Deliverable number: D4.1

Deliverable title: Final Report on clusters coordination activities

Deliverable type	Report
Deliverable responsible partner	EBC
Contractual date of delivery	Month 48
Actual date of delivery	Month
Dissemination level	Public
Status of deliverable	Achieved

Grant Agreement information table	
Grant Agreement number	825348
Project acronym	EBRA
Project title	European Brain Research Area
Start date	November 1st 2018
Duration	48 months

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825348

Contents

1. Introduction

Effective and efficient collaboration and cooperation among various researchers, large scale research projects and initiatives are often identified as a key success factor to achieve brain research full impact. Although the European Commission has made outstanding contributions to brain research and invested in some coordination activities, most research efforts are still quite fragmented and poorly coordinated. To tackle this, the EBRA consortium carefully selected 6 brain research communities in need of coordination – the so-called EBRA clusters:

- EPICLUSTER
- Prevention of Severe Mental Disorders (PSMD) cluster
- TRISOMY21 cluster
- BRAINFOOD cluster
- PREMOS cluster
- ECIB cluster

EBRA supported them by creating the conditions for real and effective cross fertilization, dialogue and building consensus. More precisely, each cluster organized 2-4 coordination activities (e.g., meetings, workshops, conferences) in which one or more needs of their community were addressed. In total, 18 cluster activities were organized. Those activities allowed strengthening of the information flow in the clusters, acceleration of the exchange of experience on the on-going and future research projects and dialogues between the cluster members, relevant stakeholders (e.g., transdisciplinary experts, industry, patient organizations, regulators, research infrastructures, funders) and other major brain research initiatives and projects at European level and beyond. The concrete outcomes of those meeting were written down in 7 high level peer-reviewed articles and several meeting reports and minutes.

The cluster activities addressed major coordination needs and priorities of which several were overlapping between the different clusters. The most important ones can be found here below:

1. ***Extension of the cluster*** Interactions between existing projects, networks (e.g., the ECNP networks and Thematic Working Groups) and partners need to be maintained. Additionally, new connections must be fostered with relevant other neuroscience and health projects and partners within Europe. In particular, a focus should be put on multi-disciplinary and sector collaboration including public-private partnerships. Finally, liaising should not be restricted to researchers and clinicians but should also focus on patients and patient organizations, caregivers, industry (e.g., pharmaceutical, food), charities, regulators, funders, charities, non-governmental organizations, and citizens.

2. ***Patient engagement*** The engagement with persons with brain disorders, their representatives and caregivers need to increase.

3. ***Coordination of research infrastructures*** Mechanisms for coordination of research infrastructure need to be explored and established, and links with existing infrastructures in which cluster members already take part need to be further promoted.

4. ***Coordination of resource-sharing (experimental models, IPSc, clinical protocols, etc.) with a particular focus on:***

a. ***Coordination of (pre)clinical studies*** Clinical trials structures need to be enhanced and a preclinical network needs to be developed. Therefore, attention should be given to harmonizing and standardising protocols for (pre)clinical research, enabling better comparisons among studies.

b. ***Coordination of the data ecosystem*** Data sharing should be encouraged. Therefore, common computerized research databases need to be created which also allow for multinational data management. Therefore, core assessment, outcome measures and interventional research strategies should ne standardised.

5. ***Funding*** Clusters need more funding that allows them to sustain the excellence of their research and to continue with facilitation coordination in their communities. Therefore, EU-grants and global funding initiatives should be explored, and funding initiative across agencies should be developed.

6. ***Visibility*** Increase the visibility of brain research and their communities through activities directed towards an increased public understanding of their brain research topic.

These meetings and outcomes prepared the clusters to develop innovative and exciting initiatives in their research field and supported them in applying together for future funding (especially in the EC).

Here below, the cluster objectives, activities and related outcomes are described.

2. EPICLUSTER

The primary objective of EPICLUSTER is to establish a collaborative framework for the coordinated actions of epilepsy research in Europe, based around shared partnerships and research priorities.

Key objectives are:

- Maintaining the cooperation started under EpiXchange that brought together several large-scale epilepsy research projects and bring in new partnerships/projects and stakeholders.
- Agree shared priorities and work toward addressing these including in the area of (1) data sharing (large scale sequencing, preclinical, clinical data), (2) preclinical studies and improving translation, (3) access and sharing of research infrastructures and training.
- Develop and pursue funding of joint research programmes of scale in Europe and beyond.

The Cluster's leadership team is comprised of 10 internationally recognized scientists and clinicians in the field and the leaders of the seven projects that came together under EpiXchange as well as leaders from patient and professional organisations. Collectively, they have supervised over 250 doctoral and postdoctoral researchers, contributing to over 2500 publications on the topic of mechanisms, treatment, and biomarkers of epilepsy. Emphasizing their excellence, the average H-index is over 50 and average over 13000 citations. Several are Directors of major national research centers (e.g., Henshall, FutureNeuro) and lead Task Forces under the auspices of the ILAE's Commissions.

