Sensible Guidelines for the
Conduct of Clinical Trials - 2012

Special Regulatory Issues in Different Regions: South America

Álvaro Avezum, MD, PhD
Director, Research Division
Dante Pazzanese Institute of Cardiology
São Paulo, Brazil

Agenda

- Clinical Trials density: worldwide and South America
- Regulatory Process: South America in perspective
- Summary of causes for inefficient regulatory approval
- Potential solutions to overcome delays and contingencies

Summary based on past experience in SA

- Regulatory processes vary from country to country
- Problems and inconvenient from regulatory process are multi-factorial, not having one single factor to explain it
- Regulatory process may vary depending on the government perspective and, therefore, is not linear overtime
- Even taking into account the current limitation, a lot of progress had been made towards efficiency and system organization
- A single agenda for all SA countries is not feasible at the present time (heterogeneity of the process)

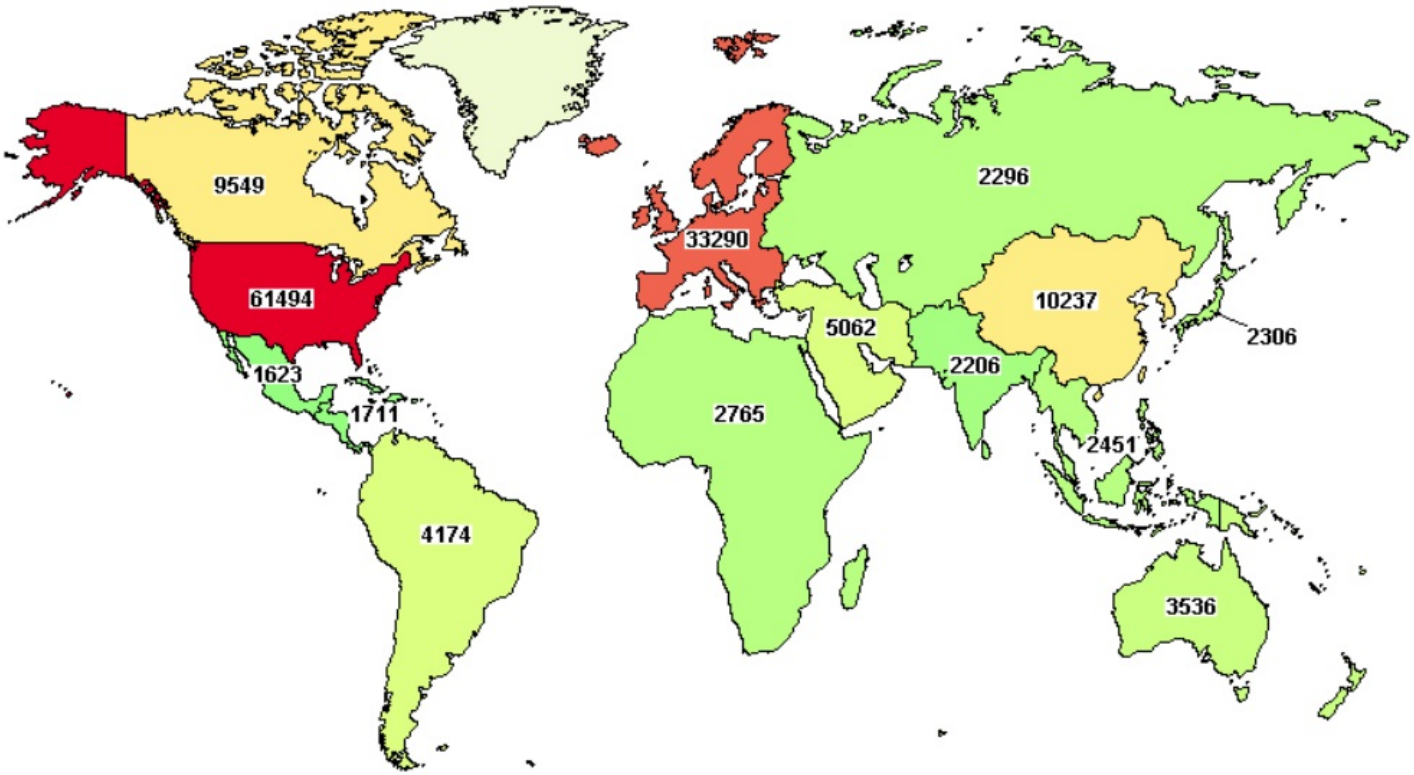
Reasons why sponsor and ARO have expanded into South America

