Cancer clinical research in Latin America: current situation and opportunities. Expert opinion from the first ESMO workshop on clinical trials, Lima, 2015

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ABSTRACT

Latin America and the Caribbean have not yet developed strong clinical cancer research programmes. In order to improve this situation two international cancer organisations, the Latin American Society of Clinical Oncology (SLACOM) and the European Society of Medical Oncology (ESMO) worked closely with the Peruvian Cooperative Oncology Group (GECOPERU) and organised a clinical cancer research workshop held in Lima, Peru, in October 2015. Many oncologists from different Latin American countries participated in this gathering. The opportunities for and strengths of clinical oncology research in Latin American and Caribbean countries were identified as the widespread use of the Spanish language, the high cancer burden, growing access to information, improving patient education, access to new drugs for research centres, regional networks and human resources. However, there are still many weaknesses and problems including the long timeline for regulatory approval, lack of economic investment, lack of training and lack of personnel participating in clinical research, lack of cancer registries, insufficient technology and insufficient supplies for the diagnosis and treatment of cancer, few cancer specialists, low general levels of education and the negative attitude of government authorities towards clinical research.

CANCER RESEARCH WORLDWIDE

Cancer research has developed hugely over the last two decades. Ethical standards for research on humans were established in the 1970s. The infamous Tuskegee Syphilis Study conducted in Alabama, USA between 1932 and 1972 revealed unethical behaviour common at the time. Exposure of the failures in this and other studies led to the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research producing the Belmont Report that established three basic principles for research: respect for persons, beneficence and justice. The Belmont Report defines research as a ‘class of activities designed to develop or contribute to generalizable knowledge.’

Some years before the Belmont Report, in 1964 the World Medical Association (WMA) established ethical principles for experimentation involving human beings, which in turn gave rise to the Declaration of Helsinki. Although it is not a legal instrument, the Declaration of Helsinki has been accepted globally as a cornerstone of human research ethics and is frequently modified in order to improve it and establish clearer concepts for regulating research in humans. It was last updated in 2013.

The World Health Assembly Resolution 58.22 of 2005 recognised the International Agency for Research on Cancer (IARC) and the International Atomic Energy Agency (IAEA) for their efforts in developing cancer research. This resolution also called for increased global clinical research on the diagnosis, prevention and treatment of cancer.

Despite efforts to better understand its causes, prevention and treatment and to develop better drugs more quickly, the impact of cancer on our society has increased dramatically over the last 25 years. More patients live for more than 5 years after diagnosis, although with differences between countries and geographical zones. Indeed, the long-term survival of patients with cancer is not necessarily worse than that of those with heart failure and stroke. A recent review found that 5-year survival was about 43% for...
all cancers, 40–68% for stroke and 26–52% for heart failure. Improvements in cancer treatment include less invasive and less mutilating surgery; new radiotherapy technologies that have better results with less toxicity, more effective chemotherapy with improved toxicity control, and the development of personalised treatment and targeted therapy. There have also been recent developments in immuno-oncology with better nutrition support and improved supportive therapy that allows patients undergo simultaneous treatments. Unfortunately, these developments are accompanied by an enormous increase in cancer health costs. The total economic burden of premature death and disability from cancer worldwide was calculated at US$895 billion in 2008, which represents 1.5% of the world’s gross domestic product (GDP). This economic cost of cancer is nearly 19% higher than that of heart disease, which is second at US$753 billion.

Clinical trials help improve cancer treatment, with several collaborative oncology groups working to develop cancer therapy. Most of these groups are in the northern hemisphere and in Australia, so cancer patients from Latin America, the Caribbean and Africa are under-represented, highlighting the differences between regions of the world in access to adequate cancer treatment. Furthermore, clinical trial results usually do not reflect differences between cultures and ethnic groups, and cannot be generalised to populations in other regions. In addition, many cancers of concern in developing countries are less important in developed countries, resulting in a lack of clinical trials and little interest from the pharmaceutical industry in carrying out research on these diseases.

