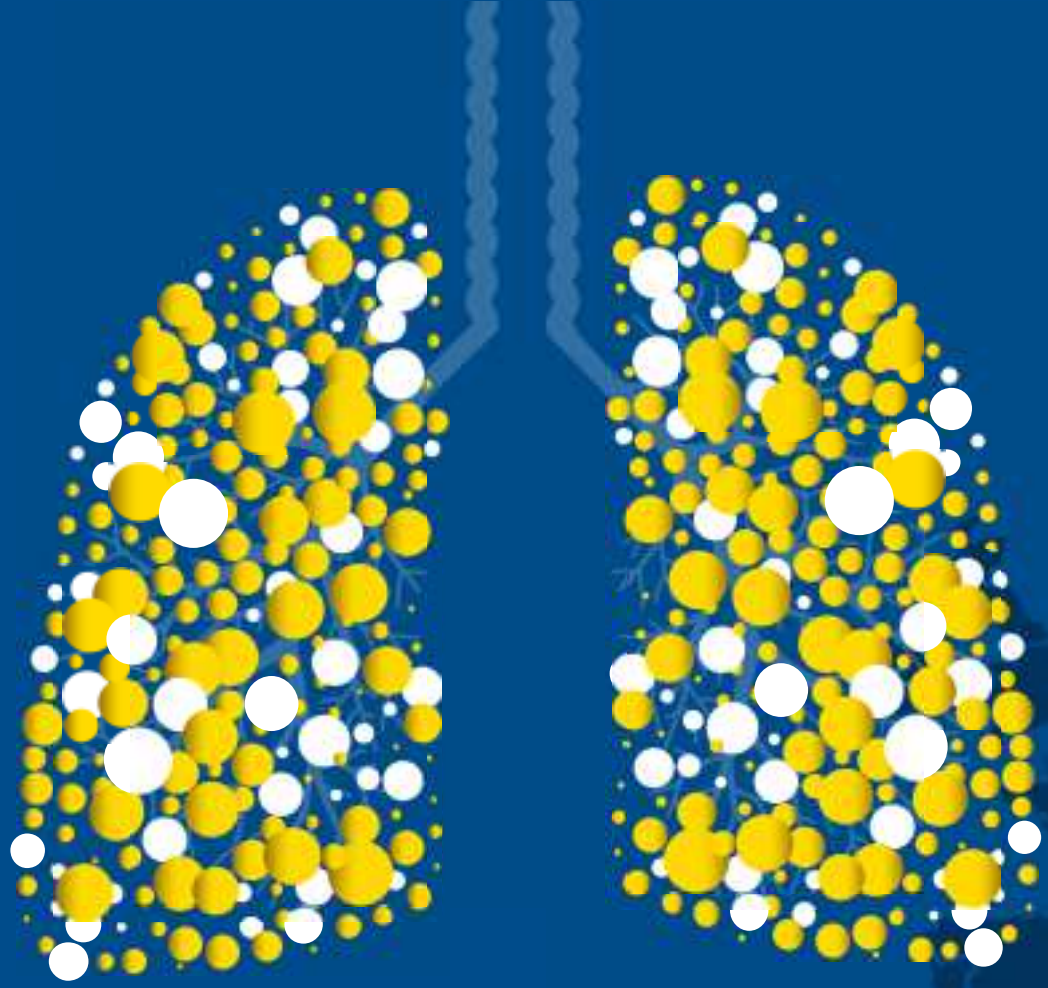


III LuCE REPORT ON LUNG CANCER

CHALLENGES IN LUNG CANCER CLINICAL TRIALS

Lung Cancer Europe

III LuCE REPORT ON LUNG CANCER

CHALLENGES IN LUNG CANCER CLINICAL TRIALS

NOVEMBER 2018

This report is dedicated to all people with lung cancer, especially those who have participated in a clinical trial. Thanks to them, we have better treatments today. Their participation and generosity have given hope to thousands of patients and families.

We will never forget the contribution they have made to research and to improving the health of patients with lung cancer.

Significant strides have been made in improving the diagnosis, treatment and care of patients with lung cancer, however survival rates remain poor and vary widely across Europe. Currently, over 1,000 of our loved ones die from this disease each day in Europe alone and numbers are projected to rise considerably within the next decade. Therefore it is imperative that we work together at the European level to continue to improve outcomes for patients diagnosed with lung cancer and their families.

Substantial developments have been made in recent years, with the advent of both targeted and immune based therapies. It is hoped that this progress will transform the lives of patients with lung cancer, meaning that our loved ones are not only living longer but are also doing so with a better and improved quality of life. We must continue this momentum for the discovery of innovative treatments by developing clinical trials suitable for all patients with lung cancer. In parallel, it is vital that we identify and address the barriers that prevent patients from accessing clinical trials. The aim of our 3rd LuCE report is to gain a better insight in to the clinical trial experience from a patient perspective and improve our understanding of patients' awareness and attitudes towards clinical trials.

A number of barriers exist in accessing lung cancer clinical trials not only across Europe but also within individual countries. These obstacles are multifaceted and exist at a protocol, clinical and patient level. At a protocol development stage, care must be taken to adequately assess the needs and concerns of patients eligible to enrol in a clinical trial, in terms of anxiety, quality of life, wash out periods, and the number of scans and follow up investigations that patients are subjected to while participating in a clinical trial. In tandem, the eligibility criteria must be expanded to allow for the inclusion of the older lung cancer population and those with a poorer performance status. Trials must be developed in concert with appropriate biomarkers and diagnostic tests to ensure that only those patients who will benefit from a drug will receive it. Clinically, it is essential that health care systems invest in infrastructure and staff, and adapt to ensure more dedicated clinical trial units are able to open and enrol patients on trials. It is critical that clinicians are aware of active clinical trials and keep patients informed.

Protocol and clinical barriers aside, patients can face a multitude of additional access issues. The stigma endured by patients with lung cancer, can result in non-engagement with the health service in terms of diagnostics and treatment, including clinical trials. A lack of knowledge and understanding of what a clinical trial is, and what trials may be available are also key issues that must be addressed. Patients must be empowered by awareness campaigns and their clinical team, to find out what participation in a clinical trial might mean for them. Other barriers include geographical issues and country borders; issues related to the cost of health care; travel to and from appointments, particularly if a great distance is involved; fear of delay in getting treatment; anxiety regarding potential side effects; and a lack of support services when a clinical trial ends.

Barriers must be overcome to ensure access to clinical trials for all patients with lung cancer

Much attention and focus is given to the idea of patient centred care. For patients this has to be more than just words. It must have a real world impact on their day-to-day lives. This includes access to, and experience of clinical trials. Patients need to have a seat at the table at the stage of protocol design and development, to enable their voices to be heard. Policy makers and trial development teams must not forget that patients living with lung cancer and their families, are the most important stakeholders. They must do everything in their power to improve clinical trial access. At the end of clinical trials, we must bridge the gaps in our health care systems to ensure rapid access to innovative drugs and companion diagnostics/genetic tests developed based on the results of clinical trials.

We want to see a future where clinical trial access is an integral part of the patient care pathway, and all patients with lung cancer have access irrespective of their socio-economic status or geographical location.

Anne-Marie Baird
Patient Advocate and Board Member of Lung Cancer Europe

Table of contents

1. ABOUT THIS REPORT

Welcome to the 3rd edition of the LuCE Report. This report is an annual initiative led by lung cancer patient organisations, with the purpose of raising awareness about the biggest challenges that patients across Europe face.

This 3rd report focusses on clinical trials and welcomes the progress made in lung cancer treatment in recent years. However, it also seeks to highlight some of the challenges still faced regarding research. These challenges include lack of funds, time delays, recruitment barriers, absent research areas and a lack of knowledge and awareness by both patients and healthcare professionals. These aspects are some of the priorities that must be addressed in order to improve the quality of, and access to lung cancer clinical trials.

In this report, we present data regarding lung cancer clinical trials and show valuable information provided by patient advocates, lung cancer experts and, of course, patients with lung cancer from across Europe. Thanks to these participants, we have been able to provide a bigger and clearer picture of the current situation, as well as better define our priorities in lung cancer research.

We believe that working together and focussing on the reality and needs of patients is the best way to address these issues. Therefore, we encourage you to read this report and to carefully consider the patient insight provided regarding the medical research and development process.

We also encourage you to access our previous reports so as to better understand our position on the most relevant challenges for people with lung cancer.

You can access both reports here:

1st Report:

www.lungcancereurope.eu/wp-content/uploads/2017/10/LuCE-Report-final.pdf

2nd Report: :

www.lungcancereurope.eu/wp-content/uploads/2017/11/II-LuCE-Report-web-version.pdf

METHODOLOGY

This report provides a description and analysis of the challenges in lung cancer clinical trials from a patient perspective. This report mainly focuses on the situation in Europe, however, we believe that most of the data could be applied to other parts of the world. These data were obtained from different information sources from February to September 2018.

a) Desktop research of primary and secondary policy sources

Objective: To explore and identify relevant data and evidence on lung cancer clinical trials. This research was also used to design the different surveys we used to collect data for this report.

- Research was conducted mainly in English.
- See the list of references at the end of the report.

b) Online survey for lung cancer patient advocates in Europe

Objective: To explore the knowledge and opinion of the advocacy community as regards the current situation of lung cancer clinical trials primarily in Europe and around the world, identifying challenges and opportunities.

- Respondents were patient advocate members of Lung Cancer Europe (LuCE).
- The survey was given to LuCE members (20 patient organizations and NGOs) in April 2018. Each organization could only complete one survey. After two months, we collected 13 responses from 12 different countries, which represented 65% of the total number of our members.
- See this survey and details of the sample in Appendix I.

c) Qualitative interviews with specialists in lung cancer research

Objective: To delve into the main challenges of lung cancer clinical trials, and to access specialized data and detailed knowledge in order to better understand the current research landscape.

- Interviewees from scientific and patient advocacy communities and the pharmaceutical industry.
- Number of interviews: 15 (completed between May to August 2018).
- See this survey and details of the sample in Appendix II.

d) Online survey for patients with lung cancer

Objective: To explore the level of knowledge, perceptions, experiences and expectations regarding clinical trials from patients with lung cancer across Europe.

- Respondents were people diagnosed with lung cancer.
- Number of respondents: 262 (collected between June and July 2018).
- Survey was translated into 10 languages: Dutch, English, Finish, French, German, Italian, Norwegian, Polish, Romanian and Spanish.
- See this survey and details of the sample in Appendix III.

HAVE YOU SEEN THIS SYMBOL IN THE TEXT?

IF SO, THIS INDICATES ONE OF THE TOP-PRIORITY CHALLENGES OF LuCE

2. LUNG CANCER CLINICAL TRIALS: A GLOBAL VISION

There has been **an improvement in lung cancer research in recent years, especially during the last decade,** according to all of the advocates and specialized medical professionals consulted. These advances and the high number of clinical studies in progress, provide clear evidence that the landscape of lung cancer treatment is evolving. These developments will result in new and improved therapeutic options for patients and lead to better outcomes. Thanks to advances in our understanding of the biology and molecular heterogeneity of lung cancer, new drug targets have emerged.

The experts and advocates consulted highlighted that **non-small cell lung cancer (NSCLC) has become one of the most focused on investigation areas in cancer research,** mainly due to better identification and understanding of the oncogenic drivers of NSCLC and to the characterization of the immunological properties of tumours. Much of the progress has been made in targeted therapy for advanced-stage patients with lung cancer with specific genetic mutations[1], which requires molecular testing as part of the diagnostic process. **Efforts are focused on identifying molecular markers for personalized medicine, as well as reducing resistance to these targeted therapies.**

INTRODUCTION OF IMMUNOTHERAPY CHANGED THE OUTCOME FOR MANY PATIENTS WITH METASTATIC, UNRESECTABLE/LOCALLY ADVANCED NSCLC.

GREG KORPANTY (MEDICAL ONCOLOGIST, IRELAND)

A large part of this progress has also been achieved due to immunotherapy for patients with NSCLC. This has changed the way we understand the immune system and how tumours hide from it. As a result, a lot of new treatments have been developed.

A lot of progress has also been made thanks to the combination of chemotherapy and immunotherapy, which has proven to be better for some patients than just using one or the other alone. Furthermore, researchers have discovered that some patients have a specific mutation, which can act as a driver that is responsible for the disease. For those specific patients, targeted therapy with tyrosine kinase inhibitors has been very effective. We must not forget that only chemotherapy was available for most patients up until a few years ago and its effectiveness was limited. So, overall, there has been progress in this field, which we

really welcome, as it has changed the treatment landscape and it has given hope to many patients with this disease.

WITH THE APPEARANCE OF TARGETED THERAPY IN THE EARLY 2000s AND THEN IMMUNOTHERAPY, WE HAVE SEEN AN IMPROVEMENT IN THE OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL OF OUR PATIENTS. THAT WAS DUE TO CLINICAL RESEARCH.

ANTONIO ARAUJO
(ADVOCATE AND MEDICAL ONCOLOGIST, PORTUGAL)

Research in lung cancer is ongoing. There are 6,390 lung cancer studies on clinicaltrials.gov (24 August 2018), of which 1,714 are underway in Europe and 400 of them are currently recruiting patients.

It is remarkable that **50% of the clinical trials on lung cancer are conducted in the United States of America.** The percentage in Europe is much lower (27%) and dramatically more so in Africa (1%) and South America (3%).

Many clinical trials are currently ongoing around the world, many of them focusing on genetic targets and systemic therapies. A review undertaken from 2004 to 2013 showed that the leading research types in lung cancer were genetics (20%), systemic therapies (17%), and prognostic biomarkers (16%). Significantly lower investment was made in diagnostics (4.3%), screening (1.8%) and quality of life (0.3%)[2].

Currently, most studies focus on immunotherapy and targeted therapies and, as the figure on the next page shows, disparities in trial sites is evident in Europe and around the globe. Western countries, like France, Italy, Spain, Germany or the United Kingdom, conduct the majority of trials in Europe, leading to enrolment disparities.

Source: www.clinicaltrials.gov (accessed 24 August, 2018)

Lung cancer clinical trials in Europe

COLOR INDICATE THE NUMBER OF STUDIES WITH LOCATIONS IN THAT REGION

LEAST MOST

Targeted therapy

Immunotherapy

Source: www.clinicaltrials.gov (accessed September, 2017)

Positive research related news - advances the standard of care, improves survival and provides patients with hope.

