Rare Disease Advisory Council
Location: IDOH YOHO
CONFERENCE ROOM
Date: October 27, 2023
Time: 2:30PM -5:00PM

Meeting Minutes

Call to Order – 2:33pm: A meeting of the Rare Disease Advisory Council was held at 2 N. Meridian St, in the YOHO Conference Room on the third floor.

In Person Attendees: Dr. D. Wade Clapp, Laura McLinn, Mindy Cameron, Dr. Jodi Skiles, Dr. Tara Jellison, Dr. Doug Cipkala, Meghann Leaird, Lucy Paskus NP, Julie Gries, Ann Alley, Allison Forkner, Carl Ellison, Dr. Ty Sullivan and Cynthia Bryant.

Online Attendees: Dr. Santiago Schnell, Dr. Patrick Milligan, Dr. Joel Feldman, Tim Arndt, Tami Barrett.

Approval of Minutes: Dr. Clapp – Council Chairman.

Approval of Previous Minutes – 2:39pm.

Reports: Article: "Defining rare conditions in the area of personalized medicine" by Dr. Schnell.

New Business: None.

Announcements: The representative for Eli Lilly has filled the last council position.

Handouts: Nord Meeting Highlights, by Dr. Tara and Mindy.

Roundtable – 3:28pm: The Council split up into their subcommittees to brainstorm about survey questions, focus groups, survey group diversity and the shape of survey questions. Each group spent 40 minutes on the discussions. The subcommittees will be used for survey discussions only.

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To Do

By law Review

Open Door Requirement Review

Survey Instrument and Waiver Discussion

Invite Dr. Nancy Swigonski to meeting

Create public polls.

Vote: Meeting Participation by Electronic Means

Include Dr. Swigonski for public poll creation discussion.

Ask Mr. Ellison about available/alternate voices for surveys

Council appointment discussion.

Create mission statement/draft agendas

Meeting adjourned at 4:48pm.

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Next Meeting: November 13, 2023, 8:00am – 10:00am.

Defining rare conditions in the era of personalized medicine

Daniel J. O'Connor, Michela Gabaldo, Annemieke Aartsma-Rus & Anneliene Hechtelt Jonker

The total number of rare conditions is debated, partly because of the variety of definitions of what constitutes rare. A broader consensus view of what rare means, based on improved understanding of individual group and patient clinicopathological characteristics, will help maximize the impact of technological advances in therapeutic development programmes. Introduction Rare conditions have been defined and categorized in a variety of ways. Traditionally, rare conditions have been described with specific clinical features and in some cases named after their discoverer. Through a panel of experts and in collaboration with the World Health Organization, an operational description of rare diseases has been proposed by Rare Diseases International: a medical condition with a specific pattern of clinical signs, symptoms and findings that affects fewer than or equal to 1 in 2,000 persons living in any World Health Organization-defined region of the world. Numerous other similar and overlapping definitions exist, including those from regulatory authorities, governments, not-for-profit organizations and patients' organizations1 . In these definitions, it is generally accepted that rare diseases are defined by their low prevalence, that patients with rare diseases face specific challenges in their diagnostic and treatment journeys, and that these patients should have the same opportunities for health care as patients with more common conditions. Despite these consensus features, there is currently no common global agreement on the impact and widespread application of advances in molecular sciences and pathology on the definition of a rare condition. Here, we discuss the impact of defining rare conditions in the era of personalized medicine, including subsetting of common conditions, subsetting of rare conditions, individualized treatment options and shared molecular entity conditions. How are rare conditions currently defined? Most definitions for rare conditions are based on low prevalence, such as the definition in the European Union, in which a rare condition is one that affects no more than 5 in 10,000 people. In addition, definitions may include qualitative indicators, such as aspects of disease severity, including whether the disease is life-threatening and whether a treatment currently exists. In addition, some conditions are defined in terms of being ultra-rare or by the amount of research attention they have been given, such as neglected or under-researched diseases. Specific groups of rare diseases can be qualified according