Cluster leadership	Expertise/interests	Projects/Responsibilities
David C. Henshall, PhD (Coordinator) **RCSI/FutureNeuro**	Basic/translational neuroscience Mechanisms, treatment & biomarkers of	Coordinator, EpimiRNA
Renzo Guerrini, MD	Genetics of epilepsy	Coordinator, DESIRE

Univ. Verona	Epileptic encephalopathies	
Sergiusz Jozwiak, MD **Univ. Warsaw**	Clinical neurology/epileptologist (paediatrics) Tuberous sclerosis complex	Coordinator, EPI-STOP
Merab Kokaia, PhD **Lund University**	Basic/translational neuroscience Gene therapy	Coordinator, EPI-TARGET
Asla Pitkanen, MD, PhD **U. E. Finland/Kuopio**	Basic/translational neuroscience Mechanisms, treatment & biomarkers of acquired epilepsy	Past-Secretary FENS, EPI-TARGET WP leader
Sanjay Sisodiya, MD, PhD **University College London**	Clinical neurology/epileptologist Genetics of epilepsy	Coordinator, Epi-PGX
Michele Simonato, MD **U. Ferrara/U. San Raf.**	Basic/translational neuroscience Mechanisms, treatment & biomarkers of epilepsy	Coordinator, EpiXchange IAPP
J. Helen Cross, MD, PhD **University College London/GOSH**	Clinical neurology/epileptologist (paediatrics) Patient treatment and epilepsy care	Coordinator, Epi-CARE, ILAE President-elect
Philippe Ryvlin, MD **U. Lausanne/CHUV**	Clinical neurology/epileptologist (adult)	ILAE Executive Europe, Lancet Commission
Martin J. Brodie, MD **U. Glasgow**	Clinical neurology/epileptologist	President of IBE, EAE member

The EPICLUSTER organised 4 activities of which the details can be found here below.

1. Consensus meeting, June 17th, 2020, online.
2. Funding workshop & EpiXchange II Meeting, December 1st and 2nd, 2020, online.
3. Accelerating Patient Involvement in European Epilepsy Research, October 6th, 2021, online.
4. Shaping the future of epilepsy research in Europe, September 29th, 2022, hybrid (Brussels and online)

Consensus meeting, June 17th, 2020, online.

On June 17th, 2020, the leadership of EPICLUSTER held the first meeting. The focus of the meeting was to bring together the leaderships, hear from them about the organisations (including the International League against Epilepsy - ILAE, International Bureau for Epilepsy - IBE, Epilepsy Alliance Europe - EAE and Lancet Comm) and projects (i.e., EpimRNA, DESIRE, EPI-STOP, EPI-TARGET, EPI-PGX, EpiXchange, EpiCARE) they represent, discuss the originally planned actions and priorities and assign people to responsibilities for delivery.

The second part was a multistakeholder meeting in which the EPICLUSTER leadership engaged with external stakeholders and co-created the priorities in the epilepsy field. Participants attending this 2nd part consisted of the coordinators of other European epilepsy projects (including Epi25, Solve-RD, EuroEPINOMICS, EpiEpiNet, ECMED), data and ethics (e.g., QUEST center), research infrastructures (e.g., HBP/EBRAINS), the patients and carers perspective and industry (e.g., UCB). Each participant was enthusiastic to partner with EPICLUSTER and contribute to success.

The research and coordinating objectives and priorities of EPICLUSTER and the invited stakeholders were discussed before and during the meeting.

The agenda can be found here below.

EPICLUSTER leadership

10.00 – 10.05: Welcome (DH)

10.05 - 10.15: Introduction to EBRA (KA)

10.15-10.25: Introduction to EPICLUSTER and (short) update from EPICLUSTER leadership on each project (everyone)

10.25-10.45: Q&A about EPICLUSTER (& EBRA) (everyone)

10.45-10.55: Break

10.55 – 11.10: Presentation of the proposed priorities and activities of EPICLUSTER as a network for epilepsy research in Europe. (DH)

11.10 – 11.50: Refining and discussion about the proposed priorities and consensus building (DH leads + everyone).

11.50-12.00: Conclusion and priority topics for discussion with the external stakeholders (DH).

EPICLUSTER leadership and stakeholders

13 - 13.05: Welcome (DH)

13.05 – 13.10: Introduction to EBRA (KA)

13.10 - 13.30: Introduction to EPICLUSTER and priorities (DH)

13.30 - 13.40: Short Q&A about EPICLUSTER (everyone)

13.40 – 14.00: Introduction of each stakeholder

14.00 - 15.45: Consensus building on how to work together (FD moderator; everyone)

15.45 - 16.00: Wrap-up and next steps (DH + KA).

The outcome of this meeting was written down in a consensus document which can be found here below.

Consensus document on EPICLUSTER's mission and agenda

OVERVIEW EPICLUSTER was established in 2019 under EBRA as **a coordinating action for European epilepsy research.** The leadership of EPICLUSTER comprises the coordinators of multiple large-scale epilepsy research projects along with the Epi-CARE clinical network and professional and patient-representative organisations. The objective is to work collectively to agree and action key research challenges at scale.

