Council for International Organizations of Medical Sciences

5th meeting of the CIOMS Working Group on
Clinical Research in Resource-Limited Settings

8–9 October 2019, Merida, Spain

Minutes

Draft: 29 October 2019

Meeting objectives

- To gain additional insights for the draft CIOMS guidance on clinical research in resource-limited settings from the RIBEF-CIOMS Symposium on medicine and health research in autochthonous populations of Latin America;
- To continue working on the draft guidance; and
- To agree on next steps.

RIBEF-CIOMS Symposium

(Website: https://simposiumribef.com/)

The Second Symposium of the Conference on medicine and health research in autochthonous populations of Latin America was held jointly by the Iberoamerican Pharmacogenetics Network (RIBEF) and the CIOMS Working Group (WG) at the Parliament of Extremadura in Merida on the morning of 8 October 2019 (see participant list in **Annex 1**). It followed immediately after the First Symposium, which was held jointly by RIBEF and the PHI Foundation on 6-7 October 2019.

Opening

Mr Antonio Rodriguez **Osuna**, Mayor of Merida, welcomed the participants to the event. His address was followed by opening remarks from Dr Lembit **Rägo**, CIOMS Secretary-General, who thanked the Government and the University of Extremadura—particularly Dr Adrian LLerena—for giving CIOMS this unique opportunity to obtain additional input to its draft guidance on clinical research in resource-limited settings from the rich experience of the scientists in the RIBEF network. Mr Angel **Calle** from the Extremadura Agency for International Cooperation for Development (AEXCID) expressed his thanks and commended Dr LLerena for his leading role in building a scientific network on pharmacogenetics and pharmacogenomics. Mr Antonio **Hidalgo**, Rector of the University of Extremadura, then added his words of welcome. To conclude, Mr Miguel Angel **Morales**, Vice President of the Extremadura Parliament, highlighted the value of collaboration and the role of CIOMS in supporting the rights of all to a better life through improved public health.

Merida/T'Ho Declaration

The Merida/T'Ho Declaration was announced by video[1] in three of the major autochthonous languages of Latin America (Mayan, Nahuátl and Quichua), with subtitles in Spanish and English. The declaration states three fundamental aspects for human health research and clinical implementation: 1) Consideration of population pharmacogenetics in clinical research and clinical practice; 2) Respect and knowledge of the specific sociocultural context and wisdom, including Traditional Medicine; and 3) Education of researchers on universal values and sustainable attitudes to guarantee good ethical and scientific practices during the whole research process. In addition, the declaration calls for increasing the quantity and quality of clinical research in vulnerable populations.

The declaration is published at https://simposiumribef.com/declaracion/; the English version is reproduced in **Annex 2**.

Presentations by RIBEF scientists

See list of RIBEF representatives and presentations in the participant list (**Annex** 1).

Dr Enrique Teran gave an overview of the origins, history and activities of the RIBEF network. Since 2016 the network has conducted and supported research and implementation in 31 countries. Data on genotypes, phenotypes and ancestry have been collected from over 6000 people from all over Latin America with a view to identify biomarkers that impact drug metabolism in different indigenous populations.

Experiences from Latin America, Africa and Asia

Presentations were made by Drs Eduardo Tarazona, Shyam Diwakar and Pedro Gil. The presentations highlighted the large number of ethnic and linguistic minorities (both sedentary and migrant), early life factors (e.g. frequent infections, under-nutrition) and life style factors (e.g. inappropriate nutrition favouring obesity) impacting their health, and the very important role of traditional medicine in their societies. It was emphasized that any research should aim at achieving health improvements in the population in which it is conducted.

Round Tables I and II

I – Non-clinical research: Dr Enrique Teran summarized the experiences from observational research conducted in indigenous Amerindian populations to characterize genetic and

[1] https://www.youtube.com/watch?v=FjHq2Gjvo1M

environmental factors affecting the response to various classes of medicines, e.g. antihypertensives, hypoglycaemic agents and others.

II – Clinical research: Dr Carlos Galaviz summarized the lessons learned from studies conducted in Mexico and Ecuador. Genetic and environmental factors increase the risk of indigenous populations for obesity, diabetes mellitus type 2 (DMT2), cardiovascular conditions and other non-communicable diseases. These in turn increase women's risk for childbirth complications such as pre-eclampsia and post-partum haemorrhage.