BUT THERE IS STILL A LOT TO DO.

LET´S TACKLE THE NEXT CHALLENGES TOGETHER!

3. CHALLENGES REGARDING LUNG CANCER CLINICAL TRIALS

3.1. Lack of research funding

Is lung cancer research underfunded? This question has long been asked. Despite the latest treatment advances, **lung cancer continues to be under researched and underfunded compared with other cancer types[3].**

Even though we recognize the progress that has been made over the years, investment in lung cancer research still remains lower than that made in other less-disease-burdening cancers. We must consider that, according to GLOBOCAN 2018, lung cancer remains the leading cause of cancer incidence and mortality, with 2.1 million new lung cancer cases and 1.8 million deaths predicted in 2018, representing close to 1 in 5 (18.4%) cancer deaths. In Europe, the average five-year survival rate for people with lung cancer is only 11.2% for men and 13.9% for women [6]. Despite this, it receives **only 5.6% of total cancer research funding [2].**

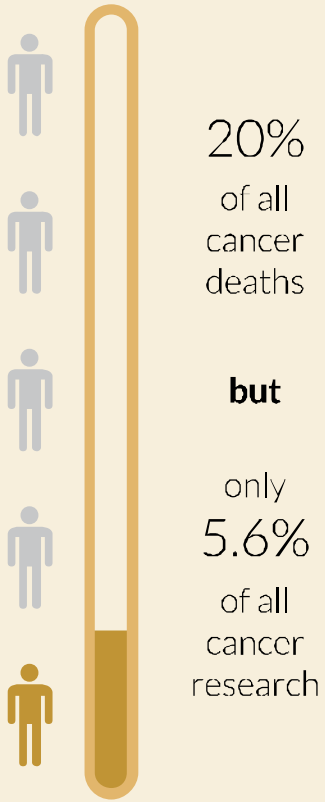
Considering the health, social and economic burden associated with lung cancer, the level of research output lags significantly behind that of research on other malignancies [2]. Therefore, we find that there is a weak correlation between the disease burden from the different cancers and the amount of research performed. For instance, a study found that the central nervous system was over researched in 2011–2013 (expected output 3129, observed output 5887; $p < 0.001$ on Poisson distribution with one degree of freedom) and lung cancer was significantly under researched (expected output 18,262, observed output 4271, $p < 0.001\%$) [3].

IN MOST COUNTRIES, LUNG CANCER RECEIVES THE LOWEST AMOUNT OF FUNDING COMPARED WITH OTHER COMMON CANCERS. FOR CLINICAL TRIALS, SOME IMPROVEMENTS HAVE BEEN MADE IN TERMS OF THE NUMBERS OF TRIALS AVAILABLE AND THE NUMBERS OF PATIENTS RECRUITED, BUT THESE ARE STILL NOT CLOSE TO OTHER CANCERS.

ANNE-MARIE BAIRD (ADVOCATE, IRELAND)

We urge the fostering of research and the reduction of these deaths. European health authorities have the responsibility

to foster innovation and allocate long-term funds for research so that we can improve patient outcomes. It requires greater investment in research centres and the formation of advanced biological and clinical data sets for research results [6].



Lung cancer is the main cause of cancer related deaths. It causes more deaths world-wide than breast, colon and prostate cancers combined.

Lung cancer is associated with the highest economic burden compared with other types of tumours.

But lung cancer receives only 7% of the funding breast cancer receives in the US (on a per-death basis), which is representative of the rest of the world [7].

THERE HAS BEEN A BIG IMPROVEMENT OVER THE YEARS, BUT I FEEL THAT IT IS STILL UNDERFUNDED. I BELIEVE THERE ARE SEVERAL AREAS REQUIRING FURTHER RESEARCH, INCLUDING EARLY DIAGNOSIS, ADVANCED DISEASE AND SUPPORTIVE AND PALLIATIVE CARE.

TOM HASWELL (ADVOCATE, UNITED KINGDOM)

There are different strategies to try to improve lung cancer research. We as patient advocates want to emphasize the importance of support from society. There are two main challenges/opportunities relating to raising awareness on the importance of obtaining more investment for lung cancer clinical trials:

- **Public engagement around lung cancer**

  Population support is crucial in encouraging authorities and research promoters to show greater commitment to, and make bigger investments in lung cancer clinical trials. Our perception is that **there is still a low level of support from society,** despite the troubling statistics of lung cancer mortality rates. Thorough analysis is required to understand the reasons for this lack of support.

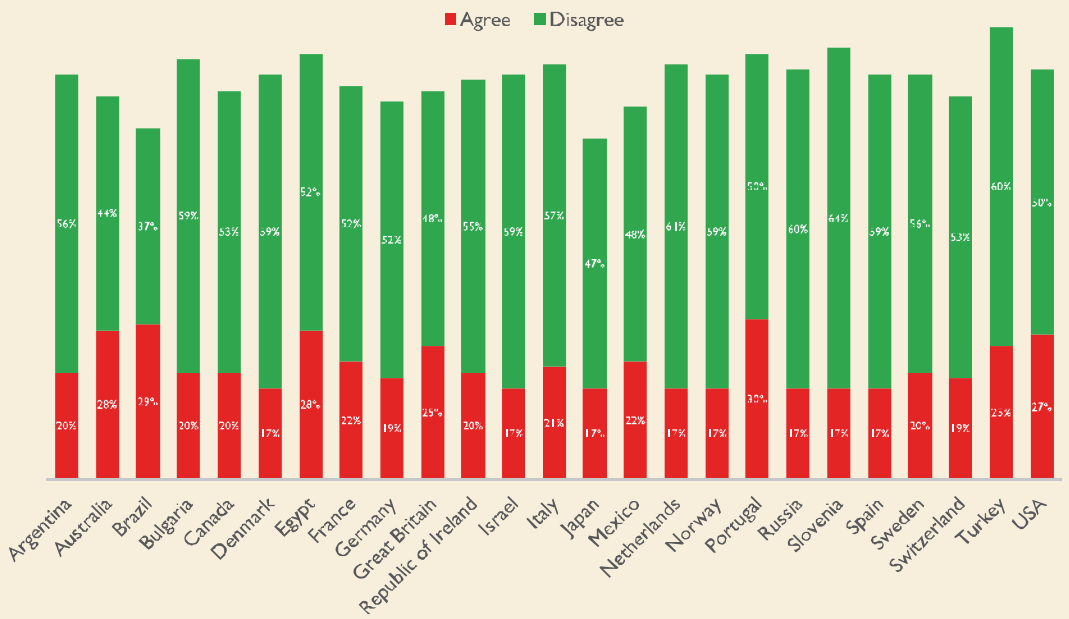
  According to a Global Lung Cancer Coalition (GLCC) report on `Symptom awareness and attitudes to lung cancer´, even when lung cancer is thought to be the cancer responsible for the greatest number of deaths in their country, **a significant percentage of the population feel less sympathy for people with lung cancer than people with other types of cancer[8].** According to the GLCC survey, one in five (21%) people agreed that they have less sympathy for people with lung cancer than other forms of cancer (see graphic in next page). At Lung Cancer Europe (LuCE), we believe that **lung cancer is highly stigmatized,** probably because these patients are often blamed as being responsible for their illness.

- **Strengthening the advocacy community for patients with lung cancer across Europe**

  We need advocates committed to supporting and representing the interests of other patients with lung cancer. LuCE is working to make the patient advocacy community stronger and to achieve policy changes that improve the lives of patients. However, the high **mortality rate and the high disease burden, as well as the stigma associated with the disease, do not facilitate the involvement of many patients in advocacy.**

  As such, **we ask for support to strengthen our network** across Europe and to be able to better advocate for change in the unfair allocation of resources for research and to obtain more investment in order to continue lung cancer studies.

Source: Global Lung Cancer Coalition (2017). Symptom awareness and attitudes to lung cancer. Findings from a global study.



Lung cancer is mainly caused by smoking cigarettes and other tobacco products. Bearing this in mind, to what extent do you agree or disagree with the following statement: "I have less sympathy for people with lung cancer than for people with other types of cancer". (excluding neither agree nor disagree)

SO MANY LUNG CANCER PATIENTS ARE OLDER AND FRAILER, AND THEY MAY HAVE FEWER FINANCIAL RESOURCES THAN OTHER PATIENTS. ALONG WITH THE TOTALLY UNFAIR STIGMA, I THINK LUNG CANCER PATIENTS' VOICES ARE EXPRESSED LESS FREQUENTLY AND HEARD LESS OFTEN THAN THE VOICES OF OTHER CANCER PATIENTS.

LINDA COATE
(MEDICAL ONCOLOGIST, IRELAND)

3.2. Research for specific patient groups

As we have previously highlighted, great progress has been made in lung cancer research, but it has been largely focused on non-small-cell lung cancer (NSCLC). Much of that progress relates to treatments for patients with specific genetic mutations.

We of course welcome such advances for these patient groups, but we also need to **pay attention to other patients that are not yet benefiting from these new treatment approaches.**

We asked our advocates and specialists which lung cancer subtypes require a greater research effort. We urge greater focus to be placed on the following three main patient groups:

- **Small-cell lung cancer (SCLC):** SCLC mortality rates remain very high, so we ask for more research investment to get more effective and safer treatments. We still need research to identify targeted treatments and therapeutic options post first-line.

- **Squamous carcinoma (SC):** There are few new treatments available for these patients and the number of clinical trials relating to this lung cancer subtype is very low compared to NSCLC.

- **K-RAS positive NSCLC:** This subgroup represents around 20% of all cases of NSCLC and has been highlighted by many of the experts consulted as one of the groups in which we need to dedicate more research effort.

Number of clinical trials (clinicaltrials.gov August 24th, 2018)

4,252 NSCLC	788 SCLC	201 SC

AT THE MOMENT, THERE'S A HUGE EFFORT IN NON-SMALL CELL LUNG CANCER AND I THINK SMALL CELL LUNG CANCER ALSO DESERVES A BIT MORE ATTENTION.

ROLF STAHEL (MEDICAL ONCOLOGIST, SWITZERLAND)

KRAS MUTATIONS, A WELL-RECOGNIZED BUT STILL "UNDRUGGABLE" TARGET, ARE OF HIGH INTEREST. IN THE FIELD OF I-O, THEY ARE CALLED AN "IMMUNOLOGICALLY COLD" NSCLC, TUMOURS WHICH DO NOT RESPOND TO CHECK-POINT INHIBITION AND REQUIRE A SMART-COMBINATION APPROACH.

VICTORIA ZAZULINA (PHARMACEUTICAL INDUSTRY)

3.3. Cooperation and patient involvement

Not all lung cancer clinical studies succeed or get the results expected. A trial can fail for different reasons: wrong hypothesis, recruitment failures, design mistakes, poor correlation between phases, etc. All of these factors can lead to clinical trials being rejected or, if approved, lacking effectiveness as regards the clinical use expected.

Patients are most interested in having timely access to safe and effective lung cancer treatments. Therefore, we are more prepared to contribute to research as collaborators with each day that goes by. Our personal experience, knowledge and data are what we call **patient evidence.** This patient evidence is **unique information that can be extremely valuable in researching and developing new medicines.** The value of patient involvement is increasingly recognized by all health care stakeholders and, even though the topic is quite unknown among many patients with lung cancer, 75% of patients consider the contribution as being positive, according to our survey.

But patients, as research collaborators, are not yet involved in clinical trials. Only 1 advocate out of the 14 consulted believed that patients are already involved, whereas 5 advocates believed that patients are rarely invited to collaborate and, if they are, it is at the end of the process when no major changes can be made. According to LuCE advocates, some of the reasons explaining the lack of involvement include undervaluing of patient input, worries about delay or protocol alteration, lack of research knowledge among patient advocates and shortfalls in human resources in patient groups.

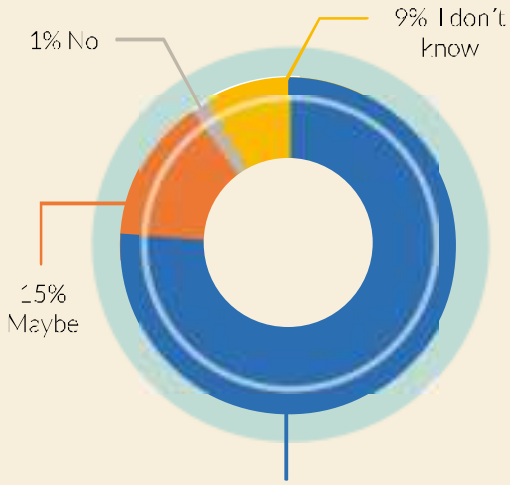
PATIENTS ARE NOT YET INVOLVED IN CLINICAL TRIAL DESIGN AND DEVELOPMENT IN FINLAND, BUT THE SITUATION IS CURRENTLY CHANGING, AS FUNDING AGENCIES FOR ACADEMIC RESEARCH REQUIRE ACTIVE PATIENT INVOLVEMENT.

MIRJAMI TRAN MINH (ADVOCATE, FINLAND)

PATIENT ADVOCATES IN

NOT OUT

Do you think it´s valuable for patients to work with researchers in the clinical trial development process?



75% of patients believe it's beneficial for patients to work with researchers in the clinical

According to our surveys and interviews, patient involvement can contribute to research in many different ways. We will now highlight what we consider to be the most relevant benefits of patient involvement in research and how we can contribute from the design stage to dissemination of results.

- **Sharing investigation priorities:** Patient experience can help to define what areas of investigation deserve more research time and resources.

- **Defining what is clinically meaningful for patients:** Selecting patient-oriented outcomes as a primary aim of the clinical trial. This is defined by others, but patients are the most appropriate stakeholder to explain the most meaningful aspects and the reasons why.

- **Defining better inclusion and exclusion criteria,** better adapted to real-world patients. Advocates can help to better define the sample because sometimes the desired patient population is far from the reality, which affects the possibility of recruiting patients.

- **Improving recruitment and retention:** Patient groups can help in recruitment processes, disseminating the ongoing trials among their communities and providing education about them. This is an appropriate way to eliminate stigma and myths associated with research, and to build trust among society.

