Pediatric Rare Disease Enrollment Case Study in Latin America

Agenda

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2. Enrollment Challenges in Pediatric Rare Diseases Clinical Trials
3. Statistics about Latin America and Rare Disease Trials
4. Latin America Clinical Trial Challenges
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6. The Landscape – Doctors & Patients
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Learning Objectives

1. *To review the enrollment challenges of pediatric rare disease trials*
2. *To understands the challenges and opportunities within the Latin American environment and culture*
3. *To apply best practices to meet enrollment targets in a rare disease pediatric study in **Latin America***

Enrollment Challenges in Pediatric Rare Diseases Clinical Trials

Pool of Patients is limited

- ≈50 percent of patients with rare diseases are children[1]
- Eligibility criteria may further limit # of available subjects & may take > patients to get data results[3]
- Protocol must account for vulnerability of patient population & address ethical considerations, particularly if the study design mandates discontinuation of ongoing therapy[2]
- Co-morbidities often co-exist, therefore, **multiple specialties** i.e., neurology, gastroenterology, psychiatry, endocrinology, cardiology and physical therapy often needed
- Longer process for diagnosis confirmation[3]

Complexity of disease & trial can be limiting

- Adhering to exceptional standards of care influences every decision
- >7,000 rare diseases with unique diverse symptomatology, so **problem solving and passion are key**[3]

[2] http://dx.doi.org/10.1016/j.ymgme.2008.10.003

3http://www.clinicalleader.com/doc/rare-disease-patient-recruitment-and-retention-0001

[1] http://info.evaluategroup.com/rs/evaluatepharmaltd/images/2014OD.pdf

Enrollment Challenges in Pediatric Rare Diseases Clinical Trials

Logistics, Timelines & Care need to be considered

Regulatory by country needs to be understood for timelines

Trials require global outreach, therefore patients mostly have to travel to sites[2]

Additional burden is placed on family, for time & resources

Standard of care and treatment pathways within each country can affect the enrollment of a trial, e.g., needing to add a site can add a much longer time frame to overall enrollment targets

Care coordination can be a challenge[3], such as

- Obtaining medical histories
- Having all doctor specialties informed of the protocol & to understand risks involved in an interventional study of which pediatric patient is enrolled

[1]http://info.evaluategroup.com/rs/evaluatepharmaltd/images/2014OD.pdf

[2]http://dx.doi.org/10.1016/j.ymgme.2008.10.003

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Enrollment Challenges in Pediatric Rare Diseases Clinical Trials

Culture needs to be understood

Cross-communication between doctors and main treating doctor is important for the care of the child

Greater need for awareness campaigns in rural areas

- Potential patients
- Doctors not necessarily trained in rare diseases

[1]http://info.evaluategroup.com/rs/evaluatepharmaltd/images/2014OD.pdf

Statistics - Environment

Latin America has 26 countries

> 626.7 million people live in Latin America & the Caribbean representing **8.63%** of the total world population

- US = 318.9 million, almost ½ MORE than the U.S.

