If "YES, I refer less patients", why? (multiple choice possible)
- ☐ I treat less cancer patients than the pre-pandemic outbreak
- ☐ I was working in departments dedicated to the COVID-19 emergency
- ☐ There is less availability of early phase clinical trials
- ☐ More logistical difficulties for patients due to measures to limit the spread of the virus
- ☐ Early phase studies require excessive medicalization in a pandemic era
- ☐ I select more cautiously patients to refer to early phase studies
- ☐ During the pandemic the increase in the care workload has reduced the possibility of collaboration with other centers

14. If "YES, I refer less patients ", What is the entity of reduction?
- ☐ Reduction < 25%
- ☐ reduction between 25% and 50%
- ☐ reduction between 50% and 75%
- ☐ reduction > 75%

15. If "YES, I refer more patients ", why? (multiple choice possible)
- ☐ Potentially superior treatment options are available compared to the standard treatment
- ☐ Centers with early phase clinical trials have "clean" pathways
- ☐ Other:

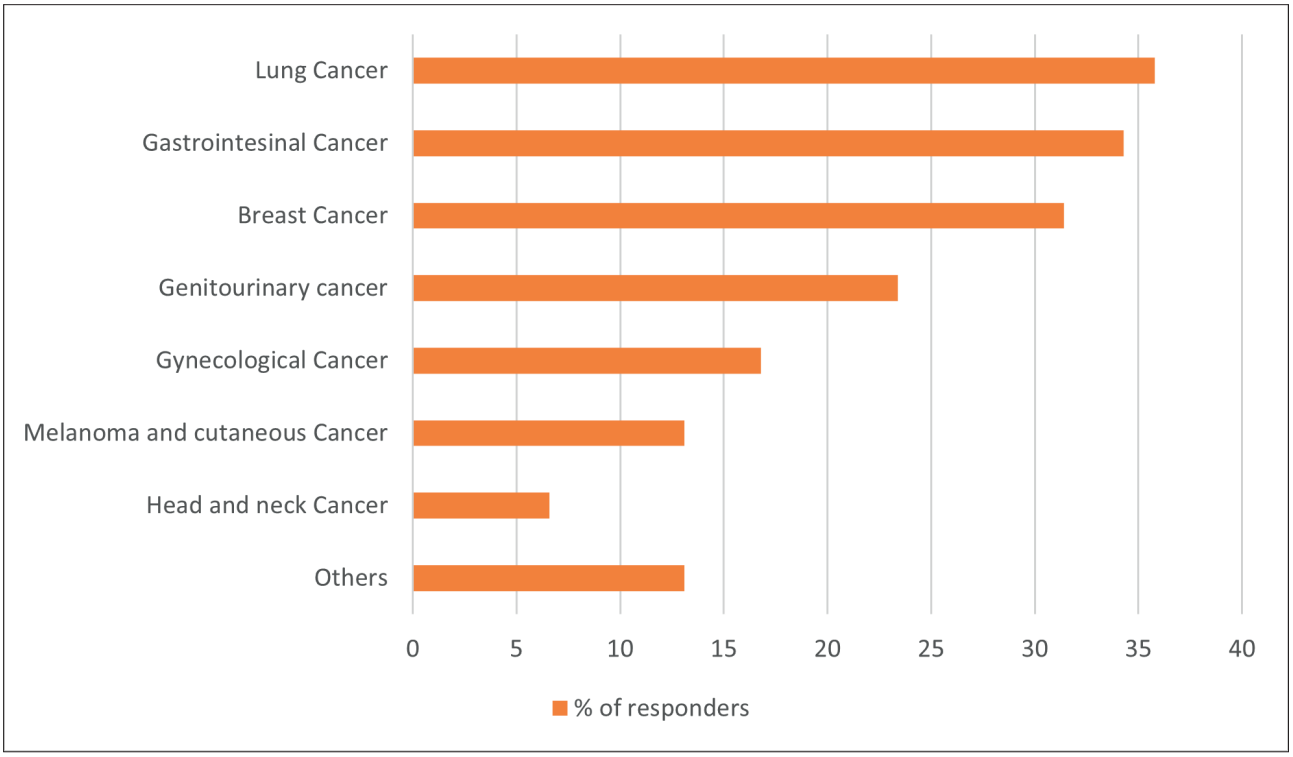
16. If "YES, I refer more patients", to what extent have you increased compared to the pre-pandemic attitude?
- ☐ increase < 25%
- ☐ increase between 25% and 50%
- ☐ increase between 50% and 75%
- ☐ increase > 75%

17. If "NO", why? (multiple choice possible)
- ☐ The pandemic has not changed my clinical practice
- ☐ The benefits of an early phase clinical trial outweigh the risks related to the pandemic
- ☐ I work in a center with an early phase Unit
- ☐ Other:

18. How long do you think it will take to return/go back to a pre-pandemic level?
- ☐ Within 6 months
- ☐ Between 6 and 12 months
- ☐ In more than 12 months
- ☐ I don't think there are any differences with the pre-pandemic period

19. How do you think we could facilitate patients' access to early phase clinical trials? (multiple choice possible)
- ☐ Thinking back to a homogeneous territorial distribution of early stage centers
- ☐ Establishing alliances between main centers and satellite centers
- ☐ By encouraging the use of telemedicine to reduce hospital visits
- ☐ Other:

20. Do you think the COVID-19 pandemic could have an impact on the development and availability of new drugs in the coming years? (multiple choice possible)
- ☐ Yes, because I believe fewer studies have been opened and we will have fewer drugs available
- ☐ Yes, because I believe that fewer patients have been enrolled and it will take longer for new drugs to become available in clinical practice
- ☐ Yes, because most of the resources have been devoted to research on COVID-19
- ☐ No, I don't think there will be an impact in the next few years



Supplementary figure 1. *Diseases of interest among responders.*

	N = 137	%
Do you think the COVID-19 pandemic could have an impact on the development and availability of new drugs in the coming years?		
No, I don't think there will be an impact in the next few years	38	27.7
Yes, because I believe fewer studies have been opened and we will have fewer drugs available	28	20.4
Yes, because I believe that fewer patients have been enrolled and it will take longer for new drugs to become available in clinical practice	44	32.1
Yes, because most of the resources have been devoted to research on COVID-19	32	23.4

Supplementary table I.

	N = 137	%
How do you think we could facilitate patients' access to early phase clinical trials?		
Thinking back to a homogeneous territorial distribution of early stage centers	51	37.2
Establishing alliances between main centers and satellite centers	82	59.8
By encouraging the use of telemedicine to reduce hospital visits	38	27.7

Supplementary table II.