P1181

Utility and Implementation of a Federated Research Infrastructure to Assess Lack of Disease Stability as a Real-World Surrogate of PIRA, by Combining MS Clinical Trial and Real-World Cohort Data (The INTONATE-MS Consortium)

J Oh,[1] J Smolders,[2] F Buijs,[3] R Pedotti,[3] F Dahlke,[4] L Kaczmarek,[3] A Kemmisetti,[5] V Sharma,[6] D Heinzmann,[3] B Tackenberg,[3] A Bar-Or,[7] H Wiendl[8]

[1]University of Toronto, St. Michael's Hospital, Department of Neurology, Toronto, ON, Canada; [2]Erasmus MC, MS Center ErasMS, Department of Neurology, Rotterdam, Netherlands; [3]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [4]impulze GmbH, Zürich, Switzerland; [5]Genentech, Inc, South San Francisco, CA, USA; [6]Roche Diagnostics, F. Hoffmann-La Roche, Santa Clara, CA, USA; [7]University of Pennsylvania Perelman School of Medicine, Department of Neurology, Philadelphia, PA, USA; [8]Department of Neurology with Institute of Translational Neurology, University of Münster, Münster, Germany

OBJECTIVE

Evaluate the novel concept of 'lack of disease stability', as assessed in routine clinical practice, and explore its utility as a surrogate of PIRA in PwMS on high-efficacy treatment (HET) by leveraging and assessing the utility of a federated data infrastructure across participating centres

CONCLUSIONS

To date, this study has shown that a federated network can be implemented between public and private research centres as an innovative approach to overcome research bottlenecks that impede data-driven science

A federated research approach through the INTONATE-MS consortium will generate a better knowledge of PIRA and will help to better understand rwPIRA and its applicability and relevance in a clinical setting

This consortium provides a unique opportunity to identify solutions around development and validation of novel real-world endpoints and explore its utility in clinical practice in a single research setting

The current study sets the stage for future research involving clinical, biological and imaging data that have the potential to innovate and accelerate research in the field of neuroscience

BACKGROUND

Among people with multiple sclerosis (PwMS), it is increasingly being recognised that progression occurs even during the earliest stages of the disease[1–3]

Data from clinical trials[1,4] and observational studies[2,5] have indicated progression independent of relapse activity (PIRA) to be a dominant driver of progression in PwMS in early stages of the disease[2,3]

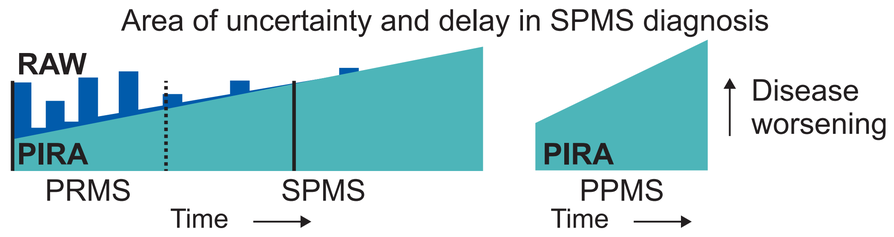
While PIRA can be extracted from clinical trial and registry data, it is unclear whether this measure can be readily utilised in routine clinical care

Research network bottlenecks, such as country-specific legalities of privacy and data protection, data ownership challenges, technical data sharing issues and administrative hurdles, limit scientific collaboration on data across borders and institutions, limiting scientific progress and innovation in the field of neuroscience

The INTONATE-MS collaborative federated research approach provides an opportunity to overcome these hurdles

BACKGROUND

Threshold to identify PIRA events in clinical practice is high due to lack of or infrequent assessments of disease worsening, including EDSS, as compared with RCTs



EDSS, Expanded Disability Status Scale; PIRA, progression independent of relapse activity; PPMS, primary progressive multiple sclerosis; RAW, relapse-associated worsening; RCT, randomised-controlled trial; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

METHODS

Consortium

- INTONATE-MS is a public–private research consortium between Universitätsklinikum Münster, Penn Medicine, Unity Health Toronto, Erasmus MC and Roche