to clinicopathological features, and a disease that is rare in one region does not necessarily qualify as such in another region, driven in some cases by patterns of infectious agents or specific ethnic features of the local population. Impact of personalized medicine on defining rare Personalized medicine is a broad term that may refer to a medical model using the characterization of the phenotypes and genotypes of individuals (including lifestyle data) to tailor the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention. The term is sometimes used interchangeably with therapies individualized to a single patient, alongside referring to therapies targeted to groups of patients. Three areas can be considered when determining the impact of personalized medicine approaches on the definition of a rare condition. • Subsetting of common conditions to rarer entities; for example, a common cancer subdivided by a specific biomarker • Subsetting of rare conditions; for example, based on different specific variants in a gene that cause the condition • Shared molecular entity conditions; for example, a 'new condition' comprising different diseases that have a shared (often drug-targetable) common feature. Subsetting of common conditions. Owing to the availability of more sophisticated molecular research tools, knowledge on disease a etiology and pathology has increased, and traditionally described common diseases are increasingly being redefined based on biomarkers and other genetic characteristics2 . The implication of defining these subsets of common conditions is that, from a prevalence perspective, they may fulfil the criteria for rare conditions. Consequently, if these subsets are formally considered rare by organizations such as regulatory agencies, this will affect the policy provisions and the total number of rare conditions. A rare subset of a common condition and a traditionally described rare condition share many of the same challenges when considering research involving small populations. The total number of patients eligible for clinical trials may be very limited, which affects the choice of study design and the statistical methodology. The development programme for a potential therapy may necessitate the coordination of numerous clinical study sites throughout the world and there may be challenges in recruiting the necessary number of patients. Furthermore, smaller studies are more susceptible to the effects of variability and missing data are likely to be more critical, with a greater impact on the conclusions. Requirements for statistical efficiency should be balanced against the need for drawing clinically relevant and scientifically robust conclusions. Given these challenges, scientific advice from regulatory authorities on issues such as the acceptability of novel and innovative methodologies may be valuable in the design of clinical trials in both scenarios. Check for updates nature reviews drug discovery Volume 22 | November 2023 | 857–858 | 858 more common conditions. Small-population research is increasingly recognized as a key part of the activities of pharmaceutical, medical technology and academic sectors, despite the challenges. If we are to maximize the benefits of

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twenty-first-century science, a common view of rare that incorporates the fast-evolving diagnostic landscape is needed5 . Reaching a consensus will strengthen the foundations of small-population research that can be applied to help develop approaches to address the high unmet medical need. To move towards a more harmonized and inclusive definition of rare conditions, we suggest that future work in this field explicitly considers the issues raised in this article. Daniel J. O'Connor1,2 , Michela Gabaldo1,3, Annemieke Aartsma-Rus1,4,5 & Anneliene Hechtelt Jonker1,6 1 Therapies Scientific Committee, International Rare Disease Research Consortium, Paris, France. 2 The Association of the British Pharmaceutical Industry, London, UK. 3 Aptuit, an Evotec company, Verona, Italy. 4 Department of Human Genetics, Leiden University Medical Center, Leiden, the Netherlands. 5 Dutch Center for RNA Therapeutics, Leiden, the Netherlands. 6 University of Twente, Enschede, the Netherlands. e-mail: doconnor@abpi.org.uk Published online: 8 September 2023 References 1. Richter, T. et al. Rare disease terminology and definitions—A systematic global review: Report of the ISPOR Rare Disease Special Interest Group. Value Health 18, 906–914 (2015). 2. Kesselheim, A. S., Treasure, C. L. & Jofe, S. Biomarker-defined subsets of common diseases: policy and economic implications of Orphan Drug Act coverage. PLOS Med. 14, e1002190 (2017). 3. Kim, J. et al. Patient-customized oligonucleotide therapy for a rare genetic disease. N. Engl. J. Med. 381, 1644–1652 (2019). 4. Zanello, G. et al. Targeting shared molecular etiologies underlying multiple rare diseases. EMBO Mol. Med. 15, e17159 (2023). 5. Seydel, C. Personalized medicine is having its day. Nat. Biotechnol. 41, 441–446 (2023). Competing interests A.A.-R. discloses being employed by LUMC, which has patents on exon skipping technology, some of which have been licensed to BioMarin and subsequently sublicensed to Sarepta. As co-inventor of some of these patents, A.A.-R. is entitled to a share of royalties. A.A.-R. further discloses being an ad hoc consultant for PTC Therapeutics, Sarepta Therapeutics, Regenxbio, Dyne Therapeutics, Lilly, BioMarin Pharmaceuticals., Eisai, Entrada, Takeda, Splicesense, Galapagos and AstraZeneca. Past ad hoc consulting has occurred for Alpha Anomeric, CRISPR Therapeutics, Summit, Audentes Santhera, Bridge Bio, Global Guidepoint and GLG consultancy, Grunenthal, Wave and BioClinica. A.A.-R. also reports having been a member of the Duchenne Network Steering Committee (BioMarin) and being a member of the scientific advisory boards of Eisai, Hybridize Therapeutics, Silence Therapeutics and Sarepta Therapeutics, and a past member of the scientific advisory boards for ProQR and Philae Pharmaceuticals. Remuneration for these activities is paid to LUMC. LUMC also received speaker honoraria from PTC Therapeutics, Alnylam Netherlands, Pfizer and BioMarin Pharmaceuticals and funding for contract research from Italfarmaco, Sapreme, Eisai, Galapagos, Synnafix and Alpha Anomeric. Project funding is received from Sarepta Therapeutics and Entrada. The other authors declare no competing interests. The views of the authors are their own and do not necessarily reflect their respective affiliations. Related links

