Sensible Guidelines for the Conduct of Clinical Trials - 2012

Special Regulatory Issues in Different Regions: South America

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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 multifactorial, 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)
Number of Studies with Locations in South America
Biomedical Research Law in Brazil

Lei 6360/76 – Health Surveillance

- RDC 305/2002 EET
- RDC 68/2003 EET
- RDC 350/2005 Drug importation

RDC 39/2008 Clinical Research

- R CNS 196/1996 Human beings
- R CNS 251/1997 NEW key areas
- R CNS 292/1999 International Cooperation
- R CNS 301/2000 Placebo
- R CNS 340/2004 Human genetics

CEP-CONEP

Agência Nacional de Vigilância Sanitária
www.anvisa.gov.br
CONEP*
Intl Cooperation
Genetics, Human reproduction
New devices/equipment
Indigenous population
Biosafety and LEC criteria

Study Invitation
Site selection
Regulator package submission

30 d
LEC (site 1)
LEC (other sites)

60 d
CONEP approval

30 d
ANVISA submission

90 d
Contracts

SIV

Recruitment

45 d

21 d

30 d

90 d

*ANVISA
Phase III sd - Intl cooperation
Phase III sd – public health
7-day time

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 Decree 017 2006-SA

Amended by:

Supreme Decree 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 approval:
- 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

- **Peru**: 60 days (EC Approval) + 60 days (MoH approval) = 120 days
- **Mexico**: 45 days (EC Approval) + 75 days (MoH approval) = 120 days
- **Chile**: 45 days (EC Approval) + 75 days (MoH approval) = 120 days
- **Argentina**: 30 days (EC Approval) + 90 days (MoH approval) = 120 days
- **Brazil**: 90 days
- **Colombia**: 90 days
- **SA mean**: 130 days
Potential Solution for Optimization 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 Optimization 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;