


# Developing Multicenter Consortia in Liver Disease in Latin America: Challenges and Opportunities

Manuel Mendizabal <sup>1,2</sup> and Marcelo O. Silva<sup>1,2</sup>

<sup>1</sup>Hepatology and Liver Transplant Unit, Hospital Universitario Austral, Pilar, Provincia de Buenos Aires, Argentina;

<sup>2</sup>Latin American Liver Research, on behalf of the Latin American Liver Research, Educational and Awareness Network

The development of consortia has been useful for exploring challenging scenarios and uncharted territories in liver disease treatments. Several consortia already developed in the United States and Europe have become key factors in patient care decision-making processes and medical education, and they have also impacted policy makers' decisions. In Latin America, the situation is different. As a result of a combination of different factors, our region has not been able to develop networking advantages in research and education in liver diseases. Thus far, most of the initial experiences focused on the development of collaborative groups established to investigate a particular topic, which were dissolved once the questions were answered. It is the aim of this review to describe those difficulties we confront in developing multicenter liver consortia in Latin America, to identify those challenges we face, and also to describe the opportunities we have for improvement.

*Liver Transplantation 23 1210–1215 2017 AASLD.*

Received March 23, 2017; accepted May 31, 2017.

Multicenter consortia are usually composed of a group of people or associations with similar interests and a common mission. These partnerships allow for coordination of efforts and resources in pursuing pre-established goals. Within biomedical sciences in general and in the field of hepatology in particular, several

consortia have emerged in the past decade.<sup>(1-3)</sup> They tend to pursue similar aims/goals such as the promotion of basic, epidemiological, and clinical research in specific pathologies. An indirect asset of their activity is the rapid generation of original data in fields where the industry usually has poor interest and/or where the prevalence of studied cases is low. The original data generated in these networks have the potential to become a key factor in patient care decision-making processes, medical education, and impacts on policy makers.

In Latin America, most health systems are segmented and fragmented with no vertical programs to approach liver diseases as a whole. Only a minority have nonintegrated programs in isolated fields such as viral hepatitis and/or liver transplantation. As a result, data necessary to build up disease burden models and to determine sanitary health interventions are scanty and not always reliable. Therefore, a lack of integrated public policies and systematic approaches toward tackling liver diseases conspire not only against regional academic development, but also and more compelling, against a patient's quality of care.

These research and educational gaps have been partially compensated for by the pharmaceutical and diagnostic industries, although in a biased manner. This has been possible due to the technological leap reached by the development of new therapeutic molecules and

*Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALEH, Latin American Association for the Study of the Liver; APASL, Asian Pacific Association for the Study of the Liver; DILI, Drug-Induced Liver Injury; EASL, European Association for the Study of the Liver; ECHO, Educational Community Healthcare Outcomes; HCV-TARGET, Hepatitis C Therapeutic Registry and Research Network; HEP-NET, German Network of Competence for Viral Hepatitis; LALREAN, Latin American Liver Research, Educational and Awareness Network; LATINDILIN, Latin American Drug Induced Liver Injury Network; LILACS, Latin American Literature in Health Sciences database; NGO, nongovernmental organization.*

*Address reprint requests to Marcelo O. Silva, M.D., Hepatology and Liver Transplant Unit, Hospital Universitario Austral, Pilar, Provincia de Buenos Aires, 1629, Argentina. Telephone: 54 2322 482884; FAX: 54 2322 4482236; E-mail: msilva@cas.austral.edu.ar*

*Copyright © 2017 by the American Association for the Study of Liver Diseases.*

*View this article online at wileyonlinelibrary.com.*

*DOI 10.1002/lt.24793*

*Potential conflict of interest: Nothing to report.*

diagnostic platform tests. These advances have represented an invaluable contribution to medicine and patients by significantly promoting knowledge and improving life expectancy in this discipline. On the other hand, regional scientific societies and policy makers' agendas aimed to study and control the burden of liver diseases have had a less important role in this part of the world.

As previously mentioned, consortia usually try to supplement information in areas that are not in the central scope of the pharmaceutical and diagnostic industries. Thus, they provide very valuable complementary data on what we can call "orphan pathologies" and/or real-life settings, allowing for a better understanding and management of cases. Consolidated data from these groups usually provide valuable information on epidemiology, risk factors, natural history, prognostic indicators for disease progression, indicators for lack of response to therapy, and real-life evidence on outcomes of new drugs and treatment regimens. These relevant data allow us to find answers to questions not responded to by clinical trials conducted by pharmaceutical companies. Consequently, they become a critical step forward in decision-making processes when confronting different clinical care alternatives of our patients.