Mission

Establish a collaborative framework for the coordinated actions of epilepsy research in Europe

Strategic objectives

- Promoting collaborations at both European and global level and contributing to European Policy
- Enhance European Epilepsy Training
- Increasing translation of project generated knowledge and innovative approaches into new health interventions
- Supporting internationalisation of participating industry partners
- Improve access to and optimise the use of research infrastructures and data sources

- Explore possibilities for broader scale cooperation at global level

R&I priority topics

- Disease modifying and personalised medicines for epilepsy and their delivery systems
- Target led biomarker and diagnostics discovery and validation
- Innovative models for diagnostics and target development
- Digitalisation and personal monitoring for independent living in epilepsy
- Coordination of research infrastructures and the Epilepsy data ecosystem
- Funding initiatives and integration to society, industry, and regulatory space

Four activities are planned

- EPICLUSTER consensus meeting
- EPICLUSTER general conference
- Sustainability policy forum
- Synthesis forum

The first of which was a meeting focused on reaching broad consensus for the cooperation among the different groups and the identification of the main objectives and actions.

EPICLUSTER consensus meeting On June 17th, 2020, the leadership of EPICLUSTER held the first meeting. The focus of the meeting was to bring together the leadership, hear from them on the organisations they represent, discuss the originally planned actions and priorities and assign people to responsibilities for delivery. The second part of the meeting was attended by a number of stakeholders from outside the EPICLUSTER leadership, facilitated by EBRA, including coordinators of other European epilepsy projects, experts in big data, preclinical and clinical data sharing, the patient's perspective and industry. Each participant was enthusiastic to partner with EPICLUSTER and contribute to success.

Meeting attendees

In total, 23 participants joined the meeting. The following epilepsy stakeholder groups were represented during the meeting: Patients, caregivers and patient organizations, basic and clinical researchers, clinicians, industry, research infrastructures and data experts.

Toward consensus The research and coordinating objectives and priorities of EPICLUSTER and the invited stakeholders were discussed before and during the meeting. These include (1) facilitating infrastructure, data and biosample sharing, (2) increasing translation of basic to clinical science, (3) joint funding initiatives of scale and (4) supporting the longer-term vision of a multi-stakeholder epilepsy research community.

EPICLUSTER will also input to the content of the planned European Forum on Epilepsy to be held in 2021. The actions will be achieved through expanding the membership of EPICLUSTER to include affiliated members and activities will be coordinated through EPICLUSTER's different working groups. The working groups are:

(1) Synthesis

(2) Policy & sustainability

(3) Innovation & industry

(4) Data and research infrastructure

EPICLUSTER will represent the entire epilepsy research community. Within this, several stakeholder categories can be identified, each of which has common as well as individual priorities. As part of the preparation for EPICLUSTER, these are acknowledged below and are written by the leadership and based on Pitkanen et al *Advancing research toward faster diagnosis, better treatment, and end of stigma in epilepsy,* Epilepsia 2019:

Basic and translational science perspective Major advances have been delivered by the various large-scale projects in terms of understanding mechanisms of genetic and acquired epilepsies. This has generated new targets, compounds and

procedures for treatment and diagnosis and has increased the high-quality science in the field. Challenges for the future include accelerating the translation of novel therapies and biomarkers from the laboratory to the clinic, attracting and retaining talented researchers, increasing the pace of adoption of technologies such as iPSC, organoids and multi-omics and developing a comprehensive model of the epileptic brain.

Clinical perspective Delivery of epilepsy care is changing, requiring transition to care outside of the hospital facilitated by eHealth platforms and digital healthcare. Creation of virtual epilepsy centres to optimize and deliver care across the community was the vision for European Reference Network (ERN) for Rare and Complex Epilepsies EpiCARE (https://epi-care.eu), to enhance cross border care, but also has relevance on a national level. Beyond better control of seizures, research is required into the various co-morbidities and their management. Artificial intelligence and machine learning offer ways to obtain deeper insights into clinical data that may generate findings on epileptogenesis, drug resistance mechanisms, comorbidities, prognosis and outcome. Advanced technologies are also enabling breakthrough progress in the fields of seizure detection and forecasting and on-demand therapies, which can lessen the impact of unpredictable seizures. Emerging biotechnologies such as gene therapy herald opportunities for discoveries by basic science on genetics of epilepsies to move into a therapy development pipeline. Investigator led clinical trials are badly needed in many epilepsy fields, including antiepileptogenic treatment, surgical therapies (including gene therapy) and prevention of premature mortality and additional outcome measures (secondary endpoints) are needed to assess meaningful efficacy in addition to seizure control.

Infrastructures The different epilepsy projects have created unique biosample and data resources. These remain largely siloed, however, and are not yet community resources. There is now an opportunity to create a European Epilepsy Data Ecosystem to harmonize resources and establishing efficient mechanisms to share and exchange preclinical and clinical data between groups and projects and access expertise outside the epilepsy field. Further opportunities exist for data science analytics of multi-omics data to identify novel targets for therapy. Establishment of cooperating preclinical laboratories could provide a network for drug validation to de-risk new drug development pipelines. The recently established ERNs offer a unique opportunity of a high expertise network of hospitals, to perform academic trials with innovative therapies, and share data, which were acquired during routine clinical work for data analytic sciences. Now, EPI-CLUSTER should maximize opportunities to collaborate with infrastructures outside the field (e.g. Human Brain Project, ELIXIR, European Pediatric Translational Research Infrastructure, EpiCARE etc).