- Accessibility of human subjects (different ethnicity in Brazil);
- Ease of recruitment;
- Population without previous access to treatment (naïve patients)
- “Low cost”
- “Ease of study approval”
- Some countries require local clinical trial data for product registration (e.g. Brazil, China, Nigeria, Philippines, etc)

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Map of All Studies in ClinicalTrials.gov

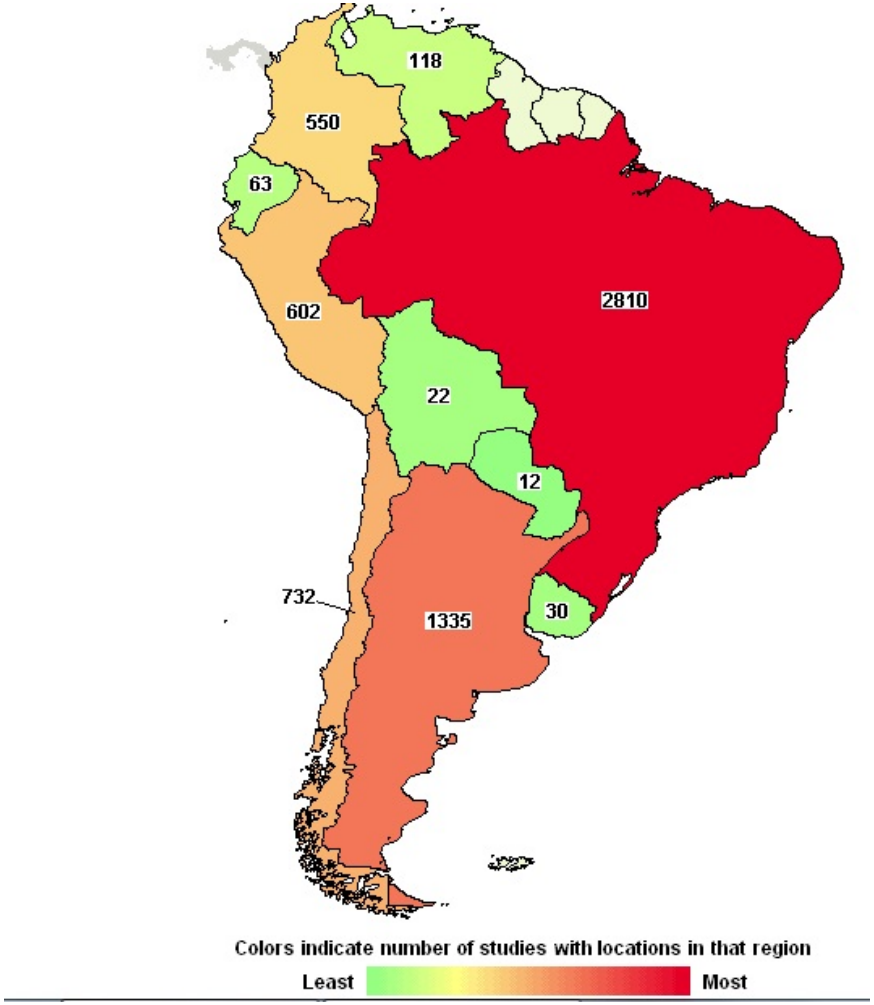


http://clinicaltrials.gov/ct2/home

ClinicalTrials.gov

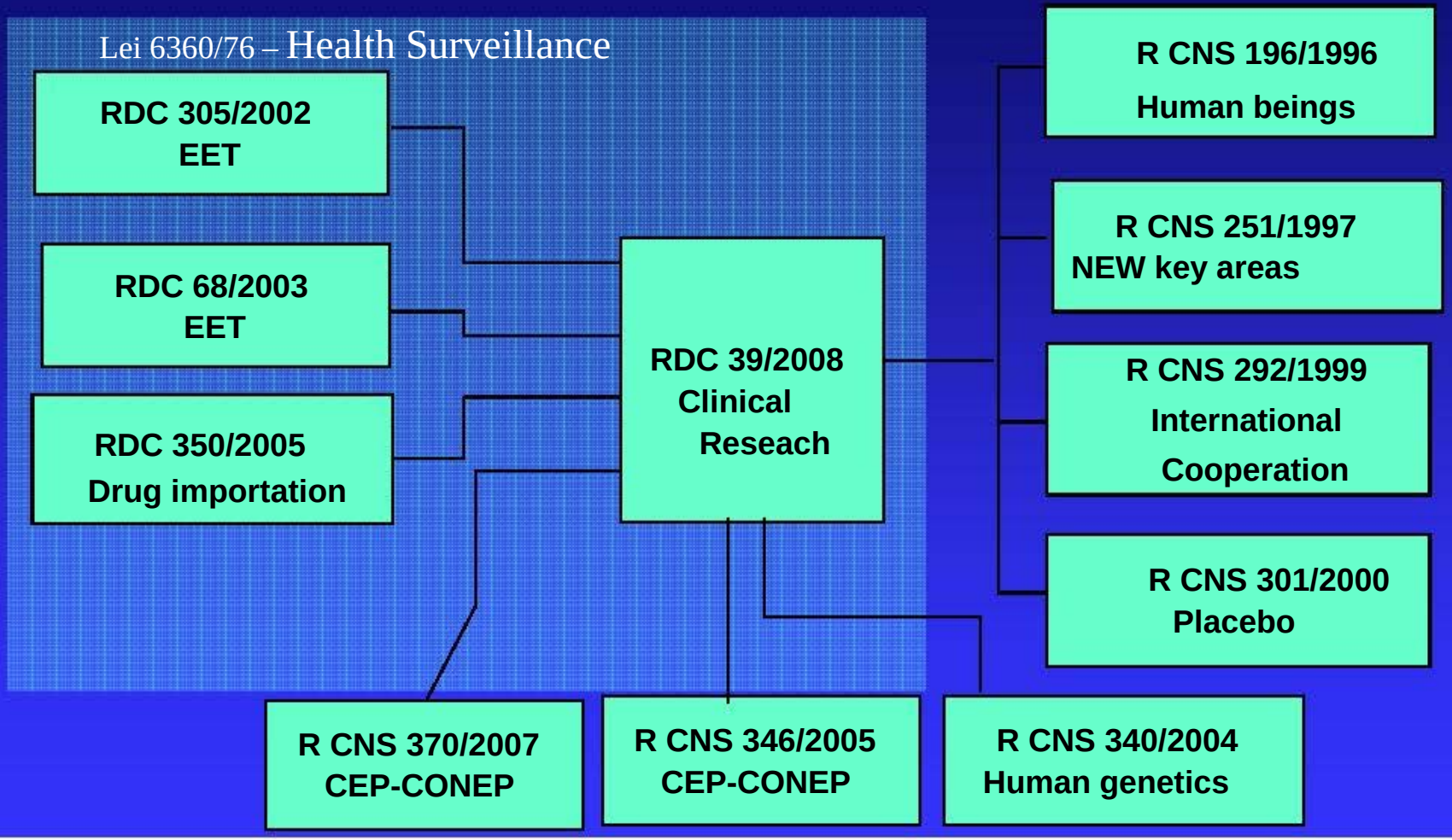
A service of the U.S. National Institutes of Health