Cohort Selection

- An MS patient cohort was selected retrospectively at each site, with inclusion criteria being multiple sclerosis (MS) diagnosis and HET (ofatumumab, ocrelizumab, natalizumab and alemtuzumab) in any line between 2004 and 2022
- Institutional review board approval was received at each site for use of data in this network, with informed consent procedures followed according to local guidelines

Data Harmonisation[a]

- Clinical and biosample data are harmonised locally at each site according to a common data standard and data model[6] to enable federated analysis across all sites

Data Storage

- The harmonised dataset is stored locally, with the anonymised study data transferred to a local on-premise or private cloud isolated compute environment (owned and controlled locally) called a 'node'

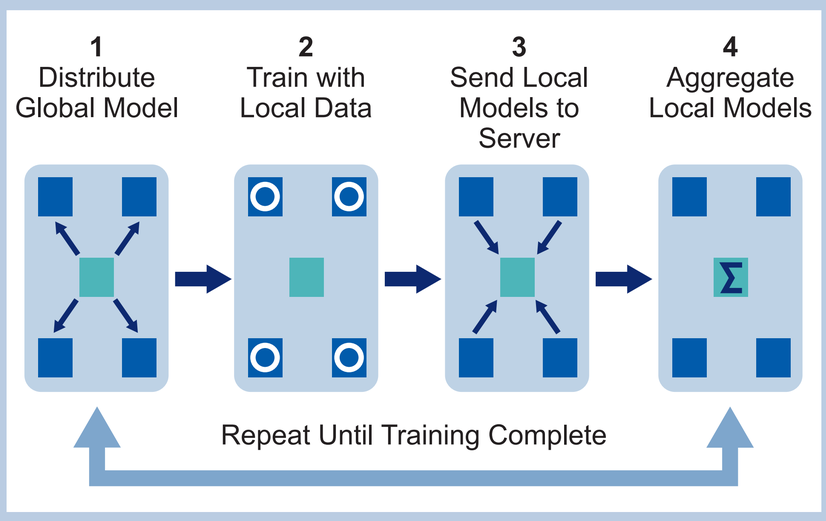
[a]Data harmonisation is supported by The Hyve, Utrecht, Netherlands.[6]

Lack of Disease Stability

- Characterise the novel endpoint 'lack of disease stability', defined as deterioration of neurological function measured by clinical and paraclinical variables collected in PwMS on HET
- Extract and describe named parameters' proportional contribution to 'lack of disease stability' assessing disease activity and disability worsening
- Deduce a meaningful, novel real-world definition of PIRA (rwPIRA) as a putative key component of the disease state 'lack of disease stability', which can be adapted to clinical practice

'Real-world' PIRA

- Assess the proportional contribution of clinical or paraclinical parameters to 'lack of disease stability' and map them to different existing PIRA definitions from the literature[1–5, 7–10]
- Define how PIRA can be inferred from sparse clinical data available in a real-world setting and derive a robust definition of rwPIRA from these clinical cohorts
- Focus on PwMS receiving HET ensuring that focal inflammation and relapse biology is mostly abrogated facilitating the identification of a potentially more meaningful "true" PIRA concept



Model of federated architecture used, based on local nodes and a central aggregation server approach[11]

Federated Architecture

- Data are harmonised locally and transferred to local nodes
- A secure local federated analysis is performed without the local data having to be shared between sites, i.e. no transfer of patient data taking place, in any form, between participating sites
- Analyses are exchanged between sites coordinated by a central aggregation server (Apheris GmbH,[12] Berlin, Germany)
- Local analysis output is combined into a single aggregate result and received by the data scientist executing the query in the form of (anonymous) aggregate statistics
- The federated approach provides scale-enabling assessment of the relevant number of patients required for the purpose of this study

RESULTS

Federated Architecture of the INTONATE-MS Consortium

- All participating sites and their connection to the federated network
- Each site provides SoC or RCT and biosample data to the network
- Data are harmonised locally (ETL) into a CDM. The harmonised, anonymised dataset is transferred to the local node (cloud or on premise) and made available for the federated analysis
- The central aggregation server orchestrates the federated query and aggregation of the results

ETL, extract, transform, load; RCT, randomised clinical trial; SoC, standard of care.