Patient perspective Persons with epilepsy are major stakeholders and, with patient organisations, have a key role to play in advocacy and awareness around their disease, the process of research selection, drug-discovery, the development of new devices, the assessment of new neurosurgical techniques, and the design of clinical trials. New developments in rare and ultra-rare epilepsies is demonstrating the need for truly collaborative relationship with patients as partners to researchers, clinicians and industry, which is critical for conceiving, developing and establishing transformational treatment options. Experience from rare diseases can serve as a model for the more common epilepsies. Patients perform a vital role at the intersection of medicine and new digital technologies. For example, via education and empowerment to collect and report real-world data through digital diaries and wearable devices, which can drastically change the way we do epilepsy research and care for persons with epilepsy.

Industry perspective Epilepsy has to be seen as a more attractive field for investment by industry and new technology companies. This can be achieved through strengthening biology and target validation, more clinical trials with clear differentiation and stratification of patient populations that will benefit for both rare and common epilepsies. Industry is recognizing the need to focus more on disease-modifying therapies that target specific mechanisms of disease and the underlying pathophysiology. There is a need for more validated therapeutic targets and truly innovative approaches, for more SME and biotechnology companies to enter the field. This is starting to happen for some of the rare epilepsies. Industry would benefit from access to preclinical trial capabilities and expertise distributed throughout the EPICLUSTER network.

Funding workshop & EpiXchange II Meeting, December 1st and 2nd, 2020, online.

On December 1st and 2nd 2020, EPICLUSTER's second activity took place. On the first day, the EPICLUSTER leadership and wider stakeholder group met for a workshop on funding. On the second day, EPICLUSTER organised and ran EpiXchange II, a community-building meeting based on the format of EpiXchange I (2018). The meeting brought together various FP7 and Horizon 2020 epilepsy projects with stakeholders to review progress and future directions in key research areas including genetics, biomarkers, therapeutics, co-morbidities, and biobanks/resources.

Dec 1st, 2020, EPI-CLUSTER Funding, governance and Patient Engagement Workshop

Time: 14:00 – 17:00 CET; By Microsoft Teams (virtual)

The main part of the workshop was on funding for epilepsy. To drive the discussion among leading epilepsy researchers on how we identify, plan, develop and secure large-scale funding in the future. The main target in this regard is Horizon Europe but other opportunities include through partnering with US-based agencies such as NINDS or philanthropy/patient representative groups. The second half of the meeting featured presentations from MULTI-ACT on a framework for our Cluster to improve our governance and ensure the inclusion of key stakeholders.

There were 25 attendees at the workshop. This included the complete EPICLUSTER leadership group, several of the affiliated members from other projects and patient representatives, members of EBRA and the invited speakers.

The agenda can be found here below:

EPICLUSTER: Funding, governance and patient engagement meeting

December 1st 2020, 2 - 5 pm Central European Time
Virtual meeting using Microsoft Teams

14:00 – 14:15	Welcome and introduction (DH)
	Epilepsy Research Funding
14:15 – 14:30	Current (FP7 and H2020) and future (HE-Health Programme) funding landscape for epilepsy in Europe *Tim Ramaekers, DG Research and Innovation, European Commission*
14:30-14:45	NIH/NINDS funding landscape for epilepsy: now and the future *Vicky Whittemore, Programme Director for Neuroscience (epilepsy), NINDS*
14:45-15:30	Promoting and funding patient-focused research: private organisations and philanthropic perspective *Laura Lubbers, Cure Epilepsy Foundation, USA* *Simona Borroni, President, Gruppo Famiglie Dravet, European Dravet Federation* *Francesca Sofia, Chief Scientific Officer, Italian Epilepsy Foundation*
15 :30 – 16 :00	Multistakeholder discussion [ALL]
16:00 – 16:15	Break
	EPICLUSTER's governance and patient engagement strategy
16:15 – 16:25	Introduction to the MULTI-ACT framework [Paola Zaratin]
16:25 – 16:35	EPICLUSTER's baseline analysis + summary of recommendations [Deborah Bertorello +Andrea Gavazzi]
16:35 – 16:55	Multi-stakeholder discussion + actions [ALL]
16:55 - 17:00	Wrap up and next steps [DH]

The outcome of this meeting was written down in a meeting report which can be found here below.

Meeting report

The first presentation focused on previous and future (HE-Health Programme) funding landscape for epilepsy in Europe and was presented by Tim Raemaekers *(DG Research and Innovation, European Commission)*. The presentation covered recent spending on epilepsy and other brain diseases and examples of recent, successful projects funded by the EC with relevance

to epilepsy. Also, likely funding instruments in the coming programme which include NEURON, JPND and HBP. A "Brain Health Partnership" funding instrument could be possible (2025?).

Next, Vicky Whittemore from the NINDS/NIH gave an overview of the organisation of NINDS and funding instruments – *NIH/NINDS funding landscape for epilepsy: now and the future*. There has been steady investment in epilepsy-related projects which is about €200 Mio (per capita, far greater than in EU). A number of large-scale "centres without walls" collaborative programmes have been funded on epilepsy ($94Mio in past 10 years). The Epilepsy benchmarks were also presented which may drive the direction of future requests for proposals.

The next presentation – *CURE epilepsy funding and patient-focused programming* - was from Laura Lubbers, the CEO of the private charity CURE Epilepsy. They have raised over $70Mio and offer regular funding calls for junior and more established investigators over 1 – 3 year time frames. Focus is on transformative ideas for prevention and disease modification. They are open to any countries.