Number of Studies with Locations in South America

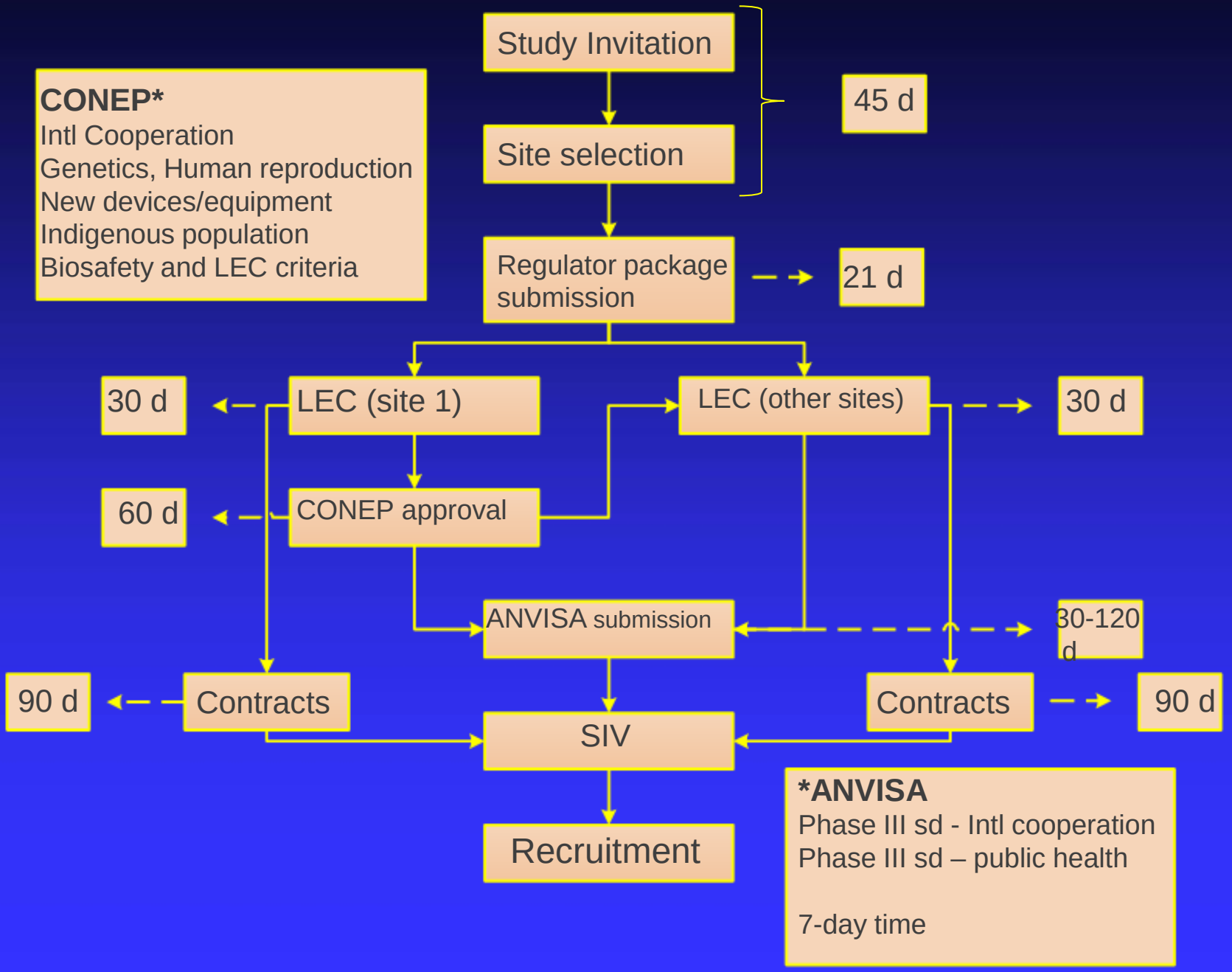


http://clinicaltrials.gov/ct2/home

Biomedical Research Law in Brazil



Regulatory Process – BRAZIL



“Independent” Predictors of Regulatory Approval Delays

- Inadequate translation of study protocol and informed consent
- Incomplete documents submitted to the LEC and NEC
- Non-adherence of the available dates provided by LEC, NEC and lack of proper follow up on those processes
- Lack of clear information on study legal responsibility (Pharma, CRO, ARO, government funding)
- Unavailability of approval in the country where study was first initiated
- Lack Insurance Policy for patient safety (local regulatory requirement)
- Demanding for Insurance Policy for site and investigators (sponsor requirement for site/PI adherence to research GCPs)

“Independent” Predictors of Regulatory Approval Delays

- Unilateral benefit in the research contract (ex where should be the venue for dealing with any legal problem related to the study);
- Unclear description (itemized) of study budget
- Lack of skilled, research-trained attorney in the sites and language barriers
- Inclusion of genetic component and substudies of the main trial (addtl. delay)
- Lack of well-trained staff at the site level (project management and research SOPs)
- Lack of reassurance from sponsor , patient will receive treatment (if positive results) for free (NEC requirement)
- Biological bank outside South America (access should be clearly assured to country investigators)