In order to improve participation and representation, collaborative teams and groups should be set up in regions historically under-represented in clinical trials. For example, the Central European Cooperative Oncology Group (CECOG) was set up in 1999 in Vienna, Austria. This group represents patients from its 23 member countries, with almost 200 oncology patients per year included in phase III and II clinical trials, and participation in phase I clinical trials. This effort has resulted in articles published in prestigious journals, high representation at the most important oncology conferences, and recognition within the oncology community as one of the foremost collaborative groups in cancer research worldwide (http://www.cecog.org).

There have been some attempts in Latin America to create collaborative groups to promote research on cancer treatment. For example, LACOG (the Latin American Cooperative Oncology Group) has built a network of regional oncology investigators with the same aims as CECOG but has not yet achieved the same results.

**Cancer Research in Latin America**

Globalisation has had a favourable impact on the development of clinical trials in Latin America. The best results were achieved in 2007 when three Latin American countries were ranked in the top 25 countries with high participation in pharmaceutical clinical trials: Argentina was in 15th place (trial density 19), Brazil in 17th place (trial density 4) and Mexico in 19th place (trial density 6.2).

There are large disparities in research spending among Latin American countries. Brazil is the only country to spend more than 1% of its GDP on research and development, although this figure is lower than the 2% recommended by WHO. Only 4% of all scientific publications published worldwide in 2013 originated in South America. Two thirds of these came from Brazil with 46 306 articles, with Argentina in second place with 9337 articles and Chile in third place with 6794 articles. Other countries contributing over 1000 publications each during 2013 were Colombia with 4556, Venezuela with 1315 and Peru with 1044, while Uruguay had 799, Ecuador had 524, Bolivia had 222, Paraguay had 87, French Guiana had 69, Surinam had 25 and Guyana had 20. Venezuela is the only country in the region to see a decrease in the number of publications, with 29% fewer in 2013 compared to 2009.

A literature review identified 1972 Latin American abstracts submitted to four of the most important annual scientific meetings on oncology and haematology from 2000 to 2010. Brazil had the most submissions (51%), followed by Argentina, Mexico, Peru, Chile and Uruguay; these six countries provided 95% of the submissions from Latin America. Of the submitted abstracts, 18% were published in full, with Brazil accounting for 60% of publications, followed by Mexico, Argentina, Peru, Chile and Cuba.

In 2012, Latin America participated in only 1665 (4.6%) of the 35 471 clinical trials in cancer worldwide. The same year 21 300 clinical trials were conducted in the USA, 12 times more than in Latin America. Over 65% of all clinical trials in Latin American centres in 2012 were sponsored by the pharmaceutical industry, with the remainder funded by academic centres or other financial sources. Excluding Brazil, Chile provides the most public funds for clinical studies in South America followed by Argentina, with Uruguay, Paraguay and Bolivia providing very little.

Although public funding for research has decreased due to the economic downturn, there is optimism that research on health, including cancer, will become more important in Latin American countries as part of the Millennium Development Goals.

**The Future of Clinical Research in Latin America**

During 2011 Latin America spent only 0.65% of its GDP on research and development, 3.4 times less than in developed countries. This lack of local resources hinders research in the region which is therefore mainly funded by international pharmaceutical companies, limiting the potential to focus clinical research on the real priorities in the region. The percentages of GDP spent...
on research and development during 2008–2011 in some developed countries and in Latin American countries are compared in table 1.17

Another topic of concern is the lack of oncology specialists, including medical oncologists, haematologists, radiotherapists and oncology surgeons. For example, in Chile, a country with a population of approximately 17 million, there are only 80 medical oncologists, more than half of whom are located in the capital, Santiago, which has a population of around 6 million.18 The low number of specialists in some Latin American countries results in work overload and no time for clinical research. In addition, some countries such as Haiti, Suriname, Guyana and Belize, do not have access to radiotherapy at all.17