Simona Borroni spoke next – *Promoting and funding patient-focused research* - President of Gruppo Famiglie Dravet, European Dravet Federation on the challenges and achievements of a smaller, patient-specific charity and how they have raised funding. They typically raise ~€150,000 from donations per year. The contribution of families was strongly emphasised and their expectations for the outcomes and value of research supported by such organisations. In particular, the need for more transparency with project progress and outcomes from scientists. Addressing these gaps is important to achieve impact for patients and ensure support for research continues.

Finally, Francesca Sofia spoke on *Championing the cause of epilepsy through education and engagement of people with epilepsy in research* about the importance of engaging people with epilepsy to ensure sustainable funding and urgency. Also, how patients ("e-patients") are more empowered now in promoting what matters most to patients. There is a sense that other neurological diseases (e.g. Multiple sclerosis) are further ahead than the epilepsy field in incorporating "champions" into research programmes and stigma and lack of public awareness remain major issues in epilepsy. One initiative is the IBE Academy for patients to upskill them to be active and empowered.

Summary of discussion and priorities

Tim Raemaekers/EU Horizon 2020 brought challenges as we (epilepsy) had to compete directly with other fields since there were no disease-specific topics. This will not change under Horizon Europe. Indeed, draft text for the early Health calls indicates that only "mental health" is specifically called out. We must think creatively about how to organize so we can compete. TR was challenged on the extent to which co-design was meaningful in the design of the programme. TR assured that this was extensive and open. Some further clarification around the possible Brain Health Partnership was raised and whether this would replace or be instead of a "Mission". Ultimately, it depends on member states wanting this. Increasingly, patient involvement in design of studies will be important in Horizon Europe. Discussion also focused on approaches to lobbying. A subsequent comment on statistics around funding was made around Tim Raemaekers presentation. Specifically, that the figure for epilepsy (~€200 Mio) is misleading because this is based on any project that had relevance to epilepsy and not projects specifically focused on epilepsy. In fact, we think the amount of funding that went from Horizon 2020 to epilepsy is actually disproportionately low relative to disease-burden/DALYS. Other discussion covered the issue of the need to better embed patient values in the design of research.

The second part of the Workshop focused on EPICLUSTER's governance and patient engagement and maximising the impact of research for patients. The first presentation was by Paola Zaratin. The presentation provided an overview of mULTI-ACT and emphasised that multi-stakeholder involvement is key to sustainable healthcare research and alignment of R&I with societal benefits – Responsible Research & Innovation (RRI). This will be a key requirement for the next Horizon Europe programme for success. Andrea Gavazzi then followed with a baseline analysis of EPICLUSTER. Several strengths were identified but also gaps. Deficits in key areas included participatory governance and patient/stakeholder engagement. Recommendations were provided for how to address these deficits. Finally, Deborah Bertorello covered what it means to capture the patient's voice to meet RRI goals. The tools available to EPICLUSTER include a digital toolbox containing patient engagement plans, activities and measures of success.

Summary of discussion and priorities

The MULTI-ACT presenters were asked about how epilepsy community compares to other major brain diseases in terms of degree to which research is co-designed with stakeholders/patient groups. At least for MS, this is very embedded, with codesign from the beginning and with industry, although acknowledged this is still early. The ideal research "ecosystem" is a challenge for most, however. EPICLUSTER has linked with patient representatives/experts but this can be improved. The EpiCare network was mentioned as a great example of an epilepsy network with very active participation of patient experts (15 patient engagement groups). Many of these patients are motivated to be more engaged with research. FS raised the

point that the shift toward patient engagement in research brings, however, challenges in that demands from researchers to include patients in projects is outpacing the available experts and the community is too stretched. There is a need to educate more e-patients. This will be time-consuming. MULTI-ACT seeks to mitigate this aspect by making sure patient expertise is used when needed. Another point raised is that EPICLUSTER could bring forward a "white paper" that might delineate the issues around patient and stakeholder involvement in research. Last, the ILAE/IBE have managed to get the WHO to pass a resolution on epilepsy and neurological disorders. This now needs to be translated into action, including the importance of research. This puts responsibility of member states to support research on epilepsy.

Dec 2nd, 2020, EPICLUSTER General Conference

The meeting brought together various FP7 and Horizon 2020 epilepsy projects with stakeholders to review progress and future directions in key research areas including genetics, biomarkers, therapeutics, co-morbidities and biobanks/resources.

There were 91 attendees at the workshop. This included the complete EPICLUSTER leadership group, several of the affiliated members from other projects and patient representatives, members of EBRA and the invited speakers.

Here below, the agenda can be found.