Argentina

Regulatory environment

Ministry of Health: rules all clinical research activities

Resolution 1490/ 2007 ➔ Resolution 1480/ 2011

Anmat Dispositions: rules pharmacologic clinical research

Disp 5330/1997 ➔ Disp 6677/ 2010

Argentina

Regulatory Environment➔ PROs

- Since November 2010 (Disp 6677), MoH and ANMAT have consistent regulations
- Change of ANMAT head, with clear directions to streamline and facilitate processes
- Delimitation of ANMAT role to pharmacological clinical research aimed at registration of the drugs tested
- Modification of the processes of the initial clinical trial application to streamline approval process
  - Initial meeting with regulatory agents to present and discuss the study
  - Initial CTA submission in parallel to ethic committee approval process
- Clarification of the processes to report ANMAT study follow up information
- Harmonization of national and regional regulations is ongoing, aimed at streamlining approval processes

Argentina

Regulatory Environment➔ CONs

- Investigator initiated studies ruled by same regulations applicable to sponsored clinical research
  - Requirement of an insurance policy or alternative means of insurance provided by a local company
  - Payment of ethic committee, MoH and other fees
  - Standards set by MoH for on site monitoring and overall project management
- Customs:
  - Importation of study materials and drugs is subject to the same regulations/taxes& fees as importations for commercial purposes
  - Recent modification of the importation rules may badly impact importation of trial materials and drugs
- Regional regulations in specific provinces require additional approval processes

Peru

Regulatory environment

Clinical Research Rule of the Ministry of Health

Supreme Decreet 017 2006-SA

Amended by:

Supreme Decreet 006 2007-SA and 011 2007-SA

and supported by Manual of Procedures for Clinical Research

Peru

Regulatory Environment➔ PROs

- Legal provisions aimed at promoting clinical research activities set forth since 2006 have regulated clinical trials under international standards for bioethics and GCPs
- Clinical trials sponsored by LOCAL universities are exempted of payment of MoH submission fees
- Fast MoH evaluation process: 40 working days
- MoH system in place to register on line:
    - Clinical research sites (more than one CR site might be registered per medical institution)
    - Ethic committees
    - Contract research organizations
- Electronic registration of applications for authorization of a clinical trial
- 83.5% of registered sites (n=382) located in Lima (source INS-2009)

Peru

Regulatory Environment➔ CONs

- MoH approval requires annual renewals
- Frequent submissions of MoH progress reports, with timeline varying from study to study: every three, six or twelve months, as specified in the approval documents
- Expeditive reporting of ***all serious*** adverse events to MoH
- Mandatory reporting of ***non serious***, *drug related adverse events* with the MoH progress reports
- New regulation expected to come on board shortly (?)

Chile

Regulatory environment

Technical Normative Rule 37 / 2001: ruling pharmaceutical clinical trials in human beings

Law Nº 20.120, September 22, 2006 about clinical research in human beings, regulated by Decree Nº114, November 2011

Chile

Regulatory Environment➔ PROs

- Clear and stable regulations, applicable to all institutions countrywide.
- No local/regional laws
- Institute of Public Health (IPH) has a good technical team, interested in improving clinical research
- IPH started site inspections 2 years ago
- IPH role limited to pharmacological clinical research aimed at registration of the drugs tested
- CTA application performed on line by the sponsor
- Predictable study approval timelines: response to CTA should be done within 45 days

Chile

Regulatory Environment➔ CONs

- ECs
  - Studies must be approved by each individual local EC
  - Private universities and clinics may require an additional institutional EC approval
  - Some ECs have long study evaluation processes
- Investigator initiated studies ruled by same regulations applicable to sponsored clinical research
  - Requirement of an insurance policy provided by a local company
  - Payment of ethic committee, MoH and other fees. However University and Investigator initiated research can request fees exception
- Customs:
  - Importation of study materials and drugs is subject to the same regulations/taxes& fees as importations for commercial purposes