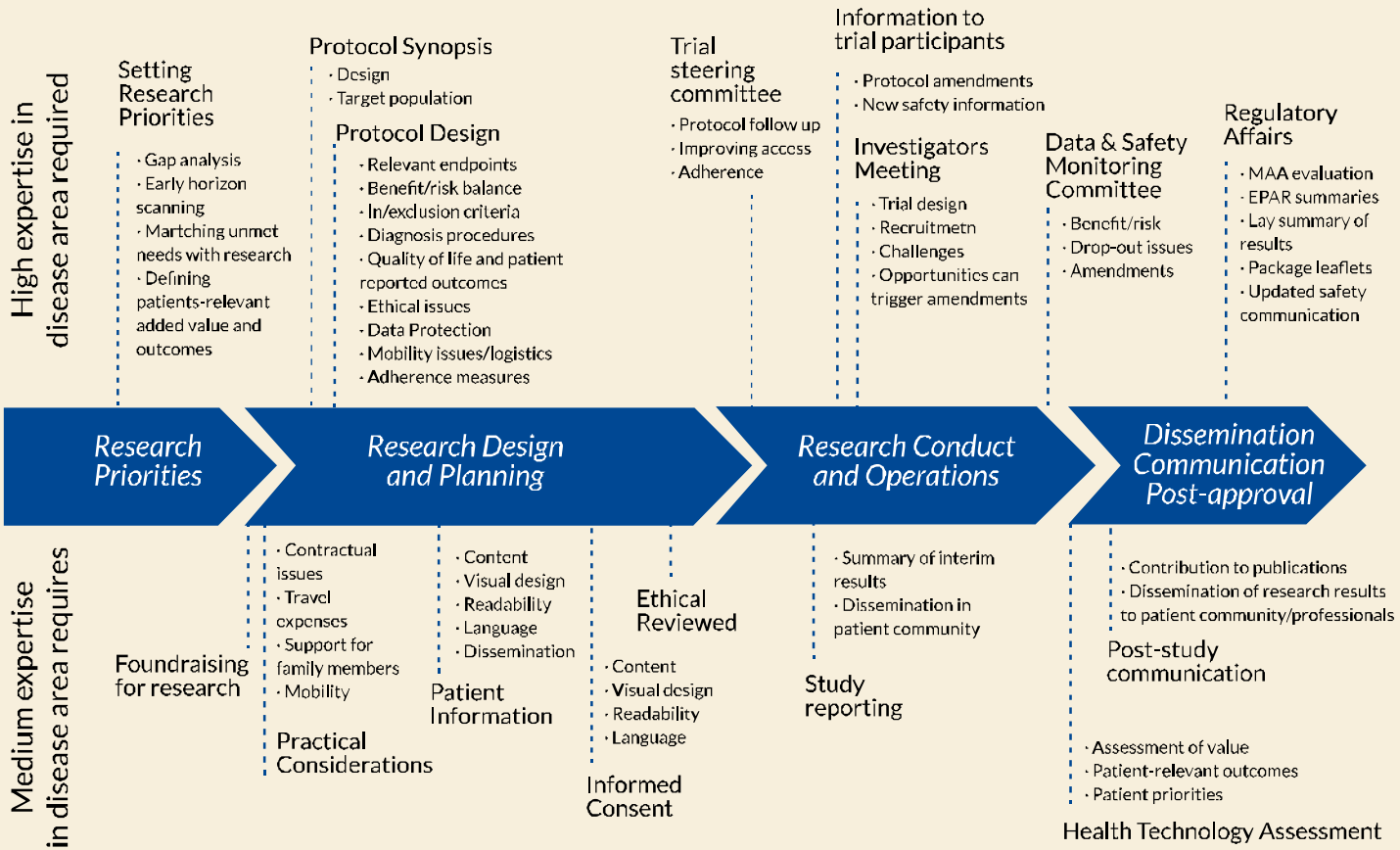
- **Improve research results by implementing adaptive designs:** Lung cancer is currently a public health concern. Trials with an adaptive design may lead into a better use of resources such as time and money and might require fewer patients than traditional fixed designs, becoming more efficient, informative and ethical.

PATIENTS SHOULD COLLABORATE IN THE DESIGN, RECRUITMENT, ANALYSIS AND RESULT REVIEWS AND THE DISSEMINATION OF RESULTS. BASICALLY, WHAT WE NEED TO KNOW IS IF WE'RE GOING TO BE ABLE TO RECRUIT PATIENTS WITH THE CRITERIA WE HAVE AND IF THE STUDY IS OF INTEREST TO PATIENTS. BESIDES CONSIDERING THAT LIFE EXPECTANCY SHOULD BE KEY, WE NEED TO CONSIDER THE QUALITY OF LIFE THEY ARE GOING TO HAVE.

ANDREA BORONDY KITTS
(ADVOCATE, UNITED STATES OF AMERICA)

Regarding the potential role of patients in research, a study identified the following key areas and opportunities for patient involvement across the medicine research and development (R&D) process, categorizing it into 4 stages: research priority setting; research design and planning; research conduct and operations; and dissemination, communication and post-approval activity [9].

Patient involvement in medicines R&D



Geissler j, Ryll B, Leto di Priolo S, Uhlenhopp M. Improving Patient Involvement in Medicines Research and Development: A Practical Roadmap. Therapeutic Innovation & Regulatory Science 1-8. 2017

Patient Voice...

PATIENTS MUST BE ABLE TO INFLUENCE WHAT TREATMENTS ARE BEING GIVEN TO THEM AND TO WORK WITH RESEARCHERS SO AS TO CONSIDER THE RISKS ASSOCIATED WITH EXPERIMENTING WITH NEW DRUGS.

(PATIENT FROM FINLAND)

WITHOUT THAT INVOLVEMENT, RESEARCHERS OFTEN COME UP WITH IDEAS FOR WHICH THEY HAVE DIFFICULTY RECRUITING PATIENTS, AS THEY FAILED TO THINK ABOUT PATIENT PRACTICALITIES OR PRIORITIES AT THE TIME.

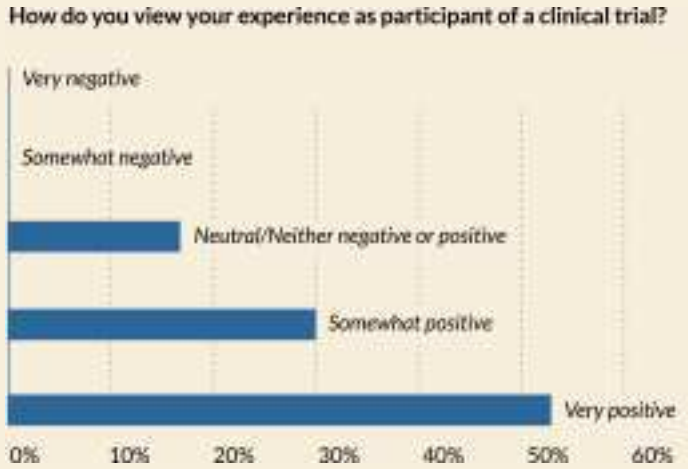
(PATIENT FROM GERMANY)

RESEARCHERS DON'T KNOW ABOUT THE NEEDS OF PATIENTS, SUCH AS HAVING FLEXIBILITY IN THE LENGTH OF TREATMENT INTERVALS AND SCANS.

(PATIENT FROM FRANCE)

Another study also attributed to patient advocates, the role of assessing patient experience [10]. Even when there are some initiatives to evaluate these experiences, advocates could collect them in a systematic way and identify solutions to improve the satisfaction of patients who participate in a clinical trial.

Of those surveyed, 11% of patients with lung cancer have participated or are currently participating in clinical trials, and we asked them about their experience. It is interesting that **none of them considered their experience as a trial participant to be negative.** More than half said it was very positive. These data should be complemented with qualitative data to explore the issues that contribute to this positive feedback and to **identify why 17% of participants did not consider it to be neither negative nor positive.** This could help in future trial designs and protocols.



PATIENTS MUST HAVE AN ACTIVE ROLE IN THE ENTIRE RESEARCH PROCESS. JOINT ACTION GIVES MORE OPPORTUNITIES AND MORE DIVERSE SOLUTIONS AND APPROACHES TO THE PROBLEM.

(PATIENT FROM POLAND)

3.4. Fostering processes

This is the aspect most frequently highlighted by the people consulted in this report when asked about the role of regulatory agencies in improving lung cancer clinical trial access and development. More than half of them specifically pointed to the **role of authorities in reducing bureaucracy** and speeding up the whole process.

THE STUDY AND PRODUCTION PHASES WOULD HAVE TO BE FASTER. IT TAKES SEVERAL YEARS FOR AN EFFECTIVE DRUG TO BE PRODUCED.

ANNETTE HANS (ADVOCATE, GERMANY)

Bureaucratic processes result in delays in patients having access to new innovative treatments, which is unacceptable, especially when they have mortal diseases. There are now many ongoing studies that have to face a wide range of national (and even regional) regulatory and reimbursement processes.

As we stated in our second report, there are still delays regarding pricing and reimbursement, which usually exceed the 180-day limit post company submission for price. This period of time depends on the country, as these decisions correspond to national governments and agencies. As such, there are **significant differences between European countries,** as the ability and willingness to pay for medicines also differ between national states [11]. Therefore, we ask for further collaboration and efforts to simplify these processes and to accelerate patient access to innovative treatments. Authorities should facilitate administrative procedures and centralize approvals.

We need also to find strategies and **solutions to accelerate study execution, especially on patient recruitment and site engagement** and activation. It takes over 12 years to complete the research and development required before a new medicine can be made available for patient use [12]. We also need to point out that trials often last longer than expected. For instance, according to a report from Cutting Edge Information, Accelerating Clinical Trials: Budgets, Patient Recruitment and Productivity (2004): phase I trials are exceeding initial expectations by 42% on average; phase II trials last 31% longer than originally scheduled; and 30% of phase III trials extend beyond initial deadlines [13].

PHARMACEUTICAL INDUSTRY, ACADEMIA AND HEATH AUTHORITIES NEED TO WORK CLOSER TOGETHER TO ACCELERATE AND SIMPLIFY THE EXECUTION OF CLINICAL STUDIES. THERE ARE MANY OPPORTUNITIES TO OPTIMIZE THE VARIOUS STEPS AND REDUCE THE TIMING FROM INITIAL SITE ACTIVATION TO CLOSURE OF RECRUITMENT.

OLIVIER PEETERS (PHARMACEUTICAL INDUSTRY)

How can trial completion time be reduced?

1. Reduce the time from site identification to site activation (ready to begin enrolment).

2. Speed up the recruitment process: disseminating information in society, working with patient organizations, extending inclusion criteria, improving physician knowledge in regional cancer centres, etc.

3. Networking between cooperative groups, academics, pharmaceutical companies and public authorities to foster processes and data and resource sharing.

4. More dedicated staff and infrastructure for research.

5. Foster and advocate for adaptive designs that might require fewer number of patients and achieve research outcomes in a shorter period of time.

3.5. Access to clinical trials

Recruitment is an essential part of the whole research process, not only because we need a minimum number of participants to carry out the clinical trial, but also to give an alternative to many patients. However, participation in clinical trials typically does not exceed 5% of patients with cancer [14] and most of the experts consulted think that **there is a recruitment deficit in lung cancer clinical trials,** so we need to find solutions to get more patients involved in them. Three of those surveyed said there was no deficit, but acknowledged that it can happen depending on the country, the hospital and the inclusion and exclusion criteria.

Participating in a **clinical trial offers an opportunity to access new therapeutic options,** frequently associated with better outcomes[15]. However, only a small fraction of patients with lung cancer are enrolled on clinical trials [16]. This means that thousands of potential candidates are not recruited and, therefore, are missing out on the opportunity to participate in clinical trials. We should give them the opportunity to get involved because, even though they may not receive a personal benefit, evidence shows that outcomes for participants in research and clinical trials are generally improved, perhaps due to the rigour of the process required by the trial [17].

Patients with lung cancer decide to participate in clinical trials because they may be the best option available to them and they are willing to face the added uncertainty of a clinical trial in the hope of better results. Other patients decide to do it because they know that it is a way of contributing to the progress of lung cancer treatment, which may benefit future patients [18].

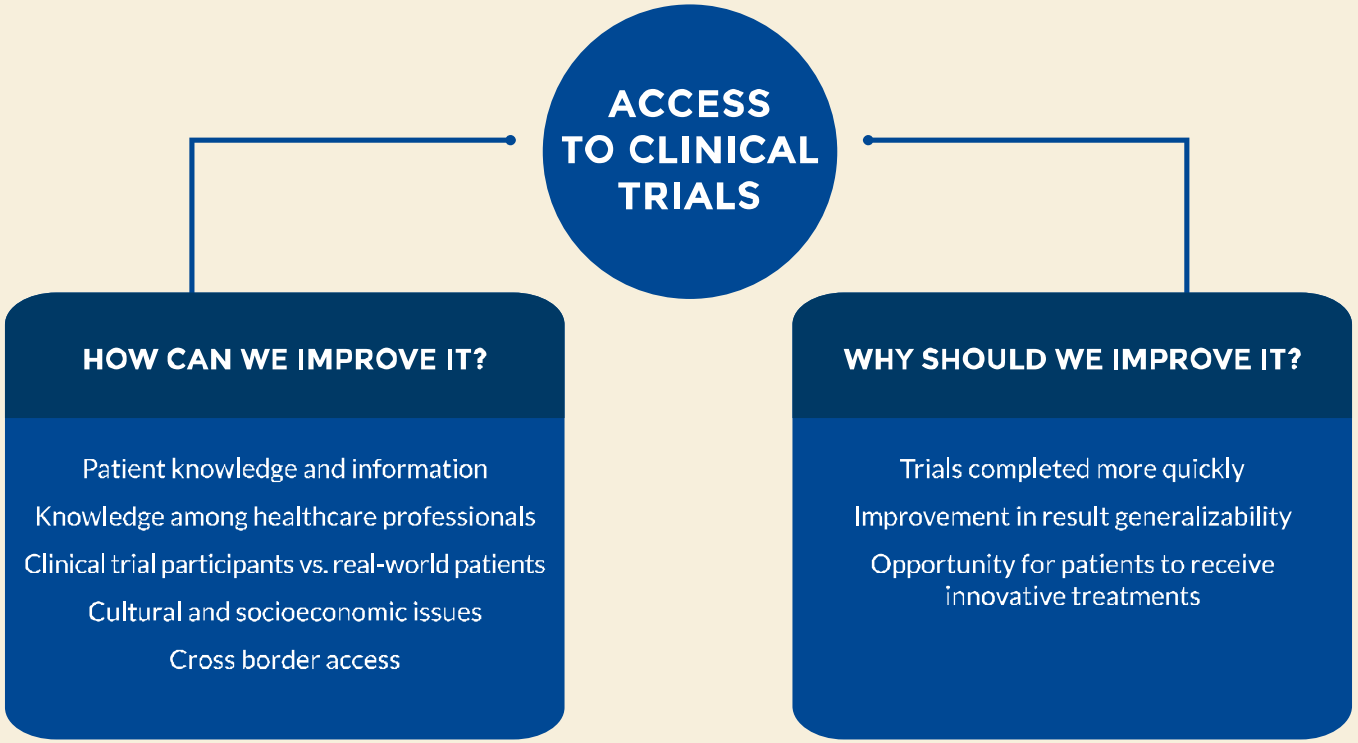
I HAVE 4TH GRADE LUNG ADENOCARCINOMA AND CHEMO STOPPED WORKING FOR ME. IN ITALY, NIVOLUMAB WAS RECENTLY APPROVED FOR NON-SQUAMOUS LUNG CANCER. I GOT THE CHANCE TO PARTICIPATE ON A TRIAL. AFTER 20 MONTHS, I AM STILL ALIVE.