REFERENCES

1. Kappos L, *et al. JAMA Neurol* 2020;77:1132–1140.
2. Portaccio E, *et al. Brain* 2022;145:2796–2805.
3. University of California, San Francisco MS-EPIC Team, *et al. Ann Neurol* 2019;85:653–666.
4. Lublin FD, *et al. Brain* 2022;145:3147–3161.
5. Graf J, *et al. Brain Commun* 2021;3:fcab229.
6. The Hyve. https://thehyve.nl/. Accessed 18 September 2023.
7. Bsteh G, *et al. Mult Scler J Exp Transl Clin* 2020;6:2055217320966344.
8. Ness N, *et al. J Neurol* 2020;267:1035–1042.
9. Prosperini L, *et al. Neurol Neuroimmunol Neuroinflamm* 2021;8:e1059.
10. von Wyl V, *et al. Mult Scler* 2021;27:439–448.
11. Rieke N, *et al. NPJ Digit Med* 2020;14;3:119.
12. Apheris. https://www.apheris.com/. Accessed 18 September 2023.

Presented at the 9th Joint ECTRIMS-ACTRIMS Meeting | Milan, Italy | 11–13 October 2023

DISCLOSURES

J Oh has received personal compensation for consulting or speaking from EMD-Serono, Sanofi-Genzyme, Biogen-Idec, F. Hoffmann-La Roche Ltd, Bristol Myers Squibb, Horizon Therapeutics, and Novartis, and has received research funding from the MS Society of Canada, National MS Society, Brain Canada, Biogen-Idec, and F. Hoffmann-La Roche Ltd. **J Smolders** received lecture and/or consultancy fees from Biogen, F. Hoffmann-La Roche Ltd, Merck, Novartis and Sanofi-Genzyme. **F Buijs** is an employee of F. Hoffmann-La Roche Ltd. **R Pedotti** is an employee of F. Hoffmann-La Roche Ltd. **F Dahlke** is an employee of impulze GmbH and provides consulting services for F. Hoffman-La Roche Ltd. **L Kaczmarek** is an employee of F. Hoffmann-La Roche Ltd. **A Kemmisetti** is an employee of Genentech, Inc. **V Sharma** is an employee of F. Hoffmann-La Roche Ltd. **D Heinzmann** is an employee of F. Hoffmann-La Roche Ltd. **B Tackenberg** is an employee of F. Hoffmann-La Roche Ltd. **A Bar-Or** has received consulting fees from Actelion, Atara Biotherapeutics, Biogen-Idec, Celgene/Receptos, Genentech/Roche, Mapi Pharma, MedImmune, Merck/EMD Serono, Novartis, Sanofi-Genzyme, GlaxoSmithKline and BrainStorm, and has received contracted research support through the University of Pennsylvania from Biogen Idec, Roche/Genentech, Merck/EMD Serono and Novartis. **H Wiendl** has received grant/research support from Bayer HealthCare, Biogen-Idec, Deutsche Forschungsgemeinschaft, Else Kröner Fresenius Foundation, German Ministry for Education and Research, Hertie Foundation, Interdisciplinary Centre for Clinical Research, Münster, Germany, Merck Serono, Novartis, NRW Ministry of Education and Research, Sanofi-Aventis/Genzyme and Teva Pharmaceutical Industries, and has received consulting fees from Bayer HealthCare, Biogen Idec, Fresenius Medical Care, GlaxoSmithKline, GW Pharmaceuticals, Merck Serono, Novartis, Sanofi-Genzyme BioVentures and Teva Pharmaceutical Industries.

To access this poster and supplemental material scan the QR code or go to the following URL:
https://ter.li/vcu0vz

ACKNOWLEDGEMENTS

We would like to thank all patients, their families and the investigators participating in this study. This study is sponsored by F. Hoffmann-La Roche Ltd, Basel, Switzerland. Writing and editorial assistance for this presentation was provided by Articulate Science, UK, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland.