Alliance Roundtables

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Regulatory Pathways Roundtable

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Executive Summary

On October 5, 2021, a multi-stakeholder group, representing various communities within the International Alliance of ALS/MND Associations' network, gathered to develop principles for a proposed global regulatory review framework that could form the basis of future advocacy by the Alliance and its individual members. The goal of the effort is to accelerate the process of regulatory review and remove regulatory obstacles for promising new therapies for people living with ALS/MND.

To lay the foundation for a productive group discussion, all meeting participants were provided multiple background documents, including several articles and a draft framework proposal for global ALS/MND regulatory review harmonization (see appendix 1). Roundtable encompassed an opening plenary, and two group discussions. The Roundtable agenda was designed to provide information from several other disease states and individual activities within certain national regulatory systems. These examples formed a baseline foundation of for Alliance members to consider a global approach for ALS/MND that could be both aspirational and feasible to achieve.

Attendees

Meeting participants included representatives from multiple global ALS/MND organizations, members of the Alliance's staff and PALS and CALS Advisory Council (PCAC), industry officials and invited expert speakers. Global regulators from multiple countries were invited but unable to attend. All sessions were facilitated by Wendy Selig, Founder and CEO of WSCollaborative, and sponsorship support for the Roundtable was provided by Amylyx, Biogen, Ionis, and Orphazyme.

Attendee Roster			
Discussion Group 1			
First Name	**Last Name**	**Affiliation**	**Country**
David	Ali	Motor Neurone Disease Australia	Australia
Jeff	Allen	Friends of Cancer Research	USA
Pablo	Aquino	Association ELA Argentina (ALS Association of Argentina)	Argentina
Vanessa	Báez	ACELA - Colombian ALS Association	Colombia
Calaneet	Balas	International Alliance, The ALS Association (ALSA)	USA
Dr. Luis	Barbeito	International Alliance, Scientific Advisory Council	Uruguay
Gorrit-Jan	Blonk	ALS Foundation of The Nederland (Stichting ALS Nederland)	Netherlands
Dr. Adriano	Chio	International Alliance, Scientific Advisory Council	Italy
Dr. Nicholas	Cole	Motor Neurone Disease Association (MNDA UK); International Alliance Scientific Advisory Council	UK

Andrea	Corazza	Biogen	Belgium
Dr. Kuldip	Dave	The ALS Association (ALSA); International Alliance, Scientific Advisory Council	USA
Dirk	De Valck	ALS Liga Belgie	Belgium
Philip	Green	International Alliance Patient and Caregivers Advisory Council	USA
Alper	Kaya	ALS-MNH Dernegi (ALS/MND Association Turkey)	Turkey
Kellie	Krake	International Alliance	Canada
Paul	Larkin	The ALS Association (ALSA)	USA
Dr Qing	Liu	International Alliance, Scientific Advisory Council	China
Dr Christian	Lunetta	Associazione Italiana Sclerosi Laterale Amiotrofia (AISLA ONLUS)	Italy
Jessica	Mabe Bernal	ACELA - Colombian ALS Association	Colombia
Machelle	Manuel	Amylyx	USA
Michele	Messmer Uccelli	Biogen	Italy
Tammy	Moore	ALS Canada	Canada
Andrea	Pauls Backman	Les Turner ALS Foundation	USA
Evy	Reviers	ALS Liga Belgie	Belgium
Marcela	Santos	ACELA - Colombian ALS Association	Colombia
Wendy	Selig	WS Collaborative	USA
Gudjon	Sigurdsson	MND Iceland	Iceland
Dr David	Taylor	ALS Canada	Canada
Dr Neil	Thakur	The ALS Association (ALSA)	USA
Eugene	Van Leeuwen	ALS Patients Connected (APC)	Netherlands
Bruce	Virgo	International Alliance Patient and Caregivers Advisory Council	UK
Discussion Group 2			
David	Ali	Motor Neurone Disease Australia	Australia
Pablo	Aquino	Association Ela Argentina (ALS Association of Argentina)	Argentina
Kristina	Bowyer	Ionis	USA
Silverio	Conte	Conslancio Onlus Italy	Italy
Carla	Flores	Familiares Y Amigos De Enfermos De La Neurona Motora AC (FYADENMAC)	Mexico
Mike	Gardner	Gardner Family	Canada
Philip	Green	International Alliance Patient and Caregivers Advisory Council	USA
Gail	Hartin	Ionis	USA
Kellie	Krake	International Alliance	Canada