There are several examples of consortia in force today. Among them, we can mention the following: Hepatitis C Therapeutic Registry and REsearch Network (HCV-TARGET), German Network of Competence for Viral Hepatitis (HEP-NET), and Trio Health, networks which provide us with a wide spectrum of information about viral hepatitis; the Viral Hepatitis Prevention Board, a consortium whose central role is to interact and discuss with health authorities mainly in the area of vaccination policies; and the European Foundation for the Study of Chronic Liver Failure, which is focused on the management of patients with cirrhosis.

The aim of this review is to describe those difficulties we confront in developing multicenter liver consortia in Latin America, to identify the challenges, and also to describe the opportunities for improvement.

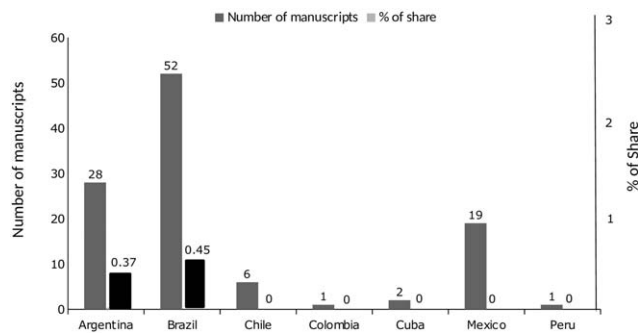
## Where Do We Stand in Latin America?

Latin America is a heterogeneous region composed of 20 countries with more than 600 million people with a big disparity in economic resources, with most of the population being in the low- or middle-income range. Insufficient incomes are commonly linked to fragile sustainability of health care systems, poor quality of

medical education, and scanty resources for research. Thus, this inequity becomes a structural barrier for the implementation of universal health care systems, the development of integrated disease management programs, and for medical science careers.

Some of the most critical consequences of this vulnerable economic condition are information gaps and poor-quality registries, both of which cause difficulties for estimating disease burden and determining future intervention plans. With poor data, it becomes hard to propose any rational and efficient health intervention or medical education plan. This has been historically worsened by the lack of continuity and or weak implementation of regional health policies. The second consequence of this disparity is the wide quality range of medical education. Most Latin American physicians obtained medical training clearly oriented toward good clinical skills, relegating academic and research activities to a second place as complementary work. This differs from developed countries where medical doctors, after completing their clinical training, have the chance to continue their careers in highly qualified academic settings. Finally, the third consequence of this income disparity is a lack of federal and private grants for basic epidemiological and clinical research in most of our countries. Only a few government agencies, medical organizations, and/or charity foundations fund research and academic careers. This contrasts with the wide range of options provided by different governmental agencies or scientific societies of Europe and the United States. For example, at the time of writing this review, the European Association for the Study of the Liver (EASL) offered a "minimum" grant of €150,000 for the formation of one or more consortia with the purpose of collecting data regarding liver diseases. In the United States, the National Institute of Diabetes and Digestive and Kidney Diseases sponsored 2 large consortia aimed at a specific pathology: the Acute Liver Failure Study Group and the Drug-Induced Liver Injury Network. Opportunities like these are extremely rare in our latitudes, and only on a few occasions do official agencies or the pharmaceutical industry end up funding projects generated by local investigators.

Low publication rates in scientific journals were reported from several Latin American countries. An interesting consideration arises from the analysis of the Latin American Literature in Health Sciences database (LILACS), where the biomedical publication rate in Argentina was evaluated. This report describes an association between the country's economic crisis and a fall in scientific production.<sup>(4)</sup> Physicians from



**FIG. 1.** Number of original manuscripts submitted to *Hepatology* and the percentage of acceptance share by Latin American countries (period 2013–2015). Countries with at least one submission were included. Data provided by K. Lindor.

Ecuador also analyzed LILACS and MEDLINE databases in order to evaluate health sciences–related studies published from 1999 to 2009.<sup>(5)</sup> Only 625 articles from Ecuador were published during the study period, mainly from private institutions. In Peru, only 8.2% of the abstracts presented at the National Congress of Gastroenterology during 1998 to 2008 were published, but 82% of these were published in the *Peruvian Gastroenterology Journal*.<sup>(6)</sup> Similar findings were described in Mexico where the abstracts awarded at the annual meeting of the Mexican Gastroenterology Association from 1998 to 2006 presented a publication rate of 48%.<sup>(7)</sup> Again, the impact of these studies was limited given that most of the manuscripts were published in journals with local distribution and only 2 articles had more than 10 citations in other international journals. The region has a very low number of publications in journals with a high impact factor.<sup>(4–8)</sup> If we consider *Hepatology* as an example, we see that between 2013 and 2015 only 7 member countries of the Latin American Association for the Study of the Liver (ALEH) sent original manuscripts for review ( $n = 109$ , Fig. 1). The data are even more alarming if we look at the acceptance rate, which was 6%, significantly lower than the 15% acceptance rate for the rest of the world (unpublished data provided by K. Lindor).