A further important limitation for clinical research in Latin America is the time to regulatory authority approval for clinical trials, which is much longer than in Europe, North America, Asia Pacific and Africa. This limits the interest of the pharmaceutical industry in conducting clinical research in this part of the world.19 Another drawback is the lack of skilled fulltime clinical researchers, which may result in low data quality. These problems must be overcome by training personnel and improving data quality.20

Approximately 40% of the population of Latin America live in rural areas, rising to 70% in some regions.21 This situation sometimes restricts access to healthcare services and to specialists. Consequently, it is more difficult to recruit patients for clinical trials compared with some developed countries where fewer people live in rural areas and there access to healthcare is more equal. Moreover, health facilities have usually not been designed with clinical research in mind as they are intended to serve the health needs of the population and not the requirements of research.

Although, as mentioned above, many factors hinder the development of clinical trials in Latin America, the region does have interesting potential for clinical research projects and for multicentre clinical trials conducted by the pharmaceutical industry.

Cancer epidemiology in Latin America differs from that in other regions.22 This could provide a regional advantage by attracting research on cancers, such as gastric, cervical and gallbladder cancer, which are more common than in developed countries.

Research on new targeted treatments needs to recruit many patients with specific characteristics and mutations, providing an advantage for multicentre collaborative trials which can enrol the required numbers of patients. However, it is important to determine if trial results are generalizable to Latin American and Caribbean patients. In the USA, Latin Americans account for 20% of the general population but for no more than 3% of trial participants.23

Good clinical development, high quality participation in cancer trials and interest from the researchers and directors of Latin American cancer centres, have provided an opportunity to increase regional cancer research networks, especially as regards collaborative multicentre clinical trials. This has also led to the creation of partnerships between cancer centres in North America and Europe and centres in Latin America.24

The majority of people in Latin America and the Caribbean live in or close to cities, with most countries having one or more cities with a population of 5 million or above. This is an important consideration for clinical trial sponsors who require centres that can recruit sufficient patients, and also for patients who can thus access centres conducting clinical trials.

Latin America has a further advantage over Europe regarding clinical trials development: most Latin America countries are Spanish speaking, while in Brazil, with a population of over 200 million, the official language is Portuguese. Consequently, translation between different languages is not required, as is often necessary in Europe, so communication between patients and their families and researchers is much easier and clearer. Many researchers also speak good English, which facilitates communication with sponsors and the main clinical trial team.

Most cancer research in Latin America is currently funded by pharmaceutical companies; however, improving educational levels and better access to healthcare is slowly resulting in increased support for and funding of cancer research by governments, universities and cancer

| Table 1  | Percentage of gross domestic product (GDP) spent on research and development during the period 2008–2011 |
|----------|---------------------------------------------|
| Non-Latin American countries | % GDP spent on research and development | Latin American countries | % GDP spent on research and development |
| South Korea | 3.74 | Brazil | 1.16 |
| Japan | 3.36 | Cuba | 0.61 |
| USA | 2.9 | Argentina | 0.6 |
| Germany | 2.82 | Costa Rica | 0.54 |
| France | 2.25 | Uruguay | 0.43 |
| Canada | 1.8 | Mexico | 0.4 |
| Czech Republic | 1.8 | Chile | 0.37 |
| UK | 1.76 | Ecuador | 0.26 |
| China | 1.7 | Panama | 0.19 |
| Norway | 1.69 | Bolivia | 0.16 |
| Portugal | 1.5 | Colombia | 0.16 |
| Spain | 1.39 | Peru | 0.15 |
| Italy | 1.26 | El Salvador | 0.08 |
| Russia | 1.16 | Guatemala | 0.06 |
| Poland | 0.77 | Paraguay | 0.06 |
| | | Nicaragua | 0.05 |
| | | Honduras | 0.04 |
centres. Consequently, more professionals will be encouraged to engage in cancer research.