(PATIENT FROM ITALY)

3.5.1. Patient knowledge and information about clinical trials

The lack of knowledge and awareness of clinical trials is a significant barrier to participation [19]. All of the advocates consulted agree that **more complete and patient-friendly information on clinical trials is needed.** Most of them feel strongly that there is a huge information gap. Even when patients with lung cancer have access to some public and private databases and websites, most are not patient-focused (not understandable for lay people), are only in English or do not include all the trials conducted. These platforms are too complex and time-consuming. Patients quite often need support to understand and find the right trial.

WE, AS PATIENT ADVOCATES, FACE SIGNIFICANT CHALLENGES REGARDING THE RECRUITMENT PROCESSES FOR LUNG CANCER CLINICAL TRIALS.



The patient advocacy community, in collaboration with other stakeholders, has the potential to greatly contribute to an improvement in patient health literacy on clinical trials, as well as to eliminate the barriers for better access to information in order to find trials suitable for each person. Therefore, **we advocate for a suitable database on lung cancer clinical trials that the general public can easily consult** and that is up-to-date and objective.

THERE ARE INTERNET PLATFORMS ON WHICH YOU CAN FIND OUT ABOUT STUDIES. HOWEVER, IT USUALLY TAKES A LONG TIME TO READ THROUGH THEM TO FIND THE RIGHT ONE FOR YOU. MOST INFORMATION IS NOT PATIENT FRIENDLY AND YOU NEED HELP TO UNDERSTAND IT ALL.

ANNETTE HANS (ADVOCATE, GERMANY)

THERE ARE INTERNET PLATFORMS ON WHICH TRIAL INFORMATION IS AVAILABLE SUCH AS THE CLINICALTRIAL.GOV WEBSITE BUT THIS CAN BE HARD TO BROWSE AND UNDERSTAND. THERE IS A DEDICATED TRIAL SITE FOR OUR COUNTRY, BUT IT ONLY INCLUDES TRIALS THAT GO THROUGH THAT AGENCY AND IT DOES NOT REFLECT ALL THE TRIALS THAT TAKE PLACE IN OUR COUNTRY. NOR DOES IT INCLUDE TRIALS TAKING PLACE IN OTHER EU COUNTRIES.

ANNE-MARIE BAIRD (ADVOCATE, IRELAND)

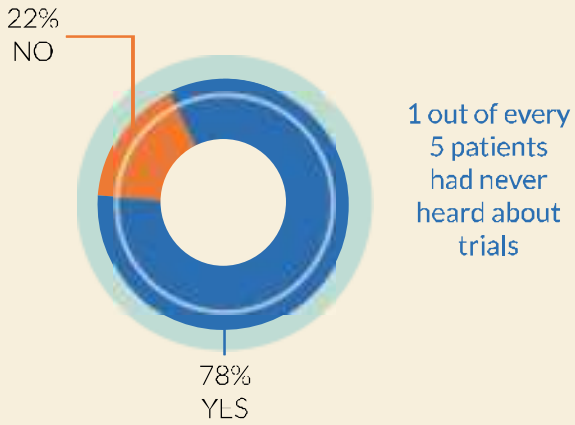
The results of our survey regarding the level of knowledge of patients with lung cancer on the matter of clinical trials are concerning, with 22% stating that they had never heard about clinical trials. **One out of every five had never accessed information on research and 13% of respondents recognized that they did not know if they have ever been a candidate** for a clinical trial.

In terms of patients that had heard about trials, we want to stress that **only 47% of them were made aware of the trials by their physicians.** We regard this percentage as being very low, considering that the sample relates to patients with lung cancer, and that doctors are deemed by patients to be one of the most reliable sources of information.

Internet and social media play an important role in finding information on clinical trials. Of the 69% of the patients (142 people) who answered this question, they confirmed that they had found out about clinical trials on the internet or/and social media. Online searches for healthcare information are common due to constant availability and anonymity [20]. However, we are cautious about the use of these channels given the risks of unreliability.

We have found that the role of patients (as individuals and groups) as sources of information is a significant factor. More than **1 out of every 3 people had heard about clinical trials from other patients and patient organisations.** This data emphasizes the relevance of patients as health educators.

Have you ever heard about clinical trials?



What are the most common sources of information on clinical trials?

Internet	*63%*
Physicians	*47%*
Social media	*31%*
Other patients	*29%*
Patient organisations	*28%*
Magazines and newspapers	*28%*
Family and friends	*16%*
Nurses	*10%*
Other healthcare providers	*10%*
Hospital hand-out material	*10%*
Other	*5%*

However, we need to consider sample bias. This survey was given by patient organizations to their members, so it is likely that this number cannot be extrapolated to the general population of patients with lung cancer.

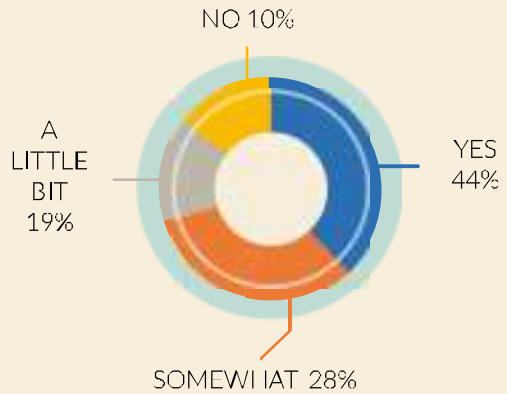
We find contradictory data regarding patient experiences of trial information, with 22% of patients stating that they have never heard about clinical trials, but when we asked if they understood what a clinical trial was, 90% confirmed that they did, or that they at least had a little bit of knowledge about them.

However, **most of them acknowledged that they did not understand completely what a clinical trial was.** As such, we identified a huge lack of knowledge among patients.

<u>When patients say they know what a clinical trial is, do they really know?</u>

According to the survey results, we can observe an inconsistency between the perception of knowledge that patients have about clinical trials and the level of knowledge they actually have.

Do you understand what a clinical trial is?



More than 50% say that they don't completely know what a clinical trial is

For instance, although 90% of respondents considered that they knew what a clinical trial was (or at least had basic knowledge), we find that there is a major misunderstanding about what clinical trials evaluate. **Only 3% of patients knew that trials generate information about efficacy and safety.**

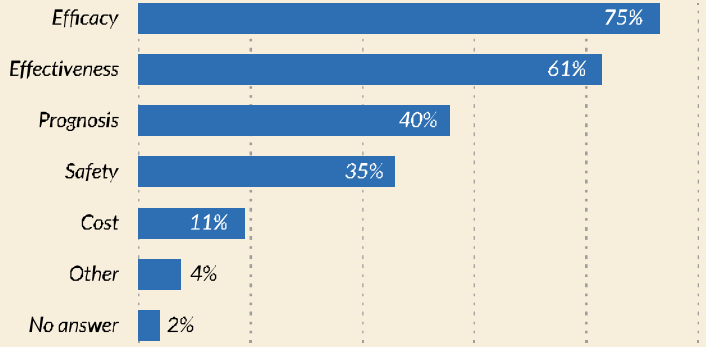
A broad majority of patients did not know that clinical trials collect data on the safety and efficacy of new treatments:

- 25% did not know that clinical trials evaluate efficacy
- 65% did not know that clinical trials evaluate safety
- 61% wrongly believed that clinical trials evaluate effectiveness
- 40% wrongly believed that clinical trials evaluate prognosis

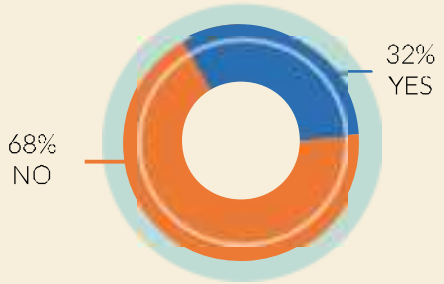
This discrepancy also arose when asked about trial phases. Despite the fact that over 60% considered that they had a very good, good or average level of knowledge about clinical trials, **only 32% said they knew the differences between Phase I, II, III and IV.**

This percentage coincides with those who said that they had very good/good knowledge, so we assume that **most of the patients with an average level of knowledge did not know the differences.**

Clinical trials are used to generate information about



Do you know the differences between a Phase I, II, III or IV clinical trial?



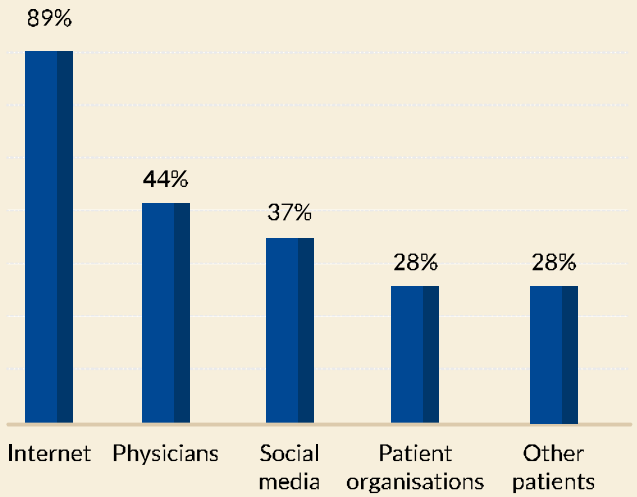
So, are patients with lung cancer actually interested in clinical trials?

According to our survey, they are.

78% said that they were interested in knowing more about clinical trials, but only 59% acknowledged that they had looked for information. Therefore, we find that there is a **high percentage of patients with lung cancer with little knowledge about clinical trials, but there is also great interest in finding out more** about them. This is an opportunity that we all need to consider.

We want to point out that of the patients who searched for information on trials (on their own initiative*), 89% of them used the internet and less than half asked their physician. The **patients surveyed prioritized the use of the internet for finding information on clinical trials over consulting their doctors.** Once again, social media and patients (both as individuals and groups) were regarded as the main information sources, way ahead of magazines/newspapers (15%), nurses (8%), other healthcare providers (11%) and family and friends (8%).

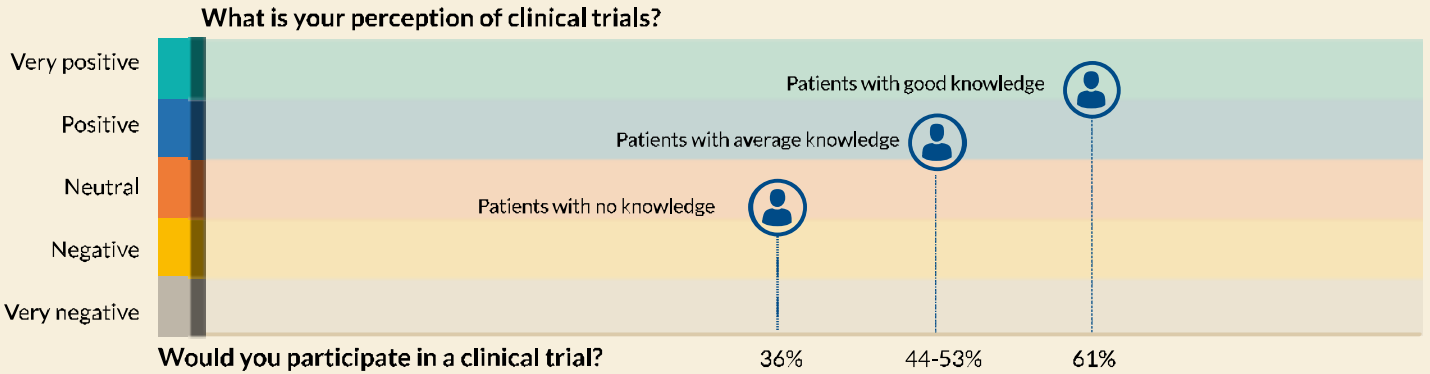
Top sources used to get information



** This is different to the previous data regarding common sources of information on clinical trials. Here we asked them about what sources they used to search for information, not about the sources through which they had heard or found data about trials. We should consider that patients sometimes find information without searching for it.*

As shown in the following table, **lack of knowledge among patients with lung cancer has a decisive influence on enrolling** to clinical trials. **The more knowledge patients have on trials, the more they are willing to participate in them.** Furthermore, we have also established a correlation between patients who look for information on their own initiative and patient knowledge and willingness to participate in clinical trials, as well as how all of these factors influence expectations of the studies.