The researchers concluded that **p**atients from indigenous Amerindian populations would benefit from personalized treatment strategies based on their genetics and ethnic background as well as cultural and environmental factors such as nutrition and traditional medicines use. The researchers called for an international policy that proposes health programs with an intercultural approach, building bridges between the dominant culture of the health care services and the culture of ethnic minorities.

The barriers, challenges and lessons learned were similar in non-clinical and clinical studies conducted in indigenous Latin American populations:

Challenges and barriers

- Finance and local human resources for research are scarce. Social and political problems lead to poverty and insecurity, resulting in "brain drain".
- Communication with study participants is hampered by language barriers and cultural differences. The study concepts are foreign to patients, making it difficult to get informed consent and provide feedback about the study findings.
- There are profound health disparities, with a low standard of care in indigenous groups.
- Widespread use of traditional medicine complicates the interpretation of study findings.
- Communities mistrust the researchers and may choose not to disclose factors that affect the study results.
- Remote locations complicate the study logistics.
- Health authorities are not interested in research, leading to delays in study approvals and failure to implement the findings
- Health care workers are not interested to adhere to standardized diagnostic criteria.

Possible solutions

- Involve social scientists in research design to improve relevance and communication
- Discuss general health issues with patients, link this to the use and effect of medicines
- Form partnerships with community leadership and health care providers, focus on local health priorities
- Demonstrate the benefits of research to the community and to leaders
- Return study results in a culturally understandable format

Discussion

The discussion was moderated by Drs Eva Peñas-Lledó and Lembit Rägo. CIOMS WG members suggested some approaches including: Cost-effective use of resources by conducting prospective research and comparative studies of drug effectiveness; combining pharmacogenomics-based programmes with therapeutic drug monitoring; inclusion of indigenous representatives in advisory boards and ethics committees, and making the case for policy-makers to implement the findings in health systems.

While indigenous populations account for as much as 10-15 percent of the Latin American population they consist of many different subgroups, some of which are very small.

Pharmacovigilance reports from these groups are scarce, so there is little awareness of drug-related problems. The subgroups are very diverse, and no single algorithm would work everywhere to optimize diagnosis and treatment.

The CIOMS Working Group thanked the RIBEF scientists for sharing their valuable experience. There were several more opportunities for interaction throughout the CIOMS WG meeting. The CIOMS group hopes that its consensus recommendations, once published, will help to address some of the issues discussed in the Symposium.

WORKING GROUP MEETING

Opening and introduction

Dr Lembit Rägo opened the meeting and informed the participants of current events at CIOMS. A new CIOMS Working Group XII on the Benefit-Risk Balance for Medicinal Products has been established to revisit the 1998 CIOMS WG IV guidance and met in Geneva in September 2019. The CIOMS Secretariat has employed a second medical writer to help support the increasing number of working groups.

Dr Rägo commended the WG for progress made with the draft guidance since the last meeting. One more face-to-face meeting should suffice to bring together the content. Thereafter, it should be possible for an editorial group to finalize the guidance.

Dr Bert Leufkens then took the chair. The participants briefly introduced themselves (see participant list in **Annex 1**). The agenda was adjusted to leave more time for plenary discussion.

The minutes of the 4th Working Group meeting were approved.

Reflections on the pre-meeting

The WG commented on the impressive accomplishment of Dr LLerena colleagues of building a very productive trial network that is generating results from a range of resource-limited settings in Latin America. The presentations provided stimulating learning cases on the challenges faced by ethnic minority groups and possible approaches to overcoming them. The WG discussed some recurring themes that emerged from the RIBEF-CIOMS Symposium.

- Mistrust towards researchers: It was suggested that this might be caused by "fake news", negative experiences from investigator-driven studies, tensions between traditional and Western medicine, and a growing distrust of the medical profession as a whole. The guidance should discuss these reasons and propose possible solutions.
- Lack of patient representation in ethics committees or drug development processes: It was noted that ethnic minorities are often particularly disenfranchised.
- Benefit-sharing: There tends to be a disconnect between researchers' goals and community needs. Worldwide there is a trend towards more patient involvement in medicines development and use,[2] especially in well-resourced settings. Policy-makers, leaders and community representatives in RLS should be involved in research from its conception.
- Communication is often hampered by language and cultural gaps; mutual understanding could be improved by involving social scientists in research design.