Regulatory Process: Colombia and Equator

Common Problems leading to prolonged delay for approva:l

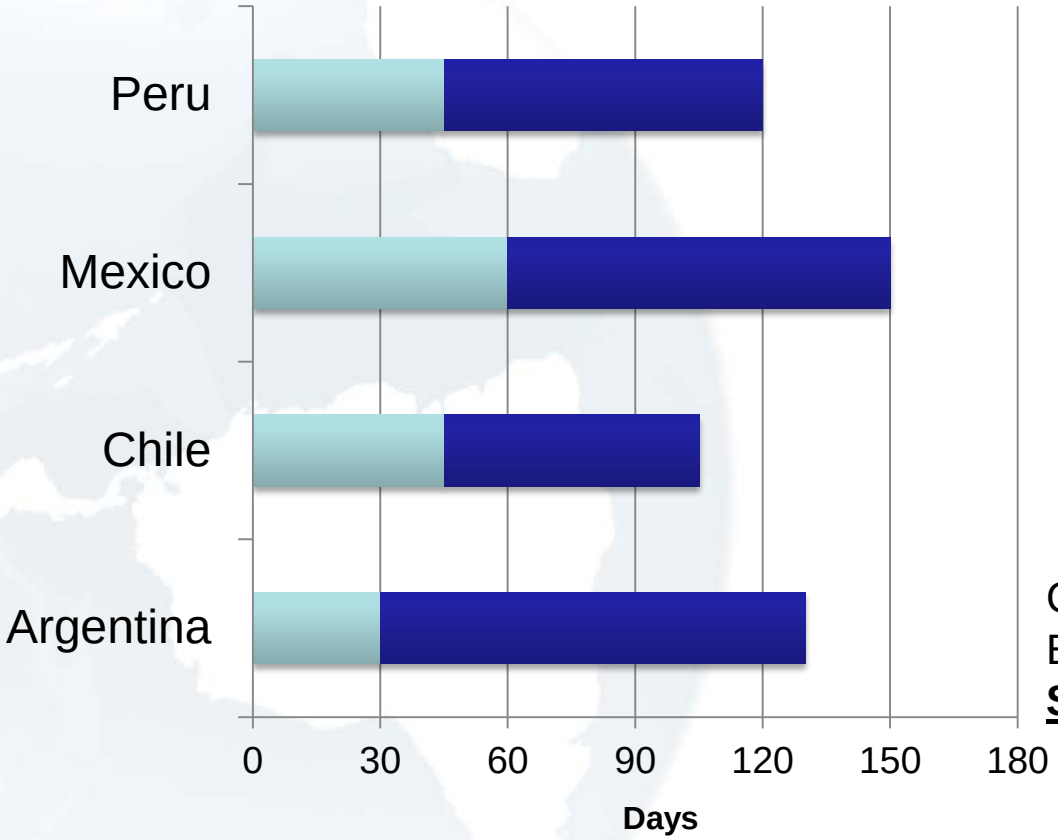
- Discrepancies between Study Protocol and Letter of Approval from LEC information content
- Lack of GCP certificate from ECs and Institutions

Suggestion for improvement:

- To reduce time for provide all documents to LEC responsible to evaluate regulatory package

Time from invitation to coordinate the study and starting recruitment of about 3 months (HOPE-3, APOLLO, OASIS-7)

Expected Regulatory Timelines for Study Start up



Colombia: 90 days
Brazil: 180 days
SA mean: 130 days

Potential Solution for Otimization and Efficiency of the Regulatory Process

- Better and efficient adequacy of regulatory documents to be submitted to all levels of the process, according to the country system and GCP (includes translation);
- To follow the dates provided by investigators and regulatory bodies;
- To facilitate the contract evaluation from both sides;
- To utilize, more often, academic research organizations (scientific leadership, long-term collaboration plus efficiency to conduct all the trial activities);
- To avoid substudies, genetic analysis or study databank at the first study submission (this should come as an amendment following study approval);
- Alliance at the national level involving academic organizations, pharma, CROs and government to establish an efficient model for clinical research;

Potential Solution for Otimization and Efficiency of the Regulatory Process

- Reassurance of country investigators access in the databank (clear stated in the protocol) ;
- To follow a template according to each country in SA not trying to make the same mistake again and again (laws to be followed until we have a better one);
- Choice of sites following essential criteria: pool of patients and access to them, PI credibility, previous experience (volume and quality of data), organized site, well trained team (research SOPs), expedite local regulatory process;
- *"Plataforma Brasil"* will innovate the Health Research field, allowing society to have full access to approved research projects, making possible LEC and NEC work in a unified way, with significant reduction in the time delay for regulatory approval;


2014
FIFA WORLD CUP
Brasil
Brasil
2014
www.EBRP.in
FIFA
WORLD CUP


Rio2016


rio2016