Scientific session	
9:00 - 9:25	**Welcome addresses** **David Henshall** (Coordinator of EPICLUSTER, RCSI/FutureNeuro Research Centre, Ireland) **Monica Di Luca** (President, European Brain Council) **Karim Berkouk** (Health Directorate, DG Research & Innovation, European Commission)
9:30	**Thematic session I: Therapeutics** *All talks are 10 minutes* *Chairs: F. Rosenow (Goethe-University Frankfurt), M. Kokaia (Lunds Universitet)* *Short overview of the current status of research, impact and gaps to be filled – Session chairs (5 mins)* ***DESIRE*** – **Fabio Benfenati (IIT, Italy)** *"New genetic strategies for epileptic encephalopathies: transcriptional activation and closed-loop molecular actuators"* ***EpimiRNA*** – **R Jeroen Pasterkamp (UMCU, Netherlands)** *"New microRNA and novel noncoding RNAs as targets in Temporal Lobe Epilepsy"* ***EPISTOP*** – **Katarzyna Kotulska (CMHI, Warsaw)** *"Preventive strategy in TSC-related epilepsy in clinical practice - lessons from the EPISTOP study"* ***EpiTarget*** – **Annamaria Vezzani (Mario Negri, Italy)** *"Drug combinations to address the complexity of epileptogenesis"* ***EpiCARE*** – **Viktoria Defelippe Diaz de Espada (Utrecht, NL)** *"Precision treatment in monogenic epilepsy syndromes and n=1 trials"* ***EpiPGX*** – **Terrence O'Brien (Monash U, Australia)** *"Valproic acid teratogenicity and genetics"* ***Q&A – 15 mins***
10:55	***Coffee Break***

11:10	**Thematic session II: Biobanks and databases** *All talks are 10 minutes* *Chairs: S. Sisodiya (UCL, UK), K. Kobow (Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany)* *Short overview of the current status of research, impact and gaps to be filled – Session chairs* ***DESIRE*** – ***Isabella Brambilla*** **(European Dravet Syndrome Foundation)** *"The Dravet syndrome European Registry"* ***EpimiRNA*** – **Morten Veno (Omiics, Denmark)** *"Every microRNA and their targets in human Temporal Lobe Epilepsy: the EpimiRNA iCLIP database and more"* ***EpiPGX*** – **Roland Krause (U Luxembourg)** *"Infrastructures from EpiPGX: now and the future"* ***EPISTOP*** – **Eleonora Aronica (U Amsterdam, Netherlands)** *"Biobanking in Tuberous Sclerosis Complex: challenges and opportunities for understanding epilepsy and cognitive and behavioral comorbidities"* ***EpiTarget*** – **Albert Becker (U Bonn, Germany)** *"Integrated human epilepsy biopsy bank – key precondition for biomarker characterization"* ***EpiCARE*** – **Davide Mei/Renzo Guerrini (U Florence, Italy)** *"Genetic discovery platform* https://epicare.discoverynexus.org/" ***Q&A – 15 mins***
12:30	***Introduction of new projects to EPICLUSTER*** **EBRA** and the European brain research agenda - Frédéric Destrebecq **EpiCC** (Epilepsy and Climate Change) Sanjay Sisodiya (UCL) **Human Brain Project** and epilepsy: The Virtual Brain - Viktor Jirsa (Marseille) and MIP and HIP platforms - Philippe Ryvlin (Lausanne) **LifeTime initiative** – Bart de Strooper (**VIB-KU Leuven Center for Brain & Disease Research)**
13:00	***Lunch***
13:45	**Thematic session III: Biomarkers** *All talks are 10 minutes* *Chairs: A. Pitkänen (U Eastern Finland), M. Simonato (Università degli Studi di Ferrara)* *Short overview of current status of research, impact and gaps to be filled – Session chairs (5 mins)* ***DESIRE*** – **Carmen Barba (U Florence, Italy)** *"Intracranial electrophysiological biomarkers of the epileptogenic zone"* ***EpimiRNA*** **– Sebastian Bauer (Goethe U Frankfurt, Germany)** *"RNA and EEG biomarkers of seizures and epilepsy"* ***EpiPGX*** – **Sanjay Sisodiya/Gianpiero Cavalleri** *"Evidence for genetic contribution to multidrug resistance"* ***EPISTOP*** **– Lieven Lagae (U Leuven, Belgium)** *"Prediction of neurodevelopment in infants with tuberous sclerosis complex using early EEG characteristics"* ***EpiTarget*** **– Asla Pitkanen (U Eastern Finland, Finland)** *"Biomarkers of epileptogenesis"*

	Q&A – 15 mins
15:00	**Thematic session IV: Genetics** *All talks are 10 minutes* *Chairs: D. J. Kwiatkowski (Harvard University), R. Guerrini (Università degli Studi di Firenze)* *Short overview of current status of research, impact and gaps to be filled – Session chairs (5 mins)* ***DESIRE*** – **Renzo Guerrini/Kristin Anderson (U Florence, Italy)** *"Building knowledge on rare diseases through international research teams -family network collaborations: the ATP6V1A model"* ***EpimiRNA*** – **Iscia Cendes-Lopes/Amanda M. Canto (U Campinas, Brazil)** *"MicroRNA genetics and comparative analysis of transcriptomic and proteomics data in different animal models of MTLE"* ***EPISTOP*** – **Franz Huschner (Proteome Factory AG, Germany)** *"Potential genetic biomarkers of epilepsy development in EPISTOP"* ***EpiTarget*** – **Michael Johnson (Imperial College London, UK)** *"Old data, new tricks"* ***Q&A – 15 mins***
16:00	***Coffee break***
16:30	**Thematic session V: Co-morbidities** *All talks are 10 minutes* *Chairs: A. Arzimanoglou (Chair, EpiCARE), S. Jóźwiak (Uniwersytet Warszawski)* *Short overview of the current status of research, impact and gaps to be filled – Session chairs (5 mins)* ***DESIRE*** – **Massimo Mantegazza (CNRS/Inserm, France)** *"Epilepsy and behavioral co-morbidities in SCN1A and SCN2A channelopathies"* ***EPISTOP*** – **Floor Jansen (UMC Utrecht, Netherlands)** *"Early brain MRI findings predict neurodevelopment in children with Tuberous Sclerosis Complex: results from the EPISTOP project"* ***EpiTarget*** – **Heinz Beck (U Bonn, Germany)** "Behavioral impairment, cellular physiology, imaging." ***Q&A – 15 mins***
17:30	***Closing remarks*** and final discussion (Co-chaired by project coordinators)
17:45	**End of conference**