In our opinion, the large quantitative and qualitative differences in biomedical publications among Latin American and developed countries are the result of a combination of several factors:

1. Income disparities.
2. Pregraduate and postgraduate training oriented toward clinical skills rather than teaching and research.

3. Insufficient grants and funding to maintain academic career development.
4. Migration of qualified physicians and researchers to countries with greater resources.
5. Lack of consortia or interest groups that are sustainable over time.

Consequently, what has been the specific situation here in Latin America regarding liver consortia? A very frustrating aspect is that most of the initial experiences have been focused on the development of collaborative groups established to investigate a particular topic. In this sense, there have been some publications, but once the questions have been answered, groups were dissolved and lost continuity.<sup>(9,10)</sup>

## Opportunities

In the described scenario, the development of a consortium for studying liver diseases or any other pathology would seem to be a utopia, but those previously described challenges should not become an excuse for a lack of development. Difficulties should be recognized and taken as opportunities for improvement. We must begin by understanding and accepting our limitations in order to overcome barriers and to be able to address challenges.

One way of facing this problem is by providing medical students and/or residents with the opportunity of knowing the “academic world.” This can be achieved with simple, low-cost interventions, such as the introduction of undergraduate subjects, for example, research methodology, or the assignment of a tutor with an academic vocation that can coach and guide students in the research area. We are certain that with more physicians interested in an academic career, scientific production would increase. A second necessary step to ensure continuity of young physicians in academic careers is their inclusion in clinical and epidemiological research. Many of them will desist if they do not have an institutional framework to promote their professional development. This scenario is where consortia may offer an appropriate academic environment and structure by facilitating recollection of information in a systematic and reliable way. With this structure, physicians within the consortia will be able to carry out research projects and spill over those new findings and knowledge to their peers, scientific community, and interested public through diverse educational programs (Table 1).

TABLE 1. Potential Goals of a Consortium

Goals	Actions
Improve quality of patient's care	Design primary and secondary prevention policies Create an evidence-based approach to clinical care Development of benchmarking data needed to evaluate Latin America outcomes
Enhance medical education	Spread knowledge among health care personnel Identify, support, and promote highly motivated physicians Diminish disparity in education and health care delivery
Promote regional research	Generate a local registry Produce original scientific data Provide reliable repository for biological samples
Collaborate with health care policy makers	Development of clinical practice guidelines Produce educative material for patients and relatives

If regionally generated data are published in peer review journals, consortia do acquire more visibility and value. This is largely because scientific publications in high-impact journals mobilize synergies with other actors in the health care system such as scientific societies, nongovernmental organizations (NGOs), pharmaceutical companies, payers, and policy makers, as well as national and supranational health organizations (Fig. 2). This moderator and/or catalyst role of consortia positions them as important players in both, European and American scientific societies impacting also their respective health care systems decisions. Therefore, it would not be risky to say that they should be even more useful in our region given that knowledge gaps are greater and that consortium implementation does not require major investments. Still, generation of

resources remains as a critical bottleneck at a time of developing and sustaining consortia productivity. Revenue for building consortia may be primarily obtained through different processes like government agencies, industry support, philanthropic donations, and research or educational grants offered by scientific societies or nongovernmental organizations. Many times, these resources are tied to political decisions and economic fluctuations.

Fortunately, some consortia with a veneer of continuity have begun to flourish in the region. For more than 6 years, the Latin American Drug Induced Liver Injury Network (LATINDILIN), with the support of the Spanish Drug-Induced Liver Injury (DILI) Registry, has been providing relevant information on hepatotoxicity.<sup>(11)</sup> Another regional consortium is the Latin American Liver Research, Educational and Awareness Network (LALREAN). It encompasses physicians' groups in more than 8 countries of Latin America and the Caribbean, covering not only viral hepatitis but other liver diseases as well.<sup>(12,13)</sup> An important endorsement for these groups has been given by ALEH, which helps with integration of partners from all over the region, diffusion of their activities, and facilitating an adequate academic environment for strategic and scientific discussions. Furthermore, in June of 2015 at the South Pacific Summit, ALEH established 5 Permanent Commissions to coordinate the development of several interest groups. These activities led to a greater dissemination of information regarding different pathologies, opening doors to all those interested in a particular subject who may then contact the coordinator of each area and raise a proposal.