KNOWLEDGE	INTEREST	INITIATIVE	EXPECTATIONS	WILLINGNESS TO PARTICIPATE
Do you understand what a clinical trial is?	*Have you ever been interested in finding out more about lung cancer clinical trials?*	*Have you ever searched for information on lung cancer clinical trials?*	*What is your perception of clinical trials?* (excluding those who have been a candidate). Score: from 1 (very negative) to 5 (very positive)	*Would you personally participate in a clinical trial for a new drug?* (excluding those already enrolled)
YES (115 patients)	87%	77%	4.30	61% YES 10% NO. 29% I DON'T KNOW
SOMEWHAT (74 patients)	77%	54%	3.79	44% YES 6% NO. 50% I DON'T KNOW
A LITTLE BIT (48 patients)	65%	37%	3.71	53% YES 13% NO. 34% I DON'T KNOW
NO (25 patients)	64%	36%	3.24	36% YES 20% NO. 44% I DON'T KNOW

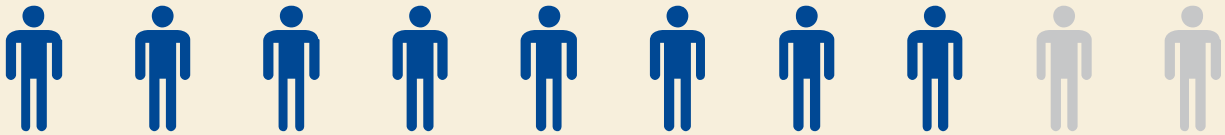


IN SUMMARY...

WHY WE NEED TO PROVIDE PATIENTS WITH GREATER AND CLEARER INFORMATION ON LUNG CANCER CLINICAL TRIALS

Because patients want to be informed:

- 81% of patients with lung cancer are interested in finding out more about lung cancer clinical trials
- 78% said that they have been interested in knowing more about them



8 out of every 10 are interested in knowing more about lung cancer clinical trials

Because only a few of them properly understand what a clinical trial is:

a) More than 50% acknowledged that they didn't completely know what a clinical trial is

b) Only 32% said they knew the differences between Phase I, II, III and IV

c) Only a small minority knew what clinical trials evaluate

Because knowledge has a decisive influence on access to clinical trials and on patient perceptions about research:

The more knowledge patients with lung cancer have on clinical trials, the better perception and more willingness they have participating in them.

a) Clinical trials are perceived as being positive by people who know what clinical trials are (4.30 out of 5); 61% of those who understand what a clinical trial is would personally participate in one for a new drug

b) Clinical trials are perceived as being neutral by those who do not know what clinical trials are (3.24 out of 5); Only 36% of people who don't understand what clinical trials are would personally participate in one for a new drug

c) 20% of people who do not know about clinical trials, are not willing to participate in them. This is 10% higher than people who know about them.

Because existing information is not always accurate, accessible and comprehensive:

a) 36% of people who did not know about trials acknowledged that they had searched for information. Therefore, this means that the information they found did not help them to understand what a clinical trial was.

b) Only 10% of people who searched for information said that they always found the information they wanted. 41% of patients said that only occasionally did they find answers to their questions.

c) We asked them why they did not find the information they wanted. These were the main barriers identified:

Information difficult to understand: too complex and scientific	*Incomprehensible language for the common man* **Patient (Norway)**	*They are written with words from the medical industry* **Patient (Italy)**	*Certain information was too scientific* **Patient (Romania)**
Information not found because of lack of accessibility or browsing difficulty	*Sometimes it's not easy to find on the internet* **Patient (Spain)**	*The information was often hidden in studies or research result files* **Patient (Netherlands)**	*Browsing the internet to find good trials is difficult* **Patient (UK)**
Lack of information about research	*Lack of public information on research* **Patient (Poland)**	*Access to information is difficult. Especially in small cell lung cancer* **Patient (Finland)**	*Information on the internet was not accessible* **Patient (UK)**
Others: language barriers and unreliable information	*Often the studies are in a foreign language* **Patient (Italy)**	*My language skills are not good enough to read the studies in other languages* **Patient (Finland)**	*It is difficult to obtain reliable data* **Patient (Poland)**

3.5.2. Knowledge of healthcare professionals on clinical trials

Certain studies highlight the fact that different levels of knowledge and attitude of healthcare professionals regarding lung cancer clinical trials influence patient decisions on whether or not to participate in them[21-22]. We believe that **physicians individually have a major role in facilitating or discouraging patient enrolment** and, therefore, they could act as a significant barrier to patients accessing trials.

WE NEED TO IMPROVE THE KNOWLEDGE OF HEALTHCARE PROFESSIONALS ON CLINICAL TRIALS. WE NEED MOTIVATION AMONG DOCTORS TO GET INVOLVED IN THEM.

EWELINA SZMYTKE (ADVOCATE, POLAND)

According to our interviews and surveys, **not all medical professionals are aware of all the clinical trials underway.** Doctors are one of the main sources of information for patients on lung cancer clinical trials. Furthermore, we as patients often decide, in most cases, to participate in clinical trials based on the recommendation of our physician. Therefore, we need to raise awareness among physicians and inform patients about ongoing lung cancer trials.

Regarding this issue, the experts consulted identified the following challenges and opportunities:

- **Knowledge depends on the geographical region.** Medical professionals may only be aware of the clinical trials taking place in their region and, therefore, professionals in countries where more trials are conducted are often keener to encourage their patients to participate. To address the lack of knowledge among professionals, national and international clinical trial registries can be helpful, both for medical professionals and patients.

HEALTH AUTHORITIES IN EACH COUNTRY COULD SUPPORT THIS AND PROMPTLY UPDATE SYSTEMS AS THEY GRANT PERMISSIONS TO START TRIALS.

VICTORIA ZAZULINA (PHARMACEUTICAL INDUSTRY)

- **Medical professionals from academic centres are more aware about the trials that are underway than those from private practice.** Less experienced professionals and centres may be less proactive in terms of helping patients to apply for a clinical trial, as it requires organization and training. As such, it is important to approach all centres that treat lung cancer in order to promote knowledge about clinical trials.

- **Difficulties to staying informed about trials** because of the high number of ongoing clinical trials. For instance, there are over 200 trials in NSCLC check-point inhibitors alone (Checked: September 2018). There should be a system

that allows for easy access to this kind of information. We believe that more publicly available information would help to increase knowledge among healthcare professionals and patients on the trials underway.

- **Personal attitudes towards research and the pharmaceutical industry.** This is an important challenge for some medical professionals. Some of them may be unaware of the importance of research and may even be influenced by a perceived bad reputation of pharmaceutical companies.

I THINK THAT SOME MEDICAL PROFESSIONALS DO NOT BELIEVE IN PARTICULAR CLINICAL TRIALS AND ARE NOT VERY KEEN ON HELPING PATIENTS FIND OUT ABOUT THEM, ESPECIALLY IN REGIONS AND COUNTRIES WHERE THERE IS LESS CLINICAL RESEARCH.

TANJA CUFER (MEDICAL ONCOLOGIST, SLOVENIA)

WE THINK THE MOST EFFECTIVE WAY TO CONNECT PATIENTS WITH TRIALS IS THROUGH THEIR CLINICAL PROVIDER. IF THE PRIMARY ONCOLOGIST IS AWARE OF THE APPROPRIATE AVAILABLE TRIALS IN THE AREA, THEY ARE MORE LIKELY TO REFER THE PATIENT.

DAVID KERSTEIN AND CHRISTIAN KRUHL (PHARMACEUTICAL INDUSTRY)

THE VAST MAJORITY OF PATIENTS EXPECT DOCTORS TO CHOOSE THE BEST TREATMENT OPTION FOR THEM AND THIS INCLUDES THE POSSIBLE SUGGESTION OF PARTICIPATING IN A CLINICAL TRIAL. HOWEVER, THIS IS NOT ALWAYS THE CASE. ESPECIALLY WHEN DOCTORS ARE NOT WORKING FOR A MEDICAL CENTRE, AS THEY OFTEN DON'T KNOW ABOUT SUITABLE TRIALS.

CHRISTIAN SCHMITT-PLANK (ADVOCATE, GERMANY)

We want to ensure that all doctors treating patients with lung cancer are fully aware and up to date about ongoing clinical trials. We also want to promote other sources of information (such as specialized websites or databases) to avoid potential barriers in accessing this data through physicians.

3.5.3. Clinical trial participants vs. real-world patients

MOST CLINICAL TRIALS ARE DESIGNED FOR FIT PATIENTS AND DO NOT REFLECT REAL-WORLD LUNG CANCER PATIENTS.

ANTONIO ARAUJO (ADVOCATE AND MEDICAL ONCOLOGIST, PORTUGAL)

This is one of the biggest points of discussion regarding clinical trials in recent years. The inclusion and exclusion criteria are sometimes so restricted that the **final sample often fails to reflect the reality of many patients** who will receive the treatment. If we do not recruit all groups of patients that will receive the drug, if approved, how can we know if the approved treatment will be effective for them? Furthermore, could we expect serious safety issues in a real word context following its approval? Ideally, the results of clinical trials should closely reflect the real-life patient population. However, according to our interviews, some of the clinicians recognize that **most trials do not include the kind of patients seen every day in clinics.** Therefore, the issue of extrapolation remains significant in lung cancer research.

ROBUST REAL-WORLD DATA IS URGENTLY NEEDED.

LINDA COATE (MEDICAL ONCOLOGIST, IRELAND)

For example, the elderly is significantly underrepresented in lung cancer clinical trials. A literature search for all phase III trials of systemic therapy for advanced NSCLC between 1980 and 2010 was performed using PubMed. A total of 248 trials were reviewed. **Among the 100 most cited trials, 33% specifically excluded elderly patients in their trial design** (age exclusion ranged from >65 to >75 years of age). The average-reported patient median age in these trials was 60.9 years, when the median age of newly diagnosed patients with lung cancer in the United States of America is approximately 70 years [23].

THERE ARE SOME GROUPS OF PATIENTS, SUCH AS YOUNG AND ELDERLY PATIENTS, THAT SHOULD BE INCLUDED MORE IN RESEARCH, AS THERE IS NOT A LOT OF DATA ON EFFICACY AND TOXICITY.

TANJA CUFER (MEDICAL ONCOLOGIST, SLOVENIA)

Could we be less restrictive regarding inclusion and exclusion criteria, thereby involving more patients in new, potentially beneficial treatment? If we do this, are we compromising patient safety? Who decides the extent to which patients should be put at risk and what responsibility do authorities have?

On this matter, we asked our interviewees whether inclusion criteria should be changed to make trials accessible for groups of patients that have not traditionally been candidates. These are the issues and opinions we found:

Considering the high lung cancer mortality rates, do you think that inclusion criteria should be changed to make clinical trials more accessible for groups of patients that have not traditionally been candidates?

Disagree	Neutral	Agree
Not at all. Usually when you have to do the studies, there is a good population range and you therefore obtain trustworthy results. However, it's often after the treatment has been approved that patients do not fall into the inclusion criteria, as they may not benefit from it.	*There is always a certain balance that needs to be observed, opening up the trial participation to more patients, while also putting measures and certain restrictions in place to minimize potential participant risks, especially at the early stages of drug development.*	*It's true that, for some studies, the criteria could be more flexible and could include patients with certain mobility. Many patients could still benefit from the trial even if it's not optimal.*
I think great care has to be taken with getting the appropriate patients onto appropriate trials, if not, more harm than good would be done.	*I'm not sure. You often need high-performance status to endure the study. On the other hand, it could be good that patients can have the new drugs as soon as possible.*	*We need to change our exclusion and inclusion criteria, as now clinical trials are for "healthy" lung cancer patients. That can't be the case, because the majority of patients aren't "healthy". If you have such strict entry criteria, you are going to shut out a lot of people.*
No, because it's very hard to mirror a real-life situation, no matter how inclusive a clinical trial is. However, there should be an investment in phase IV.	*I believe that inclusion criteria are there for a reason. However, we should take into consideration patients whose last option is entering a clinical trial, but they are not the usual candidates.*	*Yes, clinical trials should represent real-world practice. More similar to the patients seen in everyday clinical scenarios. The eligibility criteria can sometimes be quite narrow.*
		Absolutely. Yes. Especially patients with an ECOG performance status score of 2.

EXCLUSION OF SOME PATIENTS: PROTECTING OR DISCRIMINATING?

We ask our collaborators to consider the following recommendations:

- Make clinical trials accessible for groups of patients similar to those seen in everyday clinical scenarios, especially in the last stages of drug development, as there is stronger evidence regarding safety issues. Criteria should be closely aligned with the existing patient population.

- Be flexible so as to give some patients with certain mobility, people who can benefit from the trial, especially those for whom it may be the last option, the chance to participate in clinical trials.

- Promote proper dialogue with patients with lung cancer, exploring the risks they are willing to take, in order to conduct a good risk-benefit evaluation.

THE NEED TO GENERATE REAL WORLD EVIDENCE (RWE) IS CRITICAL IN TODAY'S ENVIRONMENT TO ADDRESS THE GROWING NEED FOR ACCESS TO INNOVATIVE THERAPIES OUTSIDE OF THE STRICT CONTEXT OF A CONVENTIONAL CLINICAL STUDY.

OLIVIER PEETERS (PHARMACEUTICAL INDUSTRY)

WE NEED MEDICAL STAFF TO BETTER EXPLAIN TO PATIENTS THE OPTIONS AND REASONS RELATED TO CHOOSING CLINICAL TRIALS.

SHANI SHILO (ADVOCATE, ISRAEL)

3.5.4. Cultural and socioeconomic issues

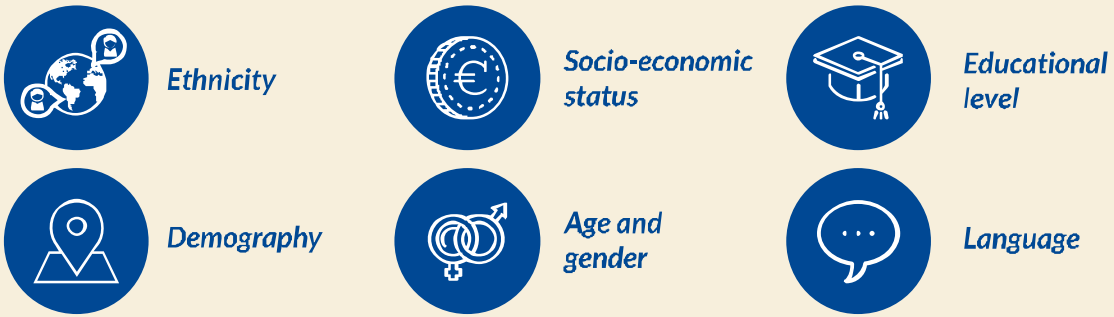
Another challenge, beyond that of assessing whether or not to change inclusion criteria, is recruiting real-world patients with lung cancer and giving equal opportunities to all of them, regardless of differences in cultural and socioeconomic status. If clinical trials are to benefit patients and research, they should be offered to all eligible patients for reasons of equity [24].