Norman	MacIsaac	International Alliance Patient and Caregivers Advisory Council	Canada
Megan	Murphy	Biogen	USA
Marcela	Santos	ACELA - Colombian ALS Association	Colombia
Tammy	Sarnelli	Amylyx	USA
Wendy	Selig	WS Collaborative	USA
Gudjon	Sigurdsson	MND Iceland	Iceland
Bugyeong	Son	Korean ALS Association	Korea
Gethin	Thomas	Motor Neurone Disease Australia	Australia
Bernice	You	International Alliance Patient and Caregivers Advisory Council	USA
Dave	Zook	Faegre Drinker Consulting	USA

Agenda

The agenda was:

Agenda Overview	
Plenary Session	Virtual
	October 5, 2021; 7:00am-8:30am ET New York
Group Discussion	Virtual
	Group 1; October 5, 2021; 9:00am-10:30am ET (New York)
	Group 2; October 5, 2021; 6:00pm-7:30pm ET (New York)
Agenda Detail	
Plenary: Tuesday October 5: 7:00-8:30am ET (New York)	
7:00-7:05	Welcome and Overview • Calaneet Balas: Chair, International Alliance of ALS/MND Associations; CEO and President, The ALS Association • Wendy Selig: Facilitator, WSCollaborative
7:05-7:10	*Perspective*: PALS • Norman MacIsaac, PALS & CALS Advisory Council Member
7:10-7:20	*Perspective*: The International Alliance of ALS/MND Associations • Calaneet Balas: Chair, International Alliance of ALS/MND Associations; CEO and President, The ALS Association • Tammy Moore: Board Director, International Alliance of ALS/MND Associations; CEO, ALS Society of Canada
7:20-7:50	*Perspective*: Project Orbis • Dr. Jeff Allen, President and CEO of Friends of Cancer Research

7:50-8:00	*Regulatory Example:* Aducanumab • David Zook, Chair - Faegre Drinker Consulting
8:00-8:10	*Regulatory Example*: Amylyx • Dr. Jinsy Andrews, Columbia University: Associate Professor of Neurology; Director of Neuromuscular Clinical Trials
8:10-8:20	FDA Guidance: ALS/MND • Calaneet Balas
8:20-8:30	Global Principles • Wendy Selig
8:30	Closing and Next Steps
Group Discussion Virtual: Tuesday, October 5; Group 1: 9-10:30am ET: Group 2: 6-7:30pm ET	
	Debrief from Plenary • Wendy Selig
	Facilitated Discussion: Global Principles • Wendy Selig
	Wrap up and Next Steps

The outcomes of the Regulatory Pathways Roundtable meeting are embedded in the document that follows.

Background

Tammy Moore, chair of the advocacy committee for the International Alliance of ALS/MND Associations and CEO of the ALS Society of Canada, provided context and background for the roundtable, noting the urgent need to accelerate the process of bringing forward new therapies for people living with ALS/MND and specifically the significance of streamlining and harmonizing the regulatory review processes for new therapies around the world. She stressed that developing beneficial new therapies is only part of the equation, with the need to ensure that people everywhere can have timely access to those treatments, regardless of where they live. The current system, where each country or geography has its own regulatory process and little collaborative engagement with other parts of the world is not acceptable given the urgency of need for people impacted by ALS/MND. Given the recent scientific and clinical progress in the ALS/MND space, where new potentially efficacious therapies are emerging through successful clinical trials, the time is right for the Alliance to take on the opportunity and the responsibility for advancing an alternative, more harmonized global approach.

In a videotaped call to action from the perspective of a person living with ALS, Norm MacIsaac described what he called the "dog's breakfast" of current approaches to regulatory review of ALS/MND therapies. He noted that the time is right to improve that reality, especially given the important convergence in 2021 of two significant trends: (1) emergence of new therapies in clinical trials thanks to the increased investment in ALS/MND research stimulated by the Ice Bucket Challenge, and (2) the exploding global access to information where people living with ALS/MND can see what is happening in other countries. The Alliance is in a position to evaluate alternate

approaches and examples from other disease states and specific geographies, moving forward with advocacy to speed up access to therapies through a more harmonized and transparent global regulatory landscape.

Expert Presentations:

Project Orbis: Jeff Allen, PhD, CEO Friends of Cancer Research

Dr. Allen provided an overview of the approach taken by Friends of Cancer Research to improve and accelerate regulatory processes for oncology products within the US FDA, including developing strong, informal partnerships with leaders at the Agency. These partnerships with regulators span a variety of different areas, including major research activities, clinical trial designs and optimization, establishment of new regulatory approaches, and creation of an Oncology Center of Excellence within FDA. He noted that the oncology leadership at FDA has been highly engaged and willing to advance regulatory innovation and process improvements to support high-quality evidence and accelerate access to new medicines.