Between these previously mentioned working groups, the one that has excelled is the LATINDILIN Registry created in 2011. This consortium is dedicated to prospectively identifying cases of hepatotoxicity induced by drugs, herbs, or dietary supplements, with

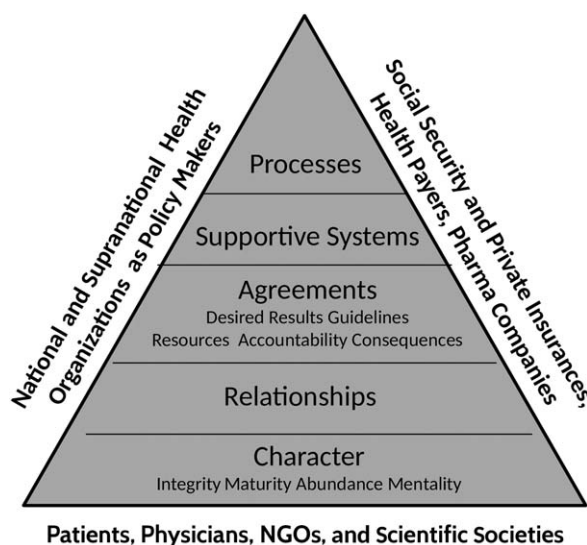


FIG. 2. Five dimensions of a win-win in consortia, potential links, and impact with different actors of health care systems.

the continued support of the Spanish DILI group. This network includes several reference centers in Latin America and has provided us with relevant information through its publications in conferences and peer-reviewed journals.<sup>(14)</sup>

More recently another group developed LALREAN, a collaborative network of research, education, and awareness based in several centers specializing in liver diseases in Latin America. This consortium followed 2 different network models: HEP-NET and Educational Community Healthcare Outcomes (ECHO). HEP-NET is a German foundation that promotes research with a horizontal and vertical integration approach. Collaboration is within academic institutions, primary care settings, and civil society actors prone to scientific publications in difficult clinical niches and in bridging basic and clinical research. On the other hand, ECHO is an outreach initiative developed by the University of New Mexico<sup>(15)</sup> which aims to promote knowledge demonopolization and multiplication, and it is mainly oriented to serve poor and isolated rural communities. This regional and national networking activity allowed LALREAN to give oral presentations at international liver meetings and publish several full articles in peer-reviewed journals in the areas of viral hepatitis and hepatocellular carcinoma.<sup>(12,13,16)</sup> Furthermore, LALREAN's outreach ECHO program has been actively sustained with spokes from 13 different deeply involved Argentinean provinces, and it is hoping to become regional soon.

The support from other sister societies like EASL, the American Association for the Study of Liver Diseases (AASLD), and the Asian Pacific Association for the Study of the Liver (APASL) can certainly play a major role in helping to improve the academic production in Latin America. We believe that ALEH should be the bridge between researchers and the different societies. Ways in which EASL, AASLD, or APASL can help Latin American investigators include the following:

1. Allow ALEH members to compete for grants sponsored by other societies.
2. Offer basic and clinical research scholarships to young investigators.
3. Support research workshops as AASLD did in the ALEH meeting held in Santiago in September 2016.
4. Evaluate interlaboratory collaboration.
5. Promote governing board meetings among societies to discuss different topics such as funding sources, consortia cooperation, and educational activities.

It is certainly possible to form networks or consortia in Latin America; LATINDILI and LALREAN are good examples of this. Keeping members interested on a continuous scientific evolution as well as generating resources for sustainability are the remaining challenges. Support of ALEH has been very important during the startup process helping with dissemination of the ideas and giving an appropriate institutional framework for development. Now, in order to be able to have continuity, we may have reached the appropriate time to request counseling from experienced European, Asian-Pacific, and North American consortia to help us to evolve into a more professional type of organization.

## Conclusion

Latin America is a culturally rich and diverse region and can continue to play a major role in academic medicine. Consortia are tools that make research more accessible and friendly. Moreover, these networks have the potential to help us articulate and synergize actions of different actors across the health system. We have already established the first consortia with continuity in the region; they should be the foundation to encourage other groups to follow the same path. Human resources are sufficient in an area that is double the population of Europe. Cooperation and counseling of already established consortia, as well as endorsements from different scientific societies, are vital to obtain the necessary support to expand the mission.