Under-enrolment of specific groups of patients because of social and cultural factors reduces the generalizability of research findings and represents a disparity in access to high-quality healthcare [25].

CLINICAL TRIALS SHOULD BE MORE ACCESSIBLE FOR PATIENTS WITH SOCIAL INEQUALITIES. THEY ARE NOT AS MOTIVATED TO PARTICIPATE IN THEM AS OTHER, MORE EDUCATED PEOPLE OR PEOPLE WHO SUFFER FEWER SOCIAL INEQUALITIES.

JESPER HOLST (THORACIC SURGEON, DENMARK)

Therefore, recruitment processes should consider the following potential barriers on access to trials:



- **Ethnicity.** Different studies suggest that **ethnic minorities are underrepresented in lung cancer clinical trials.** Therefore, we need to implement strategies to reach these populations and to ensure that these new treatments consider their specific characteristics [16]. For instance, Kwiatkowski K. et al. (2013), found that more than **80% of participants in cancer treatment and prevention trials were white,** based on 304 peer-reviewed publications between 2001 and 2010 [26]. Ethnicity diversity should be considered on clinical trial recruitment processes, because genomic differences can vary from one to another. For example, EGFR mutation might be different in African-American men compared to Asian men [27].

- **Socio-economic status.** Income is frequently associated with trial participation. Lack of transportation, inadequate insurance, additional costs related to participation or poor access to healthcare are important barriers and influence patient decisions [28]. As a result, **lower income patients are less likely to participate** in clinical trials [29]. This is a challenge for thousands of patients. We must not forget that the **incidence of lung cancer is higher among people of lower socioeconomic position** than among wealthier people, in part because smoking rates are higher in poorer populations [30] in developed countries. Therefore, financial counselling may play an important role in improving recruitment rates [31].

INCOMES CAN INFLUENCE A PATIENT'S DECISION TO PARTICIPATE IN A TRIAL. IF YOU HAVE FINANCIAL PROBLEMS, YOU ARE LESS LIKELY TO BE IN A POSITION TO AFFORD THE EXPENSES ASSOCIATED WITH THE TRIAL, ESPECIALLY IF YOU NEED TO TRAVEL LONG DISTANCES.

DIEGO VILLALÓN (ADVOCATE, SPAIN)

- **Level of educational.** Lack of education on cancer and clinical trials is a frequently reported barrier to trial access[32]. This **could influence patient capacity to understand the trial information,** especially when informed consent documents and patient information are written using specialised language and complex concepts. This could be a reason for refusal of trial participation [33]. We encourage doctors to identify when a lack of education may be a barrier to consent. We also encourage them to spend **more time talking to patients** in order to ensure that all the information has been correctly understood, allowing them to make an informed decision.

- **Demography.** Even within a specific country, place of residence can influence trial participation. **The further away you are from the trial site, the more obstacles**

I THINK TRIAL ACCESS IS GOOD IN LARGE CITIES WITH RESEARCH CENTRES, BUT MORE DIFFICULT IN RURAL/SMALL AREAS. THIS IS A DISCREPANCY.

JACKIE FENEMORE
(ADVOCATE AND LUNG CANCER
NURSE CLINICIAN, UNITED KINGDOM)

you may face. This is generally because of higher transportation costs, poorer access to health services, more time dedicated to the trial, etc. This barrier is particularly important because rural populations have higher rates of late stage lung cancer incidence and mortality compared to urban populations [34], probably because of poorer access to health services. Social workers can get involved in order to find solutions and **improve access for people living in rural, small or isolated places.**

- **Gender.** Even though the rate of female participants is now higher than it was, **women are still less likely to enrol on trials** than men [35]. This must change, because, according to recent studies, female lung cancer incidence and mortality are on the rise in most European countries[36]. Worse still is the fact that the female **lung cancer mortality rate is expected to increase by 43%** from 2015 to 2030, according to an analysis of data from 52 countries[37].

- **Age.** A recent study found that **while 37% of patients with lung cancer are 75 or older, only 9% of people of that age are represented in clinical trials** [38]. Trials designed specifically for older adults are rare [39]. As such, we find that elderly patients are underrepresented in lung cancer trials. Due to safety reasons, some trials only recruit younger participants. While researchers may think that results can be extrapolated, we worry that this cannot always be to the case in the typical elderly patient with lung cancer. We are aware that there are potential problems in recruiting this category of patient (other illnesses and medications, mental status, social support, etc.), but we suggest that older people are asked whether or not they want to participate. With regard to this challenge, the American Society of Clinical Oncology (ASCO) issued a statement including some recommendations on improving the evidence base for treating older adults with cancer[39].

- **Language.** This is a barrier if informed consent, informative materials, questionnaires, etc., are not translated into the candidate´s language. It is important to **translate these materials into different languages and to have quick and easy access to translators,** especially in minority languages [24].

3.5.5. Cross-border access

There are disparities regarding access to clinical trials across Europe, as they are usually conducted in certain countries. **Most of them are carried out in Western Europe,** so these populations have better access to lung cancer trials than patients from Eastern or even Northern Europe.

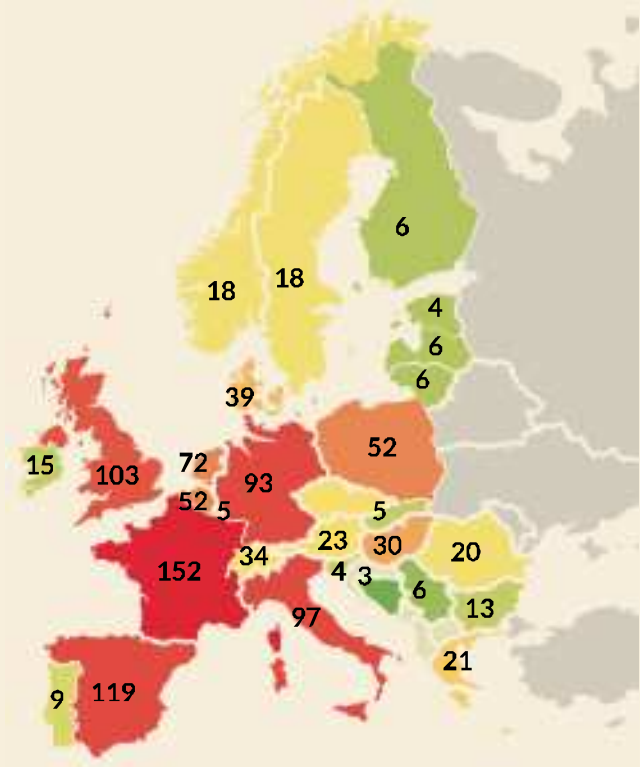
ONE POINT OF DISCUSSION IS THE TIME OF CT ACTIVATION. IT MEANS THAT THE COUNTRY IS SLOW IN ACTIVATING PROCEDURES AND NOT BECAUSE IT LACKS CAPACITY TO ENROLL PATIENTS.

SILVIA NOVELLO
(MEDICAL ONCOLOGIST, ITALY)

The reason seems to be due to the resource and economic situation, especially regarding trial activation and recruitment. These disparities are greater in academic trials than in pharma trials, as the first one largely depends on the support of the national health system, which does not always exist.

According to the website www.clinicaltrials.gov, most clinical studies are conducted in Western Europe: France, the United Kingdom, Spain, Italy and Germany. This situation causes enrolment disparities. Therefore, **depending on the country you live in, you will have more or less opportunities to access these studies.** Paradoxically, most lung cancer cases occur in less developed countries (about 61% in men and 54% in women) [40], but most clinical trials are conducted in developed countries.

The figure shows the number of lung cancer trials across Europe that are recruiting patients (www.clinicaltrials.gov; 28 August 2018).



The European Clinical Trial Regulation (No. 536/2014) ensures that the rules for conducting clinical trials are identical throughout the EU, and it facilitates access through centralized approval processes. This regulation aims to standardize and harmonize clinical trials among member states. However, according to the survey carried out for the second LuCE report, **42% of the healthcare professionals rate access to new drugs in clinical trials as poor (35%) or very poor (7.5%)** [41]. On the other hand, we need to consider that travelling across European states is demanding both physically and financially, particularly for many patients with lung cancer. Perhaps future trials may allow for enhanced community based trials at smaller centres, thus removing the need for extensive travel. Therefore, there is a lot of room for improvement.

New regulations will foster patient recruitment and promote cross-border access to clinical trials. Despite this regulation, complex health systems, infrastructure and economic issues can affect the initiation of trials in some countries. Some companies may also worry about the feasibility of trial initiation and adequate recruitment in a smaller member states.

IT IS IMPOSSIBLE FOR MOST PATIENTS TO TRAVEL TO ANOTHER COUNTRY OR EVEN CONTINENT FOR A TRIAL/TREATMENT IF TRAVEL COSTS ARE NOT COVERED BY THE ORGANIZER.

MIRJAMI TRAN MINH (ADVOCATE, FINLAND)

Addressing cross-border access to clinical trials

- Ensuring access, regardless of the place of residency, is a priority for patients with lung cancer that do not have access to routine care and clinical trials in their own country.
- Cross-border enrolment can be key to enrolling and retaining the required number of participants in a clinical trial for rare lung cancer subtypes.
- Study sites must have the staff, technology and support infrastructure to manage the transfer of medical records and to accommodate patients and families who are not fluent in the local language[42].
- Clinical trial sponsors should draw up a cross-border recruitment plan, including all relevant data a patient must consider before making a decision.
- If we only conduct trials in specific countries, are we really considering ethnical and cultural diversity in samples? Cross-border access measures would help to reduce bias.
- Identification of different lung cancer subtypes requires the development and accreditation of centres specializing in lung cancer and molecular testing, thus creating reference networks.
- Monitor the correct implementation of the EU Cross-Border Health Directive to facilitate access to safe and high-quality cross-border healthcare in the Union and to ensure patient mobility across countries.

4. KEY FINDINGS: OUR PRIORITIES

- **Lung cancer continues to be under-researched and underfunded** compared with other cancer types. It is the leading cause of cancer related death in all European countries (except in Portugal) and it accounts for approximately 20% of all cancer related deaths. We find a weak correlation between the disease burden from the different cancers and the amount of research conducted. Therefore, we urge the fostering of research and the reduction of deaths, while also raising awareness to get public engagement on the issue of lung cancer.

- **Patients, as research collaborators, are not yet involved in clinical trials.** We can contribute by providing unique information that can be extremely valuable in the research and development of new medicines. We can contribute to identifying investigation priorities, defining what is clinically meaningful for patients, defining better inclusion and exclusion criteria and improving recruitment and retention, among other aspects. Of those surveyed, 75% of patients with lung cancer consider patient involvement in research as something positive and valuable.

- **We ask regulatory authorities to reduce bureaucracy and to speed up the research process.** We need to find solutions that accelerate study execution, especially on patient recruitment and site engagement and activation.

- **There is a recruitment deficit in some lung cancer clinical trials.** We need to improve access, as it is an opportunity for patients to receive innovative treatments and it may lead to increasing the generalizability of research findings and to the quicker completion of trials.

- **56% of patients with lung cancer acknowledged that they did not completely understand what a clinical trial was.** There is also a lack of accurate information among patients who said they knew about them. For instance, only 32% said they knew the differences between Phase I, II, III and IV. As such, we can see that there is a discrepancy between the perception of knowledge that patients believe they have on clinical trials and the level of knowledge they actually have.

- **The lack of knowledge and awareness of clinical trials is a significant barrier to participation.** Of those surveyed 61% of those who understood what a clinical trial was, would personally participate in one for a new drug. While only 36% of people who didn't understand would personally participate in one.

- 78% said that they had been interested in knowing more about clinical trials, but only 59% acknowledged that they had looked for information. Therefore, we find that there is a **high percentage of patients with lung cancer with little knowledge about clinical trials, however there is also great interest in finding out more about them.** Of those surveyed, 81% are interested in finding out more about lung cancer clinical trials.

- All of the advocates consulted agree that **more complete and patient-friendly information on clinical trials is needed,** as well as a suitable database on lung cancer clinical trials that the general public can easily consult.

- **Existing information is not always accurate, accessible and comprehensive.** We found that 36% of people who did not know about trials acknowledged that they had searched for information. This means that the information they found did not really help them to understand what a clinical trial was. Only 10% of people who searched for information said that they always found the information they wanted, with 41% of patients stating that they only occasionally found answers to their questions.

- According to our interviews and surveys, **not all medical professionals are aware of all of the clinical trials underway,** which could act as a significant barrier to patients accessing trials. We want to ensure that all doctors treating patients with lung cancer are fully aware and up to date about ongoing clinical trials. We also want to promote other sources of information (such as specialized websites or databases) to avoid potential barriers in accessing this data through physicians.

- According to our interviews, the **final participants of clinical trials sometimes fail to reflect the characteristics of many patients.** This is because they do not include the kind of patients seen every day in clinics. Therefore, we wonder if we can be less restrictive regarding inclusion and exclusion criteria, thereby involving more patients in new, potentially beneficial treatment, which would also favour the generalizability of research findings, and, if so, would we be compromising patient safety?

- **Clinical trials should be more accessible to different groups of patients, regardless of differences in cultural and socioeconomic status.** If clinical trials are to benefit

patients and research, they should be offered to all eligible patients for reasons of equity. Under-enrolment of specific groups of patients because of social and cultural factors, reduces the generalizability of research findings and represents a disparity in access to high-quality healthcare. Ethnic minorities, lower income patients, people with a low educational level and elderly patients are underrepresented in lung cancer clinical trials.

- **There are disparities regarding access to clinical trials across Europe,** as most of them are carried out in Western Europe. Paradoxically, most lung cancer cases occur in less developed countries (about 61% in men and 54% in women), but most clinical trials are conducted in developed countries. Ensuring cross-border access, regardless of the place of residency, is a priority for patients with lung cancer that do not have access to routine care and trials in their own country. Furthermore, study sites must have the staff, technology and support infrastructure to manage the transfer of medical records and to accommodate patients and families who are not fluent in the local language.