In October 2015, the authors of this article participated in a workshop on clinical trials in oncology, sponsored by the Latin American Society of Clinical Oncology (SLACOM) and the European Society of Medical Oncology (ESMO) and held in Lima, Peru. More than 40 medical oncologists and radiotherapists from Peru, Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, Puerto Rico and Venezuela discussed the situation regarding clinical trials in Latin America and the Caribbean. Their conclusions are summarised below.

Weaknesses of and perceived threats to cancer clinical research in Latin America and the Caribbean

Timeline for regulatory approval
Latin America has one of the longest timelines globally from application for a clinical trial until regulatory approval. The workshop participants strongly believe that this period must be shortened so that the region becomes more attractive and competitive for pharmaceutical companies wishing to conduct clinical trials. Medical oncologists, researchers and pharmaceutical companies should work together with local authorities to shorten the time required for regulatory approval.

Economic investment
Latin America and the Caribbean have a very low level of investment in development and research compared to developed countries. In addition, few local resources are allocated to clinical research. The workshop participants agreed that governments in Latin America and the Caribbean must increase resources for cancer research. The participants also recommended that academic institutions focus more on cancer research. Links with the pharmaceutical industry should also be developed to encourage investment in cancer research in the region.

Lack of training and experience in clinical research
Few medical doctors, study coordinators and other team members working in cancer research in Latin America have previous research training; most are part-time, self-educated researchers. There is a lack of educational programmes to incentivize health professionals to participate in clinical research in cancer. The workshop participants agreed that educational programmes for health professionals in cancer research are required to encourage professionalism and improve research quality. Pharmaceutical companies involved in funding clinical trials have supported investigators in developing clinical trials in humans and following good clinical practice.

Lack of cancer registries
Latin American and Caribbean countries lack reliable cancer registries which would allow them to identify cancer burden, types and frequency, facilitate decisions on investment and help define public cancer policy. Some Latin American countries including Peru, Chile, Brazil, Mexico, Colombia, Cuba and Uruguay, have worked to improve this deficit. The workshop participants called on local health authorities to create national and/or regional cancer registries so that the prevalence of different cancers can be determined and clinical research appropriately focussed.

Lack of technology and supplies for the diagnosis and treatment of cancer
There is a deficit, although not in private cancer centres in Latin American and Caribbean countries, of resources, supplies and technologies for the diagnosis and treatment of cancer: chemotherapy treatment is inadequate, there are too few surgical and radiotherapy centres, access to diagnostic imaging is poor, few radiologists have expertise in cancer, and there is a lack of molecular and oncogenomic analysis. The workshop participants believe that patients in the region must have better access to cancer diagnosis and treatment as in North America and Europe. The deficits mentioned above reduce the chances of countries being considered for clinical trials by pharmaceutical companies. Private Latin American cancer centres supplied with good technology have a better chance of participating in clinical trials than public cancer centres with their limited resources.

Number of cancer specialists
The number of cancer specialists per head of population differs in Latin American and Caribbean countries. Uruguay and Argentina have sufficient medical oncologists, but Bolivia and Chile do not. Some countries do not have radiotherapists or palliative care personnel. The low number of specialists contributes to work overload and restricts them from participating in clinical cancer research. The workshop participants consider this situation is detrimental to the development of clinical trials and believe that local health authorities should ensure sufficient cancer specialists are employed.

Low educational levels in Latin American and Caribbean countries
There is limited access to education in Latin America and the Caribbean, resulting in illiteracy and low educational levels, both factors that militate against recruitment to clinical trials. Many potential trial participants fear they will become ‘experimental lab mice’ and so refuse to participate. The workshop participants believe that the authorities should provide good quality education in order to eradicate illiteracy.