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IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations: https://www.fda.gov/ regulatory-information/search-fda-guidance-documents/ind-submissions-individualizedantisense-oligonucleotide-drug-products-severely-debilitating-or-life Subsetting of rare conditions. Using the European Union definition, the prevalence of a rare condition is not more than 5 in 10,000 people, and it can be much lower (1 in 50,000 is typically considered ultra-rare). When considering rare genetic diseases in the context of potential personalized medicines that are expected to only be useful for a subset of people carrying a specific pathogenic variant, these subsets can be even smaller (with an estimated prevalence of one in a million), or the variants may affect just one person. It has already been shown to be feasible to develop a gene transcript targeting treatment for a single patient3 . These 'N of 1' individualized precision medicine approaches are often academic-led and based on platform technologies such as antisense oligonucleotides. However, there is a need to support standardization of the pathway from diagnosis to patient access to a treatment (such as non-clinical requirements before administration to patients) and enable scalability and sustainability. In 2021, the FDA released draft guidance for the submission of individualized antisense oligonucleotide drug products for severe and life-threatening diseases. Further proportionate and innovative approaches from regulatory agencies that recognize the unique challenges would help advance the field. Shared molecular entity conditions. Grouping patients with rare diseases based on the same underlying molecular a etiology, rather than the traditional symptom-based definition of disease, has the potential to identify groups of diseases likely to respond to the same therapeutic agent. Such disease groups could include rare diseases characterized by mutations in the same gene (for example, NLRP3 mutations), the same type of mutation affecting different genes (for example, a premature termination codon mutation), or mutations in different genes affecting the same molecular pathway (resulting in diseases with different or similar phenotypes). This could allow innovative approaches that may greatly increase the number of patients gaining access to clinical trials and experimental treatments4 . For example, the approach of evaluating a single treatment intervention for multiple diseases that share common molecular alterations is increasingly well known and used in oncology (in studies known as basket trials), and several histology-independent (or tumour-agnostic) cancer therapies have gained regulatory approval, such as kinase inhibitors for patients with solid tumours that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion. In principle, the same approach could be applied to multiple rare diseases that share the same underlying molecular a etiology. While there remain challenges to overcome to successfully implement this approach, there is the potential to accelerate drug development for patients with rare diseases that have the same underlying molecular a etiology. Success factors for this approach

include sufficient understanding of the biology across multiple rare diseases, early engagement with regulators to discuss the development approaches and application of innovative statistical methodologies such as adaptive trial designs in clinical development. Conclusion and recommendations Patients with rare conditions often have high unmet medical needs and deserve the same treatment opportunities as other patients with

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