Lung Cancer Europe

ABOUT LuCE

Lung Cancer Europe is the voice of patients with lung cancer, their families and survivors at a European level. LuCE provides a European platform for already existing lung cancer patient advocacy groups and supports the establishment of national lung cancer patient groups in different European countries where such groups do not yet exist.

LuCE aims to raise awareness about inequities regarding the access to lung cancer treatment and care in Europe. Moreover, it advocates European policies that will lead to improvements in lung cancer prevention, early detection, treatment and care. LuCE also supports national lung cancer patient groups in helping raise awareness for lung cancer among the European public.

OUR OBJECTIVES

- Reduce the mortality of lung cancer.
- Promote the best possible treatment of the different types of lung cancer.
- Equal access to lung cancer care throughout Europe.
- Raise public awareness for lung cancer about symptoms, early detection and treatment.
- Reduce the stigma associated with lung cancer and more compassion forpeople with lung cancer and their loved ones.
- Increase European funding allocated to lung cancer research.

ABOUT OUR MEMBERS

LuCE gathers its strength from the combined action of different national patient organizations across Europe. These organizations give support to patients with lung cancer, defend their rights and represent their interests on an everyday basis. They are the voice of the patients in national and international forums, and their work benefits society as a whole. We are stronger together, thus we thank each and every one of the members of LuCE for their generous contribution.

We encourage readers to learn more about these organisations and support them.

Asociación Española de Afectados de Cáncer de Pulmón
www.afectadoscancerdepulmon.com

Bundesverband Selbsthilfe Lungenkrebs e.V.
www.bundesverband-selbsthilfe-lungenkrebs.de

Israel Lung Cancer Foundation
www.ilcf.org.il

Landesverband Baden- Württemberg für Lungenkrebskranke und deren Angehörige e.V
www.lungenkrebs-bw.de

Longkanker Nederland
www.longkankernederland.nl

Lungencancerförbundest Stödet
www.lungcancerforeningen.se

Lungekreftforeningen

www.lungekreftforeningen.no

National Lung Cancer Forum for Nurses (NLCFN)

www.nlcfn.org.uk

Patientforeningen Lungekræft

www.lungekraeft.com

Pulmonale

www.pulmonale.pt

Stowarzyszenie Walki z Rakiem Pluca

www.rakpluca.org.pl
www.rakpluca.szczecin.pl

Women Against Lung Cancer in Europe

www.womenagainstlungcancer.eu

ASSOCIATE MEMBERS

LuCE associate members are organisations committed to improve the lives of patients with lung cancer. LuCE wishes to thank these organizations for their continuous support.

Community Health Association

Društvo onkoloških bolnikov Slovenije
www.onkologija.org

Dzivibas Koks
www.dzivibaskoks.lv

European Thoracic Oncology Platform (ETOP)
www.etop-eu.org

European School of Oncology (ESO)
www.eso.net

Fundación MÁS QUE IDEAS
www.fundacionmasqueideas.org

JEDRA
jedra.toraks.hr

Suomen Syöpäpotilaat -
Cancerpatienterna i Finland ry
www.syopapotilaat.fi

Pembe Hanim Turkey
http://www.pembehanim.com.tr/

If you are interested in joining LuCE, please contact us.

We will be pleased to meet you!

luce@etop-eu.org

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We would also like to thank the 262 patients with lung cancer who completed our survey. Thanks to them, we have had access to extremely valuable information on how to improve patient knowledge and access to clinical trials.

A special thanks goes out to our members. They have supported this project from the very beginning and their work in advocacy inspires us to continue growing and to keep working to overcome our shared challenges.

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- **Tanja Cufer,** Professor of Oncology, University Clinic Golnik; Medical Faculty Ljubljana, Slovenia
- **Jesper Holsts Pedersen,** Associate professor and consultant in thoracic surgery at Copenhagen University Hospital, Rigshospitalet; Chairman of the surgical subcommittee of the IASLC strategic screening advisory committee.
- **Mina Gaga,** Pulmonologist; European Respiratory Society (ERS) President 2017-2018; Medical Director, Athens Chest Hospital.
- **Greg Korpanty,** Consultant Medical Oncologist; University Hospital Limerick, Ireland.
- **Silvia Novello,** Medical Oncologist; Member of the American Society of Clinical Oncology (ASCO), of American Thoracic Society (ATS), of European Society of Medical Oncology (ESMO), and the International Association for the Study of Lung Cancer IASLC (past Board of Director Member);

Board of director of the Italian Society of Medical Oncology (AIOM); President of Women Against Lung Cancer in Europe (WALCE).

- **Rolf Stahel,** Medical Oncologist; President of the European Thoracic Oncology Platform (ETOP); ESMO Executive Board. University Hospital Zürich.

Individual collaborators from pharmaceutical industry:

- **David Kerstein and Christian Kruhl,** Global Senior Medical Director and EUCAN Medical Head Solid Tumors. Takeda Oncology.
- **Giovanni Melillo,** Head of Global Medical Affairs for Immuno-Oncology. AstraZeneca.
- **Olivier Peeters,** Regional Medical Affairs Director, EMEAC. MSD.
- **Victoria Zazulina,** Boehringer International GmbH. TA Oncology Medicine.

Lung cancer patient advocates:

- **Antonio Araújo, Portugal**
- **Anne-Marie Baird, Ireland**
- **Tommy Björk, Sweden**
- **Andrea Borondy Kitts, United States of America**
- **Alina Comanescu, Romania**
- **Regine Deniel Ihlen, Norway**
- **Jackie Fenemore, United Kindgom**
- **Anette Hans, Germany**
- **Tom Haswell, United Kingdom**
- **Merel Hennink, The Netherlands**
- **Isabel Maria Magalhaes, Portugal**
- **Per Olthuis, Norway**
- **Christian Schmitt Plank, Germany**
- **Shani Shilo, Israel**
- **Ewelina Szmytke, Poland**
- **Mirjami Tran Minh, Finland**
- **Stefania Vallone, Italy**
- **Diego Villalón, Spain**

REFERENCES

1. Chan BA, Hugues BGM. Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. Transl Lung Cancer Res 2015; 4(1): 36-54.

2. Aggarwal A, Lewison G, Idir S, et al. The State of Lung Cancer Research: A Global Analysis. J Thorac Oncol. 2016 Jul;11(7):1040-50. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27013405.

3. Begum M, Lewison G, Lawler M, Sullivan R. Mapping the European cancer research landscape: An evidence base for national and Pan-European research and funding. European Journal of Cancer. 2018, July. Volume 100: 75–84. Available at: https://www.ejcancer.com/article/S0959-8049(18)30818-9/fulltext.

4. World Health Organization. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. Available at: globocan.iarc.fr/Pages/fact_sheets_cancer.aspx

5. European Respiratory Society. European Lung White Book. Available at: www.erswhitebook.org/files/public/Chapters/19_lung_cancer.pdf.

6. European Alliance for Personalised Medicine. White paper on lung cancer in Europe. Available at: https://www.euapm.eu/pdf/EAPM_White_Paper_on_Lung_Cancer_-_PM.pdf.

7. International Association for the Study of Lung Cancer (IASLC). Lung Cancer Fact Sheet 2016 Europe. Available at: https://www.iaslc.org/lung-cancer-fact-sheet-2016-europe.

8. Global Lung Cancer Coalition. Symptom awareness and attitudes to lung cancer. Findings from a global study. 2017. Available at: http://www.lungcancercoalition.org/uploads/docs/Global%20briefing%20-%20FINAL.pdf.

9. Geissler j, Ryll B, Leto di Priolo S, Uhlenhopp M. Improving Patient Involvement in Medicines Research and Development: A Practical Roadmap. Therapeutic Innovation & Regulatory Science 1-8. 2017. Available at: https://research.pasteur.fr/wp-content/uploads/2017/07/research_pasteur-patients-et-chercheurs-vers-un-nouveau-dialogue-improving-patient-invovlvement.pdf.

10. Sacristan JA, Aguaron A, Avendaño-Sola C, et al. Patient involvement in clinical research: why, when, and how. Patient Prefer Adherence. 2016; 10: 631–640. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4854260/.

11. LuCE. Challenges in lung cancer in Europe Report, 2016. Available at: www.lungcancereurope.eu/wp-content/uploads/2017/10/LuCE-Report-final.pdf.

12. European Patients´ Academy (EUPATI) website. Available at: www.eupati.eu/clinical-development-and-trials/making-medicine-step-8-confirmatory-studies/ [Accessed July 2018].

13. Eye for pharma website. Available at: social.eyeforpharma.com/uncategorised/accelerating-clinical-trials-strategies-improve-efficiency [Accessed June 2018].

14. Fouad MN, Lee JY, Catalano PJ, et al. Enrollment of patients with lung and colorectal cancers onto clinical trials. J Oncol Pract. 2013 Mar;9 (2): e40-7. Available at: www.ncbi.nlm.nih.gov/pubmed/23814523.

15. Du W, Reeves, J, Gadgeel S, et al. Cost-Effectiveness and Lung Cancer Clinical Trials. CANCER October 1, 2003. Volume 98. Number 7. Available at: https://eurekamag.com/pdf/010/010393190.pdf.

16. Baggstrom M, Waqar S, Sezhiyan A, et al. Barriers to Enrollment in Non-small Cell Lung Cancer Therapeutic Clinical Trials. Journal of Thoracic Oncology. Volume 6, Issue 1, January 2011, Pages 98-1. Available at: www.sciencedirect.com/science/article/pii/S1556086415319018.

17. Cancer Council Australia. Optimal care pathway for people with lung cancer. Available at: www.cancer.org.au/content/ocp/health/optimal-care-pathway-for-people-with-lung-cancer-june-2016.pdf.

18. Cancer.Net website. Lung Cancer - Non-Small Cell: About Clinical Trials. Available at: https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/about-clinical-trials [Accessed: August 2018].

19. Du W, Mood D, Gadgeel S, Simon MS.An educational video to increase clinical trials enrollment among lung cancer patients. J Thorac Oncol. 2008 Jan;3(1):23-9. Available at: www.ncbi.nlm.nih.gov/pubmed/18166837.

20. Pew Internet & American Life Project. The online health care revolution [Internet]. The Project; 2000.

21. Kissane D, Bultz BD, Butow PN, et al., editors. Handbook of Communication in Oncology and Palliative Care. Oxford, UK: Oxford University Press; 2010.

22. Somkin CP, Altschuler A, Ackerson L, et al. Organizational barriers to physician participation in cancer clinical trials. Am J Manag Care. 2005 Jul; 11(7):413-21.

23. Sacher AG, Le LW, Leighl NB, Coate LE. Elderly patients with advanced NSCLC in phase III clinical trials: are the elderly excluded from practice-changing trials in advanced NSCLC?

J Thorac Oncol. 2013 Mar;8(3). Available at: www.ncbi.nlm.nih.gov/pubmed/23407560.

24. Sharrocks K, Spicer J, Camidge DR, Papa S. The impact of socioeconomic status on access to cancer clinical trials. Br J Cancer. 2014 Oct 28; 111(9): 1684–1687. Available at: www.ncbi.nlm.nih.gov/pmc/articles/PMC4453719/.

25. Hamel LM, Penner LA, Albrecht TL. Barriers to Clinical Trial Enrollment in Racial and Ethnic Minority Patients With Cancer. Cancer Control. 2016 Oct; 23(4): 327–337. Available at: www.ncbi.nlm.nih.gov/pmc/articles/PMC5131730/.

26. Kwiatkowski K, Coe K, Bailar JC, Swanson GM. Inclusion of minorities and women in cancer clinical trials, a decade later: Have we improved? Cancer. 2013;119: 2956-63. Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/cncr.28168.

27. Urciuoli B. Socioeconomic Disparity in Lung Cancer Care. Oncology Nursing News. 2018. Available at: www.oncnursingnews.com/web-exclusives/socioeconomic-disparity-in-lung-cancer-care.

28. Rivers D, August EM, Sehovic I, Lee Green B, Quinn GP. A systematic review of the factors influencing African Americans' participation in cancer clinical trials. Contemp Clin Trials. 2013 Jul; 35(2):13-32.

29. Unger J, Hershman DL, Albain KS. Patient Income Level and Cancer Clinical Trial Participation. J Clin Oncol. 2013 Feb 10; 31(5): 536–542. Avaiable at: www.ncbi.nlm.nih.gov/pmc/articles/PMC3565180/.

30. Forrest LF, Adams J, Wareham H. et al. Socioeconomic Inequalities in Lung Cancer Treatment: Systematic Review and Meta-Analysis. PLoS Med 10(2): e1001376. Available at: journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001376.

31. Virani S, Burke L, Remick S, Abraham J. Barriers to Recruitment of Rural Patients in Cancer Clinical Trials. J Oncol Pract. 2011 May; 7(3): 172–177. Available at: www.ncbi.nlm.nih.gov/pmc/articles/PMC3092658/.

32. Sharrocks K, Spicer J, Camidge DR, Papa S. The impact of socioeconomic status on access to cancer clinical trials. Br J Cancer. 2014 Oct 28; 111(9): 1684–1687. Available at: www.ncbi.nlm.nih.gov/pmc/articles/PMC4453719/.

33. Paasche-Orlow MK, Taylor HA, Brancati FL . Readability standards for informed-consent forms as compared with actual readability.N Engl J Med. 2003 Feb 20; 348(8):721-6.

34. Jenkins W, Matthews A, Bailey A, et al. Rural areas are disproportionately impacted by smoking and lung cancer. Prev Med Rep. 2018 Jun; 10: 200–203. Available at: www.ncbi.nlm.nih.gov/pmc/articles/PMC5984228/.

35. Wong M, Qian Lao X, Ho K et al. Incidence and mortality of lung cancer: global trends and association with socioeconomic status. S cientific Reports volume 7, Article number: 14300 (2017). Available at: www.nature.com/articles/s41598-017-14513-7.

36. Bosetti C, Malvezzi M, Rosso T, et al. Lung cancer mortality in European women: Trends and predictions. Lung Cancer. December 2012. Volumen 78, Issue 3, Pages 171-181. Available at: https://www.lungcancerjournal.

info/article/S0169-5002(12)00477-1/pdf.