[2] FDA. Patient-Focused Drug Development: Methods to Identify What Is Important to Patients. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-methods-identify-what-important-patients-guidance-industry-food-and (link provided by Nathalie)

- Research findings are not implemented in health systems. High-level recommendations are needed on when and how knowledge on biomarkers or genetic differences can be translated into advice in standard treatment guidelines and medicines labelling.
- Herbal and traditional medicines are a mainstay of health care in many communities and are increasingly used in all settings across the world. In many countries they are not regulated at all, and research capacity on their use and effects, including unintended ones, is often lacking. The CIOMS guidance cannot address this complex topic in detail, but should call for awareness that traditional medicines use can impact research results and pose risks for study participants.

Support of Merida/T'Ho Declaration

On the second meeting day the Working Group expressed its support of the Merida/T'Ho Declaration and agreed to promote its principles as appropriate in the CIOMS Guidance on clinical research in resource-limited settings.

Report-back on recent developments

Time was too short for a "Tour de Table" with updates from participants. On Day 2 the Chair suggested that WG members review the experiences presented at the 4th WG Meeting (see Annex 2 to the 4th Meeting minutes).

Breakout sessions

The drafting teams met in breakout sessions from 09:00 to 10:30 h on Day 2 to review and address the comments received, and to develop the draft sections further.

General discussion

Report-back from drafting teams

A brief report-back was provided by each of the three groups on Day 2 before lunch.

Group 1 : "Introduction and problem statement"

Chapter 1 will be restructured to state the problem more clearly and concisely, calling attention to the need to make clinical research more equitable. Some of the text describing obstacles and enablers will be merged into Chapter 3. The title and scope of the guidance were re-discussed with regard to:

- Definition of "clinical research": The U.S. National Institutes of Health have broadened the range of studies included in the clinicaltrials.gov register to include all interventional studies[3]. For the CIOMS guidance, a very broad definition may lead to a loss of focus, while a narrow definition limited to drug development studies only might suggest that good practices are less important for other studies. A proposed working title was "Clinical research with emphasis on product development in resource-limited settings".
- Definition of "resource-limited settings" (RLS): It was pointed out that these could exist within both high- and low-income countries. The group will look for an established definition that is not solely based on countries' income classification.

The intended scope of the guidance was described in the concept note when the WG was established (available on the shared member website). The CIOMS Secretariat will circulate this to members for consideration.

[3] See https://clinicaltrials.gov/ct2/about-studies/glossary under "Clinical trial"

Group 2: "Principles of clinical research"

One round of comments has been addressed since the 4th WG meeting. A reference to the 2016 CIOMS ethical guidelines will be added in the introduction, references to ICH guidelines will be updated, and information will be included as appropriate from the upcoming FDA open meeting on ICH guideline renovation (31 October 2019 at U.S. FDA Headquarters). Section 2.6 on Capacity-building will be expanded. Section 2.8 on implementation of ICH guidelines will follow soon. This section will point out that ICH guidelines are not literally applicable in all settings (for example with regard to names, majority age, legal guardians), and that procedures should be adapted to the local context in such a way that the validity of the research is not compromised.

Group 3: "Obstacles and enablers"

The revised chapter was projected on screen with tracked changes. The following changes were proposed:

- Upfront statement of the rationale for good ethic and scientific research practices in RLS;
- Caution that international initiatives from well-resourced research agendas should not crowd out relevant local initiatives;
- List of "show stoppers", such as undue restrictions on movement of samples;
- Call for research networks to make the research environment more sustainable e.g. with regard to data management and clinical monitoring;
- Call for publication of results;
- More discussion of standards of care in Section 3.4 on study design, with a cross-reference to the section on ethics dumping in Chapter 2; and
- Reference to the 2016 CIOMS ethical guidelines (Guideline 14) with regard to compensation for research-related injury.

Some points were discussed that emerged from the RIBEF symposium:

- Need for community engagement (see 2016 CIOMS ethical guidelines, commentary to Guideline 7)
- Mentoring of researchers to encourage publication of results
- Ancillary care: In some RIBEF studies people participated because it was their only access to health care. It was clarified that this would not be undue inducement, as the participants voluntarily give informed consent after having weighed the risks and benefits for themselves. In this context after-trial care was also discussed. The duration of this depends on the health condition being treated and national requirements. Some sponsors provide after-care until the product becomes commercially available in the country, and registration trials are only conducted in those countries where there is a prospect of subsequently obtaining marketing authorization.