Negative perception of clinical research by government authorities
The workshop participants consider that local authorities in Latin American and Caribbean countries do not regard clinical research a priority. Other barriers include laws that frustrate research. The workshop
participants concluded that it is fundamental that research teams work with local authorities to develop policies and a legal environment that allow the development of and access to cancer research.

Opportunities for and strengths of cancer clinical trials in Latin America and the Caribbean

Language and demographics

A great advantage for Latin America compared with other regions such as Europe, is that Spanish is spoken in all countries except Brazil, which is Portuguese speaking. This homogeneity simplifies communication between doctors, research teams and patients eligible for clinical trials. In addition, most people live in or near a large city, so cancer centres located in cities have access to large numbers of patients for enrolment into clinical trials.

Cancer burden

The cancer burden is increasing in Latin America and the Caribbean due to increased life expectancy, better access to health services and the westernisation of lifestyle and diet. Diagnosis and treatment has improved, but the profile of cancer differs from that in developed countries, for example there is more gastric and gallbladder cancer, and less early breast cancer at diagnosis but more local, advanced and metastatic breast cancer. Pharmaceutical companies might consider developing specific cancer trials for Latin America. If not, local research on the most common cancers should be conducted.

Better patient access to information and education

Television, mobile phones and the internet facilitate communication and can be used to educate and inform patients with cancer. Television is widely available in Latin America including rural areas. Mobile phone use is widespread, while internet access is increasing rapidly. These technologies allow better communication with patients who can be updated on treatment possibilities including participation in clinical trials.

Access to new drugs and favourable consequences for investigational centres

Participation in clinical trials allows patients to access the latest drugs. Economic support for cancer treatment is very limited in Latin America and the Caribbean, so clinical trials can provide access to new generation drugs not available as part of normal treatment, such as immunotherapy, monoclonal antibodies and targeted treatments. This also allows researchers gain experience with new drugs, and acknowledgement as innovators in cancer treatment. Institutions conducting research on cancer and participating in clinical trials obtain recognition for their work, thus becoming better known by the local community, and also by other institutions and pharmaceutical companies supporting trials.

Regional network

Clinical trials require regional networks so that researchers have access to a larger pool of patients willing to participate in clinical trials. Regional collaborative cancer groups facilitate contact with other centres and allow institutions work together towards a common objective. Such collaborative groups can become a platform for pharmaceutical companies promoting clinical trials, and for researchers seeking funding.

Human resources

Despite the lack of specialists trained in performing clinical trials, Latin American oncologists are optimistic and feel capable of conducting research in cancer. More research is being carried out and doctors and cancer centres are increasingly participating in cancer clinical trials. Indeed, some cancer centres are dedicated solely to cancer research, which would have been very unusual a few decades ago. Better cancer outcomes, new technology, improved training in cancer, and faster access to information has inspired young doctors to become cancer specialists, increasing the number of specialists and stimulating cancer research in the region.

COLLABORATIVE CANCER GROUPS AND INTERNATIONAL CANCER SOCIETIES: THEIR RELEVANCE FOR LATIN AMERICA

Groups similar to the CECOG in Europe, a successful collaborative and multicentre group, should be set up in Latin America. Indeed, there have been several attempts in the region to create collaborative groups with varying results. Some Latin American collaborative groups focussing on solid tumours are described below.

LACOG (Latin American Cooperative Oncology Group)

This multicentre collaborative cancer group is headquartered in Porto Alegre, Brazil. Most members are from Brazil but there are also some from other countries, principally Argentina, Colombia and Mexico. This group has developed its own cancer research projects which are sponsored by pharmaceutical companies, the public and government grants (http://www.lacog.org.br/).

SLACOM (Latin American and Caribbean Society of Medical Oncology)

This a regional society for medical oncologists. Although this organisation does not participate directly in clinical trials development, it does provide a network for medical oncologists (http://www.slacom.org).