Growing middle class

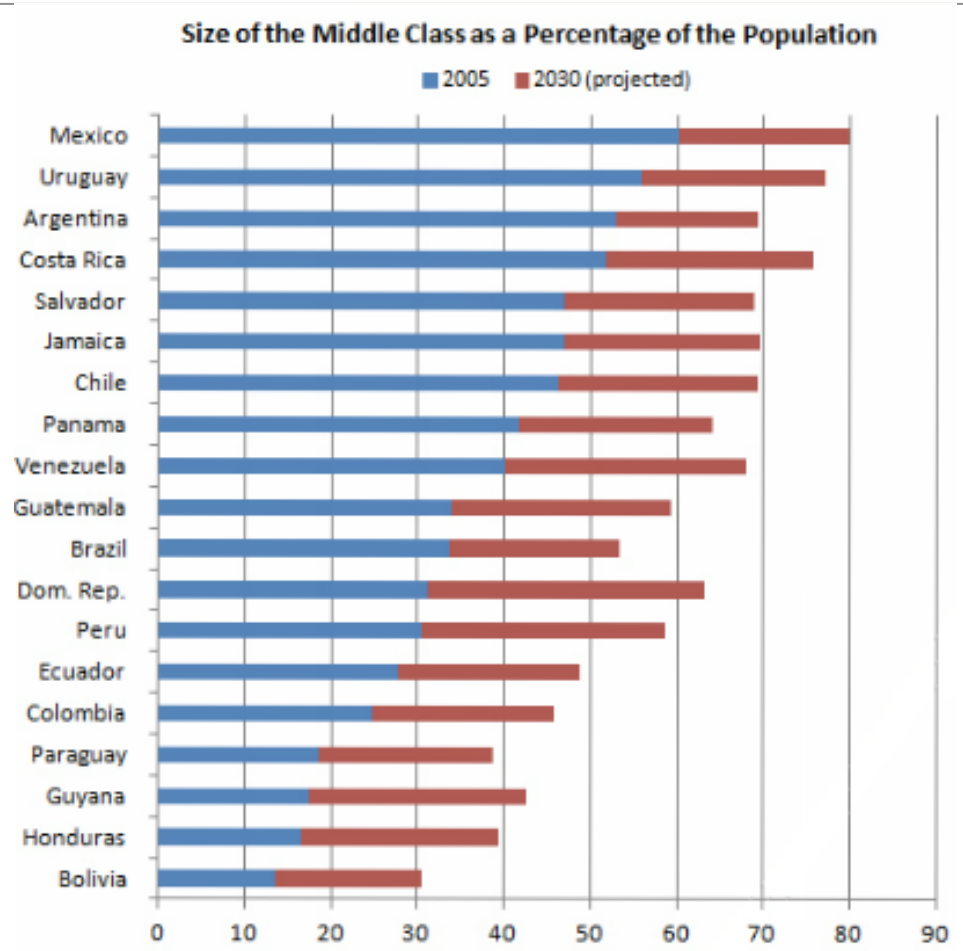
US Latino population represents **17%**

- Some rare diseases have a higher prevalence in this ethnic group, so a pool of patients from Latin America can help with enrollment targets, plus represent Latino population for the US

[1]**http://info.evaluategroup.com/rs/evaluatepharmaltd/images/2014OD.pdf**

[2]www.clinicaltrials.gov

Growth of Middle Class in Latin America[1]



[1] World Bank, 2005

Statistics-Environment

- ✓Top three countries in Latin America for conducting clinical trials are **Brazil, Argentina, and Mexico** with 70% of the population centered in large metropolitan cities.
  - ✓Sao Paulo, Buenos Aires, and Mexico City – with a combined population of 55 million citizens, make patient recruitment and clinical trial management more easily achievable from a logistics perspective[1]
- ✓Many rare disease patients in Latin America have not been in a clinical trial before
- ✓Current # of pediatric rare disease clinical trials in Latin America = 25[2]
  - ✓Argentina, Brazil, Colombia, Peru, Venezuela, Mexico, Chile
  - ✓Currently in Phase III = 7

[1]**http://info.evaluategroup.com/rs/evaluatepharmaltd/images/2014OD.pdf**

[2]www.clinicaltrials.gov

Latin America Clinical Trial Challenges

- ✓Regulatory process can take longer than US – 3 to 9 months minimum
  - (Ethics Committees vs. IRBs)
- ✓Availability of standard of care important
- ✓Quality of the ICF is important
- ✓Cultural landscape needs to be well understood
- ✓Family is critical to success of enrollment
- ✓Education about clinical trials is important
- ✓Advertising to the public can be limited
- ✓Perception of lack of quality data management

Latin America Clinical Trial Opportunities

- ✓Enrollment can be more robust
- ✓Face to face interactions go a long way - Building relationships with PIs and referring physicians can be easier than US
- ✓NGOs & advocacy groups interested in helping & getting information to potential patients
- ✓Private health centers exist
- ✓Middle class is a strong target group
- ✓Mostly Spanish speaking countries (exception Brazil)
- ✓Web info & social media growing (especially Facebook)

Latin American Opportunities

- ✓Large and rapidly rising population of trial native people
- ✓Improved regulatory standards to shorten clinical trial approval timeframes (e.g., Mexico)
- ✓Stronger knowledge & practice of ICH GCP guidelines & existing western medicine standards
- ✓Strong physician-patient relationships contributing to patient retention[1]
- ✓# of highly educated clinical investigators interested in conducting clinical research
- ✓Spanish is the main translation requirement for regulatory documents - besides Brazil
- ✓More pharmaceutical products becoming available to help with some of inclusion/exclusion
- ✓Time zones closer to the US make it easier to monitor trials[1]

[1]http://www.languageconnections.com/clinical-trials-in-emerging-latin-american-countries/