The meeting outcomes have been published as a meeting report:

Henshall DC, Guerrini R, Jozwiak S, Kokaia M, Pitkanen A, Sisodiya S, Simonato M, Cross JH, Ryvlin P, Brodie MJ, Trinka E, Sofia F. Meeting report: EpiXchange II brings together European epilepsy research projects to discuss latest advances. Epilepsy Res. 2021 Dec;178:106811. doi: 10.1016/j.eplepsyres.2021.106811.

Epilepsy Research 178 (2021) 106811

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Meeting report: EpiXchange II brings together European epilepsy research projects to discuss latest advances*

Dear Editor,

Cooperation and coordination are fundamental to modern scientific endeavour and an important mechanism for accelerating epilepsy research. Recent examples include the genetics and brain imaging consortia such as Epi25 and ENIGMA, where pooling cases and analysis expertise has resulted in major advances in the discovery of epilepsy genes and the effects of seizures on the brain. Three years ago, in Brussels, an event called EpiXchange was held to support cooperation and coordination among European epilepsy research by bringing together several large-scale epilepsy research projects along with key stakeholders (epixchange.eu). The projects were called Desire, EpimiRNA, EpiSTOP and EpiTarget. They had been funded by the EU under the FP7 work programme to deliver important advances in understanding the causes, diagnosis and treatment of epilepsy (under call HEALTH.2013.2.2.1-4: Pathophysiology and therapy of epilepsy and epileptiform disorders). Each were multi-disciplinary in nature, bringing together scientists and clinicians as well as other technical experts from outside the epilepsy world, blending basic and translational research, animal models and clinical studies and trials. Projects also featured significant participation from small and medium enterprises (SMEs) and larger industry partners. The primary objective of EpiXchange was to share the results of these different projects but an important secondary objective was to foster inter-project collaboration, define the key scientific challenges of the future, and ensure that the momentum and infrastructures were not lost. Joining the FP7 projects were other European epilepsy research projects, including EpiPGX and Epixchange, and EpiCARE, the European reference network (ERN) for rare and complex epilepsies.

EpiXchange I showcased the outstanding achievements from these projects and led to a position paper from the leadership of the event (Pitkanen et al., 2019) Important breakthroughs and advances continue to emerge from the projects including new genes identified, the mechanisms by which mutations cause disease, disease-modifying treatments proven in preclinical models and advances in biomarkers.

That could have been the end of the road but then a call was announced by the H2020 project European Brain Research Area (EBRA), coordinated by the European Brain Council (EBC), to form research "clusters" as a mechanism to support the cooperation and coordination of European brain research. Inspired by EpiXchange, EBRA funded EPICLUSTER (which stands for European cluster of epilepsy networks; https://www.ebra.eu/epi-cluster-2/) in late 2019. The leadership came from the organisers of EpiXchange and expanded to include representatives from ILAE Europe and IBE. The goal was to ensure that by working together we would sustain the momentum and continue to inform the European epilepsy research agenda and promote further investment in brain research broadly and epilepsy in particular. As part of a series of planned activities, EpiXchange II was held – slightly delayed by COVID - on December 2nd 2020. The meeting had more than 100 attendees with talks and discussions, organised into a series of thematic sessions, each chaired by a clinician and a basic scientist from the different projects. The presenters covered the core research topics that were originally addressed by the different EU projects (and remain highly topical) - Biomarkers, Genetics, Therapeutics, Co-morbidities and Databases and Biobanks. The conference showcased the wide-ranging progress made by the different consortia and included not only new discoveries about epilepsy but also developing and refining technologies, establishing and expanding bio-resources such as tissue banks, creating new databases that can transform the power of pathway discovery, and (significantly for future success) the development of new partnerships. Speakers from industry were among the presenters, drawing attention to projects helped and supported by small and medium enterprises in Europe, increasingly vital for accelerating translation of research to patients and the broader European economy.

EpiXChange II was important because it reinforced the existing collaborations and created new ones that should lay the foundations for success in delivering transformative research findings to people with epilepsy. EPICLUSTER has two further planned activities. The third, recently held in October 2021, was a workshop focused on public and patient involvement in research, "Accelerating patient involvement in European epilepsy research" (https://www.ebra.eu/news-and-events/patient-involvement-epilepsy/). Planning of the final event, to be held in 2022, is underway.

