

EDITORIAL

Open Access



# Innovative methodologies for rare diseases clinical trials

Rima Nabbout<sup>1,2,3\*</sup> and Ralf-Dieter Hilgers<sup>4\*</sup>

The European Joint Programme on Rare Diseases [1] brings over 130 institutions including all 24 European research networks (ERNs) from 35 countries:

- 26 EU Member States (Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Croatia, Ireland, Italy, Netherlands, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Spain, Sweden, Slovakia, Slovenia).
- 7 associated members (Armenia, Georgia, Israel, Norway, Serbia, Switzerland, Turkey)
- United Kingdom & Canada

aiming to create a comprehensive, sustainable ecosystem allowing a virtuous circle between research in rare diseases (RD), care and medical innovation. As clinical trials remain challenging in RD [2] even after regulatory recommendation [3], WP20 of EJP-RD aims to reach awareness of innovative trial methodology, not only limited to statistical methods. This is based on the previous developments of three FP7 funded projects (IDeAl [4], asterix [5] and InSpiRe [6]), which delivered a huge range on innovative statistical methods for small population clinical trials. However, these innovative methods need

validation in practical settings. This gap is closed by EJP-RD WP20 launching demonstration projects, i.e. EPIS-TOP-IDeAl (EPISTOP clinical trial data set re-use with statistical methodologies tailored for clinical trials in rare diseases), EBStatMax (State-of-the-art statistical design and analysis for maximal success with minimal patient burden in Epidermolysis bullosa trials) and Improve PSP (Application of improved statistical methodologies for clinical trials in Progressive Supranuclear Palsy). To further address the need for innovations for limited population trials, WP20 funded also innovation calls in clinical trials methodologies for rare diseases i.e. iSTORE (Innovative statistical approaches to improve outcome in rare epilepsies: A model for rare and ultra-rare diseases) and Evidence RND (Creating robust evidence for longitudinal progression changes and treatment effects in ultra-rare neurological diseases: the case of multisystemic autosomal-recessive ataxias).

EBStatMax deals with State-of-the-art statistical design and analysis for maximal success with minimal patient burden in Epidermolysis bullosa trials, Improve PSP with application of improved statistical methodologies for clinical trials in Progressive Supranuclear Palsy and Epi-stop-IDeAl re-uses EPISTOP clinical trial data set on epilepsy preventive therapy in Tuberous sclerosis complex with statistical methodologies tailored for clinical trials in rare diseases.

The two innovation projects aim for improvement and innovation of the methodology for trials in limited populations, for example in relation to trial design, endpoints or the statistical analysis methods. For instance, iSTORE will develop Innovative Statistical Methodologies to Improve Rare Diseases Clinical Trials endpoints in Limited Populations using Dravet syndrome [7], a rare developmental and epileptic encephalopathy, as a show

\*Correspondence:

Rima Nabbout  
rima.nabbout@aphp.fr  
Ralf-Dieter Hilgers  
rhilgers@ukaachen.de

<sup>1</sup>Reference centre for rare epilepsies Université Paris cité, Paris, France

<sup>2</sup>Assistance Publique-Hôpitaux de Paris, Hôpital Necker-Enfants Malades, Paris, France

<sup>3</sup>Institut Imagine, INSERM U1163, Paris, France

<sup>4</sup>RWTH Aachen University, Institute of Medical Statistics, 52074 Aachen, Germany



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

case [8]. EVIDENCE RND will create robust evidence for longitudinal progression changes and treatment effects in ultrarare neurological diseases: the case of multisystemic autosomal-recessive ataxias. The ambition is to reach results that might be transferrable to other rare diseases as well.

Beside these project-oriented developments, WP20 is driven by the mission to disseminate the developments and reach a higher level of trained rare disease researchers based on a survey organized by EJP-RD and having a dedicated part to clinical trials gaps and needs in the RD community. A core point are the advanced webinars; held by methodological experts and commented by a panel of experts from different stakeholders including in addition to methodologists, clinicians, patients representative, industry and members of the regulatory organisations. These webinars are recorded and made public and available at the EJP-RD site [9]. However and despite a high number of attendees, we realized that this has a limited outreach, and as science is disseminated usually by publications, WP20 was therefore very enthusiastic that *Orphanet Journal of rare diseases* welcomes to publish a series of papers dealing with these webinars and with the RD clinical trials developments. The unique series of publications allows linking the advanced webinars recordings and presentations with more insights on the topic and guarantees the ambition of reaching and training the largest rare disease scientific community.

#### Acknowledgements

The WP20 activities and research are funded by the European Joint Programme on Rare Diseases (EJP RD), EU Horizon 2020 grant no. 825575.

Published online: 07 May 2024

#### References

1. EJP RD – European Joint Programme on Rare Diseases [Internet]. <https://www.ejprarediseases.org>.
2. Hilgers R-D, Roes K, Stallard N. Directions for new developments on statistical design and analysis of small population group trials. *Orphanet J Rare Dis*. 2016;11(1).
3. CHMP. Guideline on clinical trials in small populations. [Online] 2007. [Cited: February 1, 2013]. [www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003615.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf).
4. Hilgers RD, Bogdan M, Burman CF, Dette H, Karlsson M, König F et al. Lessons learned from IDeAI — 33 recommendations from the IDeAI-net about design and analysis of small population clinical trials. *Orphanet J Rare Dis*. 2018;13(1).
5. Mitroiu M, Oude Rengerink K, Pontes C, Sancho A, Vives R, Pesiou S et al. Applicability and added value of novel methods to improve drug development in rare diseases. *Orphanet J Rare Dis*. 2018;13(1).
6. Friede T, Posch M, Zohar S, Alberti C, Benda N, Comets E et al. Recent advances in methodology for clinical trials in small populations: the InSPiRe project. *Orphanet J Rare Dis*. 2018;13(1).
7. Nabbout R, Auvin S, Chiron C, Irwin J, Mistry A, Bonner N, et al. Development and content validation of a preliminary core set of patient- and caregiver-relevant outcomes for inclusion in a potential composite endpoint for Dravet Syndrome. *Epilepsy Behav*. 2018;78:232–42.
8. Schoenen S, Verbeeck J, Koletzko L, Brambilla I, Kuchenbuch M, Dirani M, et al. Istore: a project on innovative statistical methodologies to improve rare diseases clinical trials in limited populations. *Orphanet J Rare Dis*. 2024;19(1):96. <https://doi.org/10.1186/s13023-024-03103-2>.
9. webinar – EJP RD – European Joint Programme on Rare Diseases [Internet]. <https://www.ejprarediseases.org/tag/webinar/>.

#### Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.