## REFERENCES

- 1) Potthoff A, Wedemeyer H, Boecher WO, Berg T, Zeuzem S, Arnold J, et al.; for Hep-Net B/C Co-infection Study Group. The HEP-NET B/C co-infection trial: a prospective multicenter study to investigate the efficacy of pegylated interferon-alpha2b and ribavirin in patients with HBV/HCV co-infection. *J Hepatol* 2008;49:688-694.
- 2) Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al.; for CANONIC Study Investigators of the EASL-CLIF Consortium. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013;144:1426-1437.
- 3) Brown RS Jr, O'Leary JG, Reddy KR, Kuo A, Morelli GJ, Burton JR Jr, et al.; for Hepatitis C Therapeutic Registry Research Network Study Group. Interferon-free therapy for genotype 1 hepatitis C in liver transplant recipients: real-world experience from the hepatitis C therapeutic registry and research network. *Liver Transpl* 2016;22: 24-33.
- 4) Barreyro FJ, Krabshuis J, Planzer del Campo M, Bai JC. [Why are there few publications by the Argentine gastroenterology?

- Considerations on a bibliometric analysis of Argentine publications on gastroenterology]. *Acta Gastroenterol Latinoam* 2009; 39:9-17.
- 5) Sisa I, Espinel M, Fornasini M, Mantilla G. [Scientific output in the health sciences in Ecuador]. *Rev Panam Salud Publica* 2011;30:388-392.
  - 6) Pereyra-Elías R, Ng-Sueng LF, Toro-Polo LM, Nizama-Vía A, Piscoya A, Mayta-Tristán P. [Low publication of the papers presented at the Congresses of Gastroenterology Society of Peru 1998-2008]. *Rev Gastroenterol Peru* 2011;31:124-132.
  - 7) Chávez-Tapia NC, Téllez-Avila FI, Hernández-Calleros J, López-Arce G, Franco-Guzmán A, Uribe M. [Critical analysis of awards in gastroenterology research. The Mexican experience]. *Medicina* 2008;68:135-138.
  - 8) Villamil FG. [Why is it that Argentinean hepatologists do not publish enough?]. *Acta Gastroenterol Latinoam* 2008;38: 6-10.
  - 9) Mendizabal M, Marciano S, Videla MG, Anders M, Zerega A, Balderramo DC, et al. Changing etiologies and outcomes of acute liver failure: perspectives from 6 transplant centers in Argentina. *Liver Transpl* 2014;20:483-489.
  - 10) Mendizabal M, Marciano S, dos Santos Schraiber L, Zapata R, Quiros R, Zanotelli ML, et al. Post-transplant lymphoproliferative disorder in adult liver transplant recipients: a South American multicenter experience. *Clin Transplant* 2013;27:E469-477.
  - 11) Bessone F, Hernandez N, Dávalos M, Paraná R, Schinoni MI, Lizarabal M, et al. Building a Spanish-Latin American network on drug induced liver injury: much to get from a joint collaborative initiative. *Ann Hepatol* 2012;11:544-549.
  - 12) Mendizabal M, Haddad L, Gallardo PE, Ferrada A, Soza AA, Adrover R, et al. Ombitasvir/paritaprevir/ritonavir/dasabuvir ± ribavirin is safe and effective in HCV-infected patients in a real-life cohort from Latin America. *J Med Virol* 2017;doi:10.1002/jmv.24816.
  - 13) Piñero F, Tisi Baña M, de Ataíde EC, Hoyos Duque S, Marciano S, Varón A, et al.; for Latin American Liver Research, Education and Awareness Network (LALREAN). Liver transplantation for hepatocellular carcinoma: evaluation of the alpha-fetoprotein model in a multicenter cohort from Latin America. *Liver Int* 2016;36:1657-1667.
  - 14) Bessone F, Hernandez N, Lucena MI, Andrade RJ; for Latin DILI Network LATINDILIN And Spanish DILI Registry. The Latin American DILI Registry Experience: A Successful Ongoing Collaborative Strategic Initiative. *Int J Mol Sci* 2016;17:313.
  - 15) Arora S, Kalishman S, Thornton K, Dion D, Murata G, Deming P, et al. Expanding access to hepatitis C virus treatment—Extension for Community Healthcare Outcomes (ECHO) project: disruptive innovation in specialty care. *Hepatology* 2010;52:1124-1133.
  - 16) Mendizabal M, Reddy KR. Chronic hepatitis C and chronic kidney disease: advances, limitations and uncharted territories. *J Viral Hepat* 2017;24:442-453.