One example of this innovation is Project Orbis, which began as informal communication across various country's regulatory agencies and evolved into a more formal collaboration to improve global coordination for regulatory reviews. Dr. Allen noted that Project Orbis requires additional coordination from the regulators and the sponsor companies, to facilitate simultaneous submissions rather than the more traditional sequential approach. To facilitate this new model, the regulatory groups have tried to leverage common tools, such as the assessment aid developed by the US and the ICH Common Technical Document. Importantly, each regulatory authority maintains its own decision-making during the coordinated review of similar information. Overall, a review of the data indicates that Project Orbis has enhanced coordination and global access times.

There are opportunities to expand on Project Orbis, including bringing more companies into the collaboration. There are also efforts to enhance the effort by moving to coordination in the clinical development phases (upstream from regulatory submissions) to optimize clinical trial designs and endpoints across geographies. Finally, there is an opportunity to expand the coordination process to allow additional external stakeholders (patients, caregivers, and advocates) to participate in some ways.

Alzheimer's Example: Dave Zook, JD, Government & Regulatory Affairs Group Leader, Faegre Drinker

Mr. Zook provided an overview of the clinical development process and recent regulatory decision-making in the US for approval of Aduhelm, a biologic therapy for the treatment of Alzheimer's. The crux of the discussion within the FDA pertained to review of the data using a surrogate endpoint for clinical effect in Alzheimer's interventions (reduction in amyloid plaque). He described the significant controversy that occurred within the FDA's independent advisory committee, which voted overwhelmingly not to approve the drug based on concerns about its efficacy, but was overruled by the FDA leadership, which decide to provide accelerated approval for Aduhelm. In explaining its decision, the FDA noted the significant unmet need for this population of patients, willingness of patients to accept a higher risk of lack of efficacy, and the requirement for the sponsor to conduct a longer-term efficacy study of the drug in the treated population. There have been additional complexities relating to the labeling of the drug and its high cost since the FDA's decision to approve the therapy.

Amylyx Example: Jinsy Andrews, MD, Director Neuromuscular Clinical Trials, Columbia University

Dr. Jinsy Andrews reviewed the history and clinical development timeline for a drug to treat people living with ALS by Amylyx, including the milestone publication in 2020 of results from clinical studies indicating that the drug met its trial endpoints and demonstrated an overall survival benefit. Based on these results, the ALS/MND community advocated for regulatory submission and favorable review by global regulatory agencies, including those in the US, Canada, and the European Union. In recent weeks there have been additional public discussion from the company about its plans for submission, and various regulatory bodies about their processes.

Noting that these activities – and the lack of consistency across regions and countries – have created significant concern and confusion among the ALS community (including people living with ALS and clinicians), Dr. Andrews stressed the need for more harmonization, especially when it comes to submission and review timelines, opportunities for accelerated review, and interpretation of clinical trial results (including validation of surrogate endpoints, definition of clinical benefit, and evaluation of risk vs. benefit). To reinforce her point, she provided an overview of how these various elements are addressed across regulatory processes in the US, Europe, and Canada.

Group Discussions

Roundtable participants participated in one of two group discussions to review in detail the proposed global regulatory review harmonization principles.

As stage-setting for each group discussion, Alliance Chair and ALSA CEO Calaneet Balas provided an overview of the process and status of development of regulatory guidance for ALS product review by the U.S. Food and Drug Administration (FDA). She described the context and timeline for the development of the ALS community guidance and the subsequent FDA Guidance for Industry. The goal of these collaborative, multi-stakeholder efforts, which began in 2015 and took several years, was to capture the priorities of the community and have clarity about how the regulators would approach their reviews of new therapies for ALS. Having the FDA Guidance in place along with engagement at the highest levels of FDA has proved to be especially important for the community to hold the regulators to their stated process and approach, as potential new therapies have been moving through the clinical development pipeline toward regulatory review (not only in the US but globally).

Each group then worked through the draft principles for a global regulatory harmonization framework that had been circulated in advance of the meeting, providing input and suggestions for additions and revisions. Key discussion points within the groups included:

- A desire to be aspirational
- The need to realistically assess variations in readiness and capacity among global regulatory agencies to adopt the proposed framework
- The importance of framing the needs of the community first and foremost
- A necessity of engaging multi-stakeholders, including industry partners, to operationalize such a framework

Detailed feedback from the conversations within each group session was combined, resulting in development of the following revised proposed framework. Next steps include consideration for adoption by the Alliance in its

upcoming meetings and opportunities for individual Alliance members to advocate within their own geographies to advance the proposal.