Appendices

At the end of Day 2 the status of the appendices was briefly reviewed:

1. Vulnerable individuals and groups (lead author: Roli) – to be shortened, overlaps to be addressed. To be reviewed (Ames)
2. Digital health (lead author: Luc) – Initial comments addressed; to be reviewed (Aude)
3. Electronic health records (lead author: Lembit) – One round of comments addressed, more comments will be sought from people outside the WG.
4. Paediatrics (lead author: Kalle) – Advanced draft available.
5. Outbreaks (lead author: Jerry) – Advanced draft available, one round of comments addressed. Content to be added about the Zika experience in Brazil.
6. Women of child-bearing age (lead author: Nathalie) – Draft to be shared with WG soon.
7. Pharmacogenetics (lead author: Adrian) – Draft to be shared with WG soon.

How to develop the guidance further

Illustrative case studies will be included where applicable with permission from authors.

Redundancy with the 2016 CIOMS ethical guidelines will be avoided. Any points covered in the ethical guidelines should be briefly summarized, with a reference to the 2016 guidelines. *[Note: The Preface to those guidelines states that "The final draft replaces all previous versions of the CIOMS ethical guidelines". The 2016 ethical guidelines, not previous versions, should therefore be cited.]*

The WG members agreed that a Chapter 4 should be added be added to synthesize the content of the previous chapters and introduce the recommendations.

Recommendations

The WG discussed how best to structure the recommendations for best possible impact. The recommendations should be concrete, not too numerous, and be grouped to address specific stakeholder groups who should take action: donors, regulators, ethics committees, policy makers, sponsors, researchers, communities, etc.).

The recommendations should emanate from the text, particularly Chapters 2 and 3 and the appendices. The value of the guidance and its suggested use will be highlighted in the Introduction.

WG members proposed an initial "shopping list" of recommendations to support meaningful research in resource-limited settings. The following key points were mentioned:

- (Equity) – Ensure benefit-sharing; ensure the integrity of research; engage with communities for a participatory approach
- (Scientific methodology) – Ensure data integrity through good study design; understand the physiology, genetics and behaviour of the community; use of novel/adaptive designs to optimize monitoring of incoming data; use of modern technologies (e.g. at-home technologies, electronic health records – link to appendices 2 and 3)
- Create a favourable research environment:
  - (Governments) – Maintain adequate infrastructure, security, health care services and availability of trained staff, combat inefficiency and corruption
  - (Regulatory authorities) – Clarify national requirements; reduce bureaucracy, shorten review timelines e.g. through joint review and/or reliance on, or recognition of, other authorities' decisions[4]
  - Create and maintain standing research networks ("academic CROs") with monitoring, advisory boards, training, information for researchers on relevant registries and databases
  - Raise profiles of local investigators, recognize their performance (from monitoring, audits)
- (Planning for sustainable research) – Ensure financial management capacity; respect local health systems (e.g. avoid drawing staff); adapt type of equipment and technology to local needs and capacity
- (Operational good practices) – Build good documentation systems; use of electronic data capture tools effectively, optimize data monitoring; adapt procedures to local context e.g. regarding majority age, provisions for legal guardians

[4] See draft WHO Good Regulatory Practice guidance. WHO guidance on Good Reliance Practices is under preparation. *[Note from CIOMS Secretariat: WHO guidance on medicines quality is available at https://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/, draft texts are found under "Current Projects".]*

A small group (WG chair and CIOMS Secretariat) will draft recommendations and send them to the full WG for comment.

Conclusions and next steps

The Working Group thanked Adrian LLerena for organizing a memorable meeting with stimulating interactions.

The subgroups will meet periodically by teleconference to keep the telework going. If needed a teleconference of the full WG could also be organized, https://www.bluejeans.com/ was suggested as a possible platform.

Action points

Who	Action	By when
CIOMS Secretariat	Circulate WG concept note to WG members	Done
WG members	Stay informed about ICH guideline renovation	ICH public meeting on Good Clinical practice, 31 October 2019
Drafting team leads	Coordinate further development of draft sections; contact CIOMS Secretariat for support as needed	Ongoing
Section authors	Provide drafts: Section 2.8 on implementation of ICH guidelines (Christoph) Appendix 6 (Nathalie) Appendix 7 (Adrian)	ASAP
Reviewers	Provide comments to lead authors Appendix 1 (Ames) Appendix 2 (Aude) Other comments are welcome	ASAP
CIOMS Secretariat and WG Chair	Draft a Recommendations section and circulate it to the full WG for comment	ASAP
CIOMS Secretariat	Collect updated sections and produce a revised combined version for review at the 6th WG meeting	15 April 2020

Next meeting

The 6th WG meeting will be held in Geneva. The date will be determined by Doodle vote. *[Post-meeting note: the meeting will be held on **22-23 April 2019** in Geneva.]*