Latin America Landscape – the doctors

- ✓Understanding the cultural preferences is vital, e.g.,
  - ◦Working through the Doctor/PI and/or a Sub-I vs. study coordinator is **normal**
  - ◦Face to face interactions versus email or phone, although texting/What's App getting more popular
  - ◦In general, business moves at a more relaxed pace
- ✓PI/Sub-I & team must be fully engaged due to the multi-specialty nature of a rare disease
- ✓Confirmation of a proper diagnosis is important
  - ◦Medical histories from large institutions may be difficult to obtain
- ✓Having a strong on the ground presence with the site helps execution

Latin America Landscape – the patients

- ✓Family is key
  - ◦All decisions are always family based
  - ◦Population less educated regarding clinical trials
  - ◦People tend not to travel within the country as much
  - ◦High communication to patient family engages smoother decision making and visits to the sites
- ✓Compensation can only be reimbursement for travel and food per Latin American laws
- ✓Age & educational level communication may be important for ICF, screening, etc.[1]
- ✓Advocacy groups may help pinpoint potential patients[2]
- ✓Limited ability to advertise to patients directly
- ✓Concierge approach is needed

[1] http://info.evaluategroup.com/rs/evaluatepharmaltd/images/2014OD.pdf

[2] http://dx.doi.org/10.1016/j.ymgme.2008.10.003

Case Study

PEDIATRIC RARE DISEASE STUDY – EXTENSION INTO LATIN AMERICA

Feasibility Conduct and Methodology

Who

- PIs familiar with this disease, in which the estimated incidence is approximately 1 per 155,000 male live births
- Sites were identified within LA, including Colombia, Peru, Uruguay, Argentina and Mexico that could contribute patients to the study and to determine estimated recruitment rates
- In this study, patients had to be on a currently approved treatment for their rare disease, so it was decided to go into countries where the current treatment was already in place
- Identification of KOLs who were using current treatments were considered

What was needed

- Site experience with procedures and cognitive scales; competition for patients and resources; and acceptability of country to country referrals

Number of patients needed

- 42, but was increased to 48 after statistical analysis was completed

Feasibility Conduct and Methodology

- 42 investigators in Latin America contacted, 18 responses received (43% response rate)
- 8 investigators were interested in study participation (44% interest rate)
- 6 investigators (75%) currently were managing at least 1 rare disease patient aged ≥3 to ≤8 years old, but **only 3 investigators (38%)** currently were managing at least one rare disease patient of any age
- **Argentina, Colombia and Mexico** were chosen and 1 site in each country was opened
- Planned time to bring up a site = 4-6.5 months, 3 months and 6-7 months respectively
- In reality, from submission to SIV:
  - Argentina took 12 months
  - Mexico took 11 months
  - Colombia took 13 months
- Prolonged regulatory approval timelines impacted ability to open sites & actively screen

Enrollment Challenges

Protocol Requirement Issues

- Screen failures were higher than expected (around 50%)
- PIs engaged in other responsibilities, i.e., studies, projects, etc., some were not prioritizing this study
- Some patients needed certain therapies that was not made clear to referring doctors in beginning
- Indigenous language in Mexico not considered (Tzotzil)

Cultural and Communication Issues

- Patients' families didn't want to sign the ICF
- Referring doctors had potential patients, PI not reaching out them
- Patients' families felt the travel was too far (1 site/ country)

Logistical Issues

- Sites & travel agents handled patients' travel poorly (Mexico)
- Reimbursements for patients in Mexico not processed easily
- CRO not scoped to **problem solve** in a timely manner

Enrollment Solutions

An on-the-ground team was identified to

- Provide feedback to sponsor as 3rd party
  - PI recruitment concerns/issues
  - Understand cultural landscape
- Conduct Face to Face meetings with referring physicians to connect them to the protocol and the PI
- Identify & establish relationships with local rare disease advocates
- Act as an intermediary for patient travel
- Liaison between the site, the travel agency and the family
- Provide technology solutions to increase communication
- Problem solve as needed for any logistical problems

Results

- ✓Mexico – Increased enrollment by 50%
- ✓Argentina – No patients qualified due to lower incidence of rare disease
- ✓Colombia – Selected PI was overwhelmed with other priorities, therefore didn't enroll
- ✓Additional sites in Mexico & Colombia added (still in process)
- ✓Sub-I model implemented for Mexico & Colombia
- ✓Coordinated Mexico patient travel & patient reimbursements and retention was 100%
- ✓Technology applied:
  - What's App
  - Local 800# and 24/7 logistical help line

Questions/Comments?

FARMACON