Roundtable Outcomes: Global Regulatory Harmonization Principles

Roundtable participants considered lessons learned from and applicability of several examples presented by experts, including: (1) the oncology model known as Project Orbis, (2) the recent US approval of Aduhelm for treatment of Alzheimer's Disease, (3) the current regulatory situation (in the US and Canada) of a drug developed by Amylyx for ALS/MND, and (4) the development of regulatory guidance in the US for review of new products for treatment of ALS/MND. With this information as background, Roundtable participants worked within two groups to refine and align on principles for a proposed global ALS/MND regulatory harmonization framework. Results from the discussion groups were compiled and aligned by Alliance staff and are presented in Appendix 1, along with a proposed preamble.

Appendix 1

Convention to Improve Regulatory Pathways for ALS/MND

Preamble

a) *Recall* The CONVENTION ON THE RIGHTS OF PERSONS WITH DISABILITIES AND OPTIONAL PROTOCOL emphasizes the need to recognize "the importance of international cooperation for improving the living conditions of persons with disabilities in every country particularly in developing countries";
b) *Recall* The Fundamental Rights of People Living with ALS/MND emphasizes that "each person has the right to: the highest quality treatment available within their healthcare system";
c) *Recognize* That these principles represent the ideal for individuals living with ALS/MND worldwide;
d) *Recognize* That conditions and resources in all geographies may not immediately support attaining this achievement of these aspirations;
e) *Concerned* That the urgency of ALS/MND is not well understood by regulators;
f) *Understand* That regulators will remain fully independent in making their regulatory decisions and adhering to internal timelines, but can share accountability and risk;
g) *Recognize* That medical produce sponsors are expected to meet specific criteria for regulatory review in each country.

h) *Recall T*he successful example of Project Orbis, an initiative led by the US Food and Drug Administration (FDA) Oncology Center of Excellence, which is predicated on the goal of bringing effective therapies to patients as early as possible, especially in countries where there may otherwise have been delays with regulatory submission and review.
i) *Convinced* that a comprehensive international convention to promote harmonization of regulatory approval will uphold the rights of those individuals with ALS/MND to have equal access new treatments and clinical trials, in both developing and developed countries,
j) *Recognize* that this convention represents the proposed framework all Alliance member organisations should adopt and promote.

The International Alliance of ALS/MND Associations supports the Convention for Improving Regulatory Pathways to accelerate access to therapies for people living with ALS/MND.

Article 1: Purpose

The International ALS/MND Alliance seeks to encourage all international regulatory agencies to develop a framework for global alignment in evaluating potential new therapies for people living with ALS/MND. The Alliance believes that the ALS/MND community and all stakeholders will benefit from a more cooperative global approach to evaluation of risks and benefits of novel therapies, especially given the global nature of drug development and clinical trial conduct. People living with ALS/MND – regardless of where they reside – have extraordinary unmet need and seek the fastest and widest possible access to potentially beneficial therapies. Given the devastating nature of ALS/MND, this community cannot wait for excessive procedural delays caused by sequential reviews and hand-offs.

Pivotal clinical trials in ALS/MND are often conducted internationally and these global trials are increasingly important for investigating the safety and effectiveness of ALS/MND drugs for approval. Future drug development may benefit by establishing a greater uniformity of new global standards of treatment, leading to the optimal design of these important trials. There should be a cooperative, harmonized, pathway to approval which increases effectiveness and expediency for treatments of ALS/MND guided by the following principles.

Article 2: Basic Tenets

Principle 1: Perspectives of benefits and risks, expertise, and experiences of people living with ALS/MND, their caregivers and healthcare providers should be at the core of clinical development and global regulatory review discussions.

Principle 2: Regulators from each country/region align on regulatory review with purpose to drive outcomes.

Principle 3: Regulators develop harmonized guidance and process pathway(s) encouraging sponsors to submit engagement before applications for ALS/MND products to participating countries for concurrent review.

Principle 4: Establish ongoing, regular interaction among regulators to share information and participate in mutual engagement that leads to more harmonized approval process.

Principle 5: Objective measures of progress are developed by the stakeholder community in conjunction with regulators and used in reporting

Article 3: Obligations

Principle 6: Identify Global Regulatory ALS/MND Lead within each regulatory authority.

Principle 7: Identify one Global Regulatory ALS/MND lead (or small group) (TBD) to serve as lead convener for this effort. This could be a rotating responsibility.

Principle 8: Regulators will have transparency with all stakeholders in the ALS/MND community which includes people living with ALS/MND and their caregivers; organizations who provide care, research and advocacy; academics, researchers and scientists; and representatives of product sponsor entities (to the greatest extent possible while respecting commercial and professional sensitivity)