37. American Association for Cancer Research (2018). Lung cancer mortality rates among women projected to increase by over 40 percent by 2030. Available at: https://www.sciencedaily.com/releases/2018/08/180801084051.htm.

38. Graham J (2017). Clinical trials for cancer could use more older people. The Washington Post. Available at: https://www.washingtonpost.com/national/health-science/clinical-trials-for-cancer-could-use-more-older-people/2017/07/21/c015d858-6bc7-11e7-b9e2-2056e768a7e5_story.html?noredirect=on&utm_term=.a5f69d714648.

39. Hurria A, Levit LA, Dale W, et al. Improving the Evidence Base for Treating Older Adults With Cancer: American Society of Clinical Oncology Statement. Journal of clinical oncology. November, 2015. Vol 3. Number 32. Available at: http://ascopubs.org/doi/abs/10.1200/jco.2015.63.0319.

40. World Cancer Research Fund International. Lung cancer statistics. Available at: www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/lung-cancer-statistics [Accessed: June 2018].

41. LuCE. Disparities in diagnosis, care and treatment access Report, 2017. Available at: www.lungcancereurope.eu/wp-content/uploads/2017/11/II-LuCE-Report-web-version.pdf.

42. Raimond A, Sprague J, Jaggumantri V. Cross-border enrolment of rare disease pateints. Considerations for planning and conducting global rare disease clinical trials. 2018. Available at: https://prahs.com/resources/whitepapers/Cross%20Border%20Enrollment%20of%20Rare%20Disease%20Patients.pdf.

43. Rich A, Beckett P, Baldwin D (2018). Status of Lung Cancer Data Collection in Europe. JCO Clinical Cancer Informatics - published online February 16, 2018. Available at: http://ascopubs.org/doi/abs/10.1200/CCI.17.00052?journalCode=cci.

44. Ramaswami R, Paulino E, Barrichello A, et al. Disparities in Breast, Lung, and Cervical Cancer Trials Worldwide. Journal of Global Oncology , no. 4 (August 2018) 1-11. Available at: http://ascopubs.org/doi/abs/10.1200/JGO.17.00226.

45. A Breath of Hope Lung Foundation website. Research facts & Underfunding. Available at: https://abreathofhope.org/underfunding/ [Accessed: July 2018].

46. Peppercorn J, Weeks J, Cook F, Joffe S 2004, Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review, Lancet, no. 363, pp. 263–270.

47. Tam VC, Tannock IF, Massey C, Rauw J, Krzyzanowska MK. Compendium of unpublished phase III trials in oncology: characteristics and impact on clinical practice. J Clin Oncol. 2011 Aug 10; 29(23):3133-9.

48. Penner LA, Blair IV, Albrecht TL, Dovidio JF. Reducing Racial Health Care Disparities: A Social Psychological Analysis. Policy Insights Behav Brain Sci. 2014 Oct; 1(1):204-212.

49. Henderson GE, Churchill LR, Davis AM, et al. Clinical trials and medical care: defining the therapeutic misconception. PLoS Med. 2007 Nov 27; 4(11): e324.

8. APPENDICES

APPENDIX I: Online survey for lung cancer patient advocates in Europe

Patient advocates consulted

1. Finland: Mirjami Tran Minh (Suomen Syöpäpotilaat)
2. Germany: Anette Hans (Landesverband Baden-Württemberg für Lungenkrebskranke und deres Angehörige e.V.)
3. Germany: Christian Schmitt Plank (Bundesverband Selbsthilfe Lungenkrebs e.V)
4. Ireland: Anne-Marie Baird
5. Israel: Shani Shilo (Israel Lung Cancer Foundation)
6. Italy: Stefania Vallone (Women against Lung Cancer in Europe)
7. Norway: Per Olthuis(Lungekreftforeningen)
8. Poland: Ewelina Szmytke (Stowarzyszenie Walki z Rakiem Pluca)
9. Portugal: Isabel Maria Magalhaes (Pulmonale)
10. Romania: Alina Comanescu (Community Health Association)
11. Spain: Diego Villalón (Fundación MÁS QUE IDEAS)
12. The Netherlands: Merel Hennink (Longkanker Nederland)
13. United Kingdom: Jackie Fenemore (National Lung Cancer Forum for Nurses)

Questions

1. Your name
2. Your organization
3. Do you feel there has been an improvement in lung cancer research and clinical trials in recent years? Why or why not?
4. What areas still need improvement?
5. What are the main barriers to accessing lung cancer clinical trials? How can these be overcome?
6. Patient involvement in research. Are patients included in clinical trial design/development? How? If not, why?
7. Is information about clinical trial available and easy to understand?
8. What should pharmaceutical companies do to improve lung cancer clinical trials design, development and access?
9. What should the regulatory agencies do to improve lung cancer clinical trials access?
10. Any other comments do you want to share?

APPENDIX II: Qualitative interviews with specialists in lung cancer research

Specialists consulted

- **Medical community:**
  - **Linda Coate,** Consultant Medical Oncologist and Vice Clinical Lead, Cancer Trials Ireland.
  - **Tanja Cufer,** Professor of Oncology, University Clinic Golnik; Medical Faculty Ljubljana, Slovenia.
  - **Jesper Holsts Pedersen,** Associate professor and consultant in thoracic surgery at Copenhagen University Hospital, Rigshospitalet; Chairman of the surgical subcommittee of the IASLC strategic screening advisory committee.
  - **Mina Gaga,** Pulmonologist; European Respiratory Society (ERS) President 2017-2018; Medical Director, Athens Chest Hospital.
  - **Greg Korpanty,** Consultant Medical Oncologist; University Hospital Limerick, Ireland.
  - **Silvia Novello,** Medical Oncologist; Member of the American Society of Clinical Oncology (ASCO), of American Thoracic Society (ATS), of European Society of Medical Oncology (ESMO), and the International Association for the Study of Lung Cancer IASLC (past Board of Director Member); Board of director of the Italian Society of Medical Oncology (AIOM); President of Women Against Lung Cancer in Europe (WALCE).
  - **Rolf Stahel,** Medical Oncologist; President of the European Thoracic Oncology Platform (ETOP); ESMO Executive Board. University Hospital Zürich.
- **Pharmaceutical industry:**
  - **David Kerstein and Christian Kruhl,** Global Senior Medical Director and EUCAN Medical Head Solid Tumors. Takeda Oncology.
  - **Giovanni Melillo,** Head of Global Medical Affairs for Immuno-Oncology. AstraZeneca.
  - **Olivier Peeters,** Regional Medical Affairs Director, EMEAC. MSD
  - **Victoria Zazulina,** Boehringer International GmbH. TA Oncology Medicine.
- **Patient advocacy:**
  - **Tommy Björk,** Lung cancer patient advocate, Sweden.
  - **Andrea Borondy Kitts,** Lung cancer patient advocate, United States of America.
  - **Alina Comanescu,** Lung cancer patient advocate, Romania.
  - **Tom Haswell,** Lung cancer patient advocate, United Kingdom .

Questions:

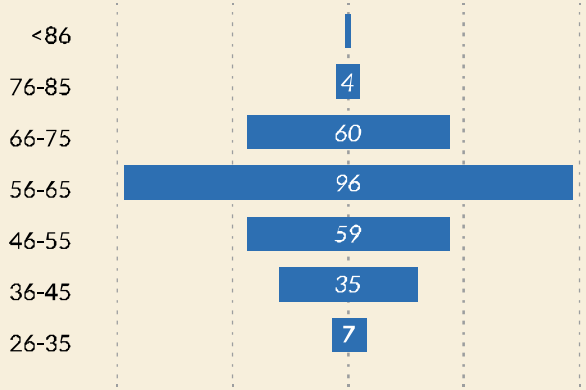
1. PRIORITY - Do you feel there has been an improvement in lung cancer research and clinical trials in recent years? Why? What areas still need improvement?
2. What subtypes of lung cancer would require more research effort? Why?
3. What therapeutic options should be more investigated? Why?
4. Considering the high lung cancer mortality rates, do you think the inclusion criteria should be changed to make clinical trials more accessible for groups of patients who have not traditionally been candidates?
5. PRIORITY - Is there a recruitment deficit in clinical trials in lung cancer? If yes, what is owed and how could it be solved?
6. PRIORITY - Do you have any knowledge if there is a disproportion in recruitment volume in clinical trials in lung cancer having in mind different parts of EU? If yes – which parts of EU have biggest and smallest volume in recruitment and why?
7. Around what percentage of the clinical trials initiated end up being approved?
8. PRIORITY - What are the main causes of failure of a clinical trial? (we mean both failure to recruit patients or the drug itself being a failure at trial stage)
9. PRIORITY - How do you think that the involvement of patients in the clinical trials process (including the CT design stage) can improve the results of the research?
10. PRIORITY - Do you think that medical professionals are aware about all the clinical trials underway? How can this knowledge be improved?
11. PRIORITY - Are medical professionals keen to help lung cancer patients to apply for clinical trial? If not – why? Are there parts of EU/countries where medical professionals are more keen to include lung cancer patients to apply for clinical trials than in other countries? If yes – do you know the reason?
12. PRIORITY - In what ways could the access of patients with lung cancer to clinical trials can be improved?
13. How can we improve access to clinical trials at the intra-community level?
14. How can the new European directives affect clinical trials in lung cancer?
15. PRIORITY - What should pharmaceutical companies do to improve lung cancer clinical trials (design, development and access)?
16. PRIORITY - What should the regulatory agencies do to improve lung cancer clinical trials access?
17. Any other comments do you want to share?

APPENDIX III: Online survey for patients with lung cancer

Sample characteristics

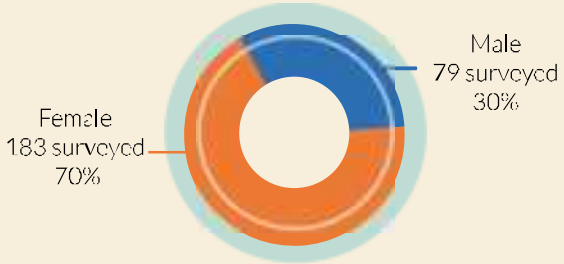
Age distribution of the sample

Average age of the sample: 53.5



Gender distribution of the sample

7 of every 10 respondents were women



Countries of residence of the sample

COUNTRY	NUMBER OF RESPONDENTS
POLAND	51
ITALY	49
DENMARK	26
SPAIN	24
FRANCE	20
THE NETHERLANDS	20
FINLAND	17
NORWAY	16
DEUTSCHLAND	13
UK	9
ROMANIA	6
BELGIUM	4
SWEDEN	4
CROATIA	2
TURKEY	1
TOTAL	262

Questions

1. **Gender**
   Male / Female
2. **Age**
3. **Country of residence**
4. **Have you ever heard about clinical trials?**
   Yes / No
   If "Yes" (to question 4)
5. **Where did you hear about clinical trials? *(Select one or more)***
   Internet / Physicians / Nurses / Other healthcare providers / Magazines and newspapers / Hospital hand-out material / Patient organisations / Social media / Other patients / Family and friends / Other (please specify)
6. **Are you interested in knowing more about clinical trials for lung cancer?**
   Yes / Maybe / No
7. **Do you understand what a clinical trial is?**
   Yes / Somewhat / A little bit / No
8. **How would you rank your overall level of knowledge about clinical trials?**
   Very good / Good / Medium / Little / None
9. **Do you know the differences between a Phase I, II, III or IV clinical trial?**
   Yes / No
10. **Clinical trials are used to generate information about: (Select one or more)**
    Safety / Cost / Efficacy / Prognosis / Effectiveness / Other (please specify)
11. **Have you ever been interested to know more about clinical trials in lung cancer?**
    Yes / No
12. **Have you ever searched for information about clinical trials in lung cancer?**
    Yes / No
    If "No" (to question 12)
13. **What are your reasons for not searching for information about clinical trials?** Open answer
14. **If you want to find information about clinical trials in lung cancer in the future, what sources would you use? *(Select one or more)***
    Internet / Physicians / Nurses / Other healthcare providers / Magazines and newspapers / Hospital hand-out material / Patient organisations / Social media / Other patients / Family and friends / Other (please specify)
    If "Yes" (to question 12)
15. **What sources have you used to get information about clinical trials? (Select one or more)**
    Internet / Physicians / Nurses / Other healthcare providers / Magazines and newspapers / Hospital hand-out material / Patient organisations / Social media / Other patients / Family and friends / Other (please specify)
16. **Did you get the information you wanted?**
    Yes, always / Very often / Sometimes / Rarely / No, never / Not sure

If "Very ofter, sometimes, rarely, never or not sure" (to question 16)

17. **Why didn´t you get the information you wanted or why are you not sure? Open answer**

18. **Are you (or have you ever been) a candidate for a clinical trial?**
    Yes / No / I don´t know
    If "No" or "I don´t know" (to question 18),

19. **What is your perception of clinical trials?**
    Very negative / Somewhat negative / Neutral/Neither negative nor positive / Somewhat positive / Very positive

20. **Would you personally participate in a clinical trial for a new drug?**
    Yes / No / I don´t know
    Could you explain your reason?
    Open question
    If "Yes" (to question 18)

21. **Have you ever participated (or are you participating) in a clinical trial?**
    Yes / No / I don´t know
    If "Yes" (to question 21)

22. **How do you view your experience as participant of a clinical trial?**
    Very negative / Somewhat negative / Neutral/Neither negative nor positive / Somewhat positive / Very positive
    If "No" or "I don´t know" (to question 21)

23. **What were your reasons for not participating, if you were a candidate for a clinical trial? Open answer**

24. **Would you personally participate in a clinical trial for a new drug?**
    Yes / No / I don´t know

25. **Could you explain your reason? Open answer**

26. **Do you think it´s valuable for patients to work with researchers in the clinical trial development process? (identifying needs, recruiting participants, reviewing the trial protocol etc.)**
    Yes / Maybe / No / I don't know

27. **Please provide a reason(s) your answer Open answer**

28. **Are there any concerns about clinical trials that you wish to share? Open answer**

ALONE WE CAN
DO SO LITTLE,
TOGETHER
WE CAN
DO SO MUCH.

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LuCE is the voice of patients with lung cancer, their families and survivors at a European level

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