FLASCA (Latin American Federation of Cancer Societies)

This federation links different Latin American cancer societies. It does not participate directly in clinical trials but does provide a network (http://www.flasca.com/).
GAICO (Argentinean Group of Clinical Research on Cancer)
This collaborative group consists of specialists and cancer centres in Argentina. One of its aims is to develop and design clinical cancer trials. It also maintains a website listing clinical trials (http://www.gaico.org.ar/).

ILOGI (Latin American Intergroup of Gastrointestinal Oncology)
This new collaborative group is based in Argentina with members from Argentina and Chile. The group is currently conducting research on cholangiocarcinoma and gallbladder cancer (http://www.ilogi.com.ar/).

GBECAM (Brazilian Group for Breast Cancer Trials)
This is a Brazilian group focused on the development of multicentre clinical trials on breast cancer in Brazil (http://www.gbecam.org.br/).

GOCCHI (Chilean Collaborative Group for Oncologic Research)
This group is focused on developing collaboration between Chilean cancer centres. It is considered important by Chilean cancer researchers, supports various clinical trials and it is a platform for new projects on cancer research (http://www.gocchi.org).

SLAGO (Latin American Symposium on Gastroenterological Cancer)
SLAGO is a biennial conference held in Chile to discuss gastrointestinal cancer and treatment options. In light of the high participation of doctors from Latin America, North America and Europe, a Latin American collaborative group on gastrointestinal cancer was set up. One of its aims is cancer research and multicentre collaboration in clinical trials.26

ONCOLGroup (Colombian Collaborative Group for Clinical and Molecular Research in Cancer)
This group was created to develop molecular and clinical research into cancer in Colombia. The group has already published several studies and is examining molecular research in cancer (http://www.ficmac.org).

GECOPERU (Peruvian Group of Oncological Cancer Research)
GECOPERU is one of the most remarkable collaborative groups in Latin America. The group focuses on the development of clinical trials, and epidemiological and basic sciences research in cancer. It has developed an international network that has allowed members to participate in a significant number of clinical trials (http://www.gecoperu.pe).

GOCUR (Uruguayan Oncological Collaborative Group)
This is a group from Uruguay focused on the creation of and participation in clinical cancer trials (http://www.sompu.org.uy/content/grupo-oncol%23%3B3gico-cooperativo-uruguayo).

CLICaP (Latin American Consortium for Lung Cancer Research)
This consortium was created in 2010 to develop collaborative studies on the biology, diagnosis and treatment of lung cancer. CLICaP has published over 20 studies involving participants from Mexico, Costa Rica, Panama, Venezuela, Colombia, Ecuador, Peru, Chile, Argentina and Uruguay. Some of this work has established genomic differences between populations for mutations in EGFR, KRAS and ALK ROS1 following analysis of over 8500 samples.

Latin American oncologists are comfortable participating in international cancer societies. Many regional oncologists are members of the American Society of Clinical Oncology (ASCO) and/or ESMO, and participate in meetings and undertake commissions. ASCO has a stronger relationship with Latin American countries, and supports meetings and educational courses such as the Multidisciplinary Cancer Management Course (MCMC) for non-cancer health professionals, principally in low income countries.27

ESMO is increasing its participation in Latin America and has focused on a closer working relationship with specialists, given their importance to the development of clinical research in the region. A recent example was the workshop on clinical trials described in this manuscript.28 This event was of great interest to Latin American researchers as it will hopefully incentivise clinical research in the region, provide tools for developing better quality research, and create a connection between Europe and Latin America, laying the foundation for a collaborative network.

CONCLUSION
Latin America has enormous potential to develop good quality cancer research. It is important to encourage research among young cancer specialists and in public and private cancer centres. Regulatory authorities, politicians and governments need to be better informed about research. Networks and strong collaborative groups must be built to improve cancer research in Latin America. The ESMO workshop achieved its main objective of describing the regional situation regarding clinical cancer research. We need to continue to work together to increase participation in cancer research.

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