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Annex 1: List of participants

CIOMS Working Group

* = new member

Regulators	Jerry **Pierson**	National Institutes of Health, U.S.
Academia/ Research	Ames **Dhai**	University of the Witwatersrand, Steve Biko Centre for Bioethics, Faculty of Health Sciences, Johannesburg, South Africa
	Walter **Jaoko**	University of Nairobi, Department of Medical Microbiology, Nairobi, Kenya
	H. (Bert) G.M. **Leufkens** WG Chair	Faculty of Science, Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht, the Netherlands
	Adrian **LLerena**	Universidad of Extremadura, Extremadura University Hospital and Medical School, Badajoz, Spain
	Irja **Lutsar**	University of Tartu, Estonia
	Roli **Mathur**	Indian Council of Medical Research, National Centre for Disease Informatics and Research, Bangalore, India
	Aita **Signorell**	Swiss Tropical & Public Health Institute
	*Honorio **Silva**	International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP)
	Nick **White**	Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand & Wellcome Trust, London, United Kingdom
Product R&D	Aude **Le Roux**	Sanofi
	Nathalie **Strub Wourgaft**	DNDi, Geneva, Switzerland
	Pol **Vandenbroucke**	Pfizer Inc. Chief Medical Office, New York, U.S.
CIOMS	Lembit **Rägo**	Secretary-General
	Janis **Lazdins**	Adviser
	Monika **Zweygarth**	Technical writer

Apologies

Regulators	Christoph **Conrad**	Paul-Ehrlich-Institut, Germany
	Alambo **Mssusa**	Tanzania Food and Drugs Authority (TFDA), Dar es Salaam, Tanzania
Academia/ Research	Kalle **Hoppu**	Children's Hospital, Helsinki University Hospital, and University of Helsinki, Finland. Pediatric Clinical Pharmacology Section, IUPHAR
	Samia **Hurst**	University of Geneva, Switzerland
	Gustavo **Kesselring**	IFAPP (represented by Honorio Silva)
Product R&D	Ruxandra **Draghia**	MSD, U.S.
	Elly **Kourany-Lefoll**	Merck KGaA, Global Health Institute, Coinsins, Switzerland
	Satu **Kujala**/Tuijia **Keinonen**	Medfiles, Finland
	Luc **Kuykens**	Sanofi (company represented by Aude Le Roux)
	*Isabel **Lakatos**	Roche (to replace Puneet Arora)
	Florent **Mbo Kuikumbi**	Drugs for Neglected Diseases initiative (DNDi), Regional HAT Platform, Kinshasa, Democratic Rep. of the Congo
	Rosanne **Rotondo**	Novartis
WHO	Samvel **Azatyan**	WHO Regulatory Systems Strengthening (RSS) Team
	Vaseeharan **Sathiyamoorthy**	WHO Research, Ethics and Knowledge Uptake (REK) unit

RIBEF-CIOMS Symposium

Moderators

- **Adrián LLerena MD PhD.** Facultad de Medicina, Universidad de Extremadura; Director del Instituto de Investigación Biosanitaria de Extremadura (INUBE); Coordinador Red Iberoamericana Farmacogenética (RIBEF)
- **Eva Peñas-LLedó PhD.** Facultad de Medicina, Universidad de Extremadura. Investigadora Instituto de Investigación Biosanitaria de Extremadura (INUBE)

Introduction

- **Enrique Terán MD PhD**. Colegio de Ciencias de la Salud, Universidad San Francisco de Quito, Director del Centro de Simulación, Cumbayá, Ecuador.
  - IberoAmerican Pharmacogenetics Network (RIBEF). On behalf of the RIBEF scientists.

Experiences from Latin America, Africa and Asia

- **Eduardo Tarazona-Santos PhD,** Universidade Federal de Minas Gerais, Belo Horizonte, Brasil. Universidad Peruana Cayetano Heredia, Lima, Perú.
  - Ancestry and Pharmacogenetics In Latin America.
- **Shyam Diwakar PhD.** Computational Neuroscience and Neurophysiology Laboratory, Amrita University. Amritapuri, Kerala, India.
  - Being Sustainable: Amrita University Case Studies.
- **José Pedro Gil PhD.** Karolinska Institute, Stockholm, Sweden, and Gulbenkian Research Institute, Lisbon, Portugal.
  - Experiences in clinical trials involving children in Africa

Round Table I: Non-clinical research in autochthonous populations (summarized by Enrique Terán)

- **Martha Sosa Macías PhD,** Instituto Politécnico Nacional, Centro Interdisciplinario de Investigación para el Desarrollo Integral Regional, Unidad Durango. México.
  - North America: Studies and initiatives in autochthonous Mexican population
- **Ronald Ramírez Roa MD PhD**, Facultad de Ciencias Médicas, Director del Centro Nicaraguense de Farmacoepidemiología, Universidad Nacional Autónoma de Nicaragua, León. Nicaragua.
  - Central Americans (Nicaragua): Studies and Initiatives in Caribbean Miskito and Mestizo Populations
- **Isabel Hernández Guerrón RN**, Facultad de Enfermería, Pontificia Universidad Católica del Ecuador, Quito, Ecuador.
  - South Americans (Ecuador): Studies and initiatives in Kwitchua and Mestizo Population

Round Table II: Clinical Research in indigenous populations (summarized by Carlos Galaviz)

- **Juan Molina Guarneros** MD, PhD. National Autonomous University of Mexico (UNAM)
  - Research in a Regional Hospital in Mexican Mestizos affected with Diabetes
- **Julio Lara Riegos QFB PhD**, Proyecto de Diabetes en población Maya, Universidad Autónoma de Yucatán, Mérida, Yucatán, México.
  - Research in Maya Indigenous Populations affected with Diabetes
- **Carlos Galaviz-Hernández MD PhD**, Instituto Politécnico Nacional, Centro Interdisciplinario de Investigación para el Desarrollo Integral Regional, Unidad Durango. México.
  - Research in Pregnant Women in México
- **Enrique Terán MD PhD**. Colegio de Ciencias de la Salud, Universidad San Francisco de Quito, Director del Centro de Simulación, Cumbayá, Ecuador.
  - Research in Diabetes and Pregnancy in Ecuador

Annex 2: Merida/T'Ho Declaration (English)

(https://simposiumribef.com/declaracion/)

"Clinical Research, drugs and health in autochthonous and vulnerable populations: Relevance of population Pharmacogenetics, socio-cultural context and education"

The RIBEF experiences, analysis and proposals in order to increase awareness about clinical research on Amerindians and vulnerable populations have been summarized as follows.

Principles. It is highlighted that these populations present genetic variability, and therefore ethnicity is a factor to be considered. Therefore, **population pharmacogenetic factors** involved in the variability to drug response should be taken into account when planning, designing and interpreting clinical trial results in these populations. This has been the objective of the RIBEF MESTIFAR project, which has revealed the existence of differences in the frequencies of genes involved in the response to drugs among American autochthonous populations.

Traditional Medicine co-exists and interacts with Allopathic Medicine in the real world and during clinical research. In support of this, there is scientific evidence showing that many patients use Traditional Medicine –which is often considered it more effective, safer, less costly and more easily available than allopathic medicines- along with Allopathic Medicine without informing their treating doctor. Since patients receiving allopathic treatment may take other (traditional) medicines concomitantly, it is useful to educate health professionals and increase awareness of Traditional Medicine in order to improve clinical trial efficiency and resource allocation as well as the efficacy and safety of treatment choices.

For this purpose, the **education** (specific training) and personal qualities of the clinical researchers are essential to effectively respond to the complex challenges posed by different sociocultural contexts. This should include the health professional´s knowledge and deep respect of the specific ancient wisdoms, their views on health and quality of life in RLS, and their education on human values and sustainable attitudes that promote open, responsible and harmonic patterns of behaviors and skills. Such Education will enable the qualified researcher to find solutions to challenges of the research process and maintain good ethical and scientific practices.

Challenges for Clinical Research on RLS countries: In summary, the RIBEF position on improving clinical research in RLS ("Declaration of Mérida/T´Hó") recognizes the relevance of three fundamental aspects for human health research and clinical implementation:

1) The **interethnic variation** in the frequencies of genes involved in the response to drugs is relevant; making it necessary to consider population pharmacogenetics in clinical research and clinical practice, that should be promoted as well as regulation.
2) The respect and knowledge of the **specific sociocultural context** and wisdom, including Traditional Medicine (Ayurveda, Amerindian traditional medicine, etc); and
3) The **education** of the researchers on universal values and sustainable attitudes to guarantee good ethical and scientific practices during the whole research process.

In addition,

4) We, the undersigned commit ourselves to increase awareness of the **necessity to improve the quantity and quality of clinical research** projects focused on vulnerable populations.

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