From the EPICLUSTER Leadership Group:

David C. Henshall, PhD (Coordinator of EPICLUSTER and EpimiRNA project).
Renzo Guerrini, MD (Coordinator of Desire project).
Sergiusz Jozwiak, MD (Coordinator of EpiSTOP project).
Merab Kokaia, PhD (Coordinator of EpiTarget project).
Asla Pitkanen, MD, PhD (Member).
Sanjay Sisodiya, MD, PhD (Coordinator of EpiPGX).
Michele Simonato, MD, PhD (Coordinator of Epixchange).
J. Helen Cross, MD, PhD (ERN EpiCARE).
Philippe Ryvlin, MD (EAE and ILAE Europe).
Martin Brodie, MD (International Bureau for Epilepsy (IBE), European Alliance on Epilepsy (EAE)).
Eugen Trinka, MD (ILAE Strategic Advisor).
Francesca Sofia, PhD (President, IBE).

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https://doi.org/10.1016/j.eplepsyres.2021.106811
Received 27 October 2021; Accepted 7 November 2021
Available online 14 November 2021

Accelerating Patient Involvement in European Epilepsy Research, October 6th, 2021, online.

With the overarching goal of showcasing ways and best practices for bringing people with epilepsy and researchers to work together on common ground, this EPICLUSTER event aimed to unveil the opportunities arising from patient involvement in epilepsy research. The workshop began with an overview of definitions, trends, and key themes around PPI and how they could successfully advance epilepsy research. Hints and case histories lead participants to learn the "why", "how", and "what" of patient involvement in research.

The programme highlights were:

- Understanding the potential of PPI in epilepsy research
- Learning how epilepsy researchers can work with people with epilepsy and their representatives
- Envisioning the way forward: how to incorporate patient involvement into epilepsy research so to fundamentally change the way policymakers, funders, and regulators view epilepsy

This event was designed to encourage researchers to learn about PPI and how to begin to integrate it into their research programs. It was relevant to students, postdocs, and faculty. People with lived experience of Epilepsy interested in getting involved with research teams were also welcomed to attend. In total, 130 participants signed up for the event.

The agenda can be found here below.

9:30 – 9:35	**Welcome and overview of the workshop**
	Prof. David Henshall, EPICLUSTER coordinator
	Dr. Francesca Sofia, President elect International Bureau for Epilepsy
Session 1	**Patient involvement and health research in Europe**
9:35 - 9:50	**Current best practice on patient involvement**
	Jim Elliott, NHS, Health Research Authority
9:50 - 10:05	**Patient involvement in research: Co-production and why it is essential now.**
	Joke Jaarsma, president, European Federation for Neurological Associations
	Erik Vandereycken, Gamian-Europe Project Manager
10:05 - 10:20	**Patient and Public Involvement in EU-funded research: the experience of a scientific project coordinator and reviewer of EU grant proposals.**
	Tsveta Schyns-Liharska, Independent consultant scientific projects
10:20 - 10:35	**Q&A**
Session 2	**Patient involvement: A beginner's guide**
Chair/Moderator:	*Donna Walsh, Executive Director, European Federation for Neurological Associations*
10:35 - 11:15	**Getting patient involvement started – practical advice.**
	- Testimonial Basic Scientist
	Dr. Heather Mortiboys

- A moderated panel discussion with Patient Engagement through Training (EUPATI) and other patient organisations

Maria Dutarte, Executive Director, European Patients' Academy (EUPATI)

Richard M Ballerand, EUPATI training fellow

Nicholas Brooke, executive director, Patient Focused Medicine Development (PFMD) and founder of The Synergist.

Valentina Strammiello, Head of Programmes, European Patients Forum (EPF)

11:15 - 11:30 **Q&A**

Session 3 **Patient involvement in epilepsy research**

Chair/Moderator: *Francesca Sofia*

11:45 – 11:55 **What are the benefits of patient involvement for people with epilepsy and what are the benefits for researchers?**

Francesca Sofia

11:55 – 12:30 **Patient involvement in epilepsy now – perspective from projects with active patient involvement**

Bojana Mirosavljevic, EUPATI training fellow

Alexandra Moutet, UCB Pharma

Simon R.W. Lees, Patient Advisory Board, RADAR-CNS

Isabella Brambilla, Coordinator EPAG Patient Group ERN EpiCARE

12:30 – 12:45 **Q&A**

12:45 - 13:00 **Closing remarks and wrap-up**

The outcomes of this meeting were written down in a meeting report (see below).

Background and context for event: Over the last decade Patient Involvement has become a central feature of healthcare, with growing evidence of its positive impact on clinical research, and increasing adoption by health authorities, regulators and industry. Patient involvement in basic and preclinical research remains limited, including in the epilepsy field. To unveil these opportunities and to set the stage for multi-stakeholder collaboration, in October 2021, EPICLUSTER organized the first workshop in Europe on patient involvement in epilepsy research. The workshop began with an overview of definitions, principles, and trends in the field. This was followed by a practical session on how to start PI addressed to researchers new to the field. Then, the event went on with a roundtable highlighting opportunities and a number of PPI-enabling initiatives. Finally, the last session presented several case histories to assess the readiness of the epilepsy field with regard to research partnerships between patients and the scientific community.

Patient involvement and health research in Europe

Current best practice on patient involvement

The workshop was opened by **Jim Elliot** (NHS, Health Research Authority) who provided an overview on the definitions and current best practices on patient involvement. To offer some insights into the underlying principles of PPI that might apply to preclinical research, Elliot shared guidelines developed in the United Kingdom to help PPI practices in clinical research. This included involving the right people, to involve enough people, to involve them enough and finally to describe how the involvement has helped the research.

Patient involvement in research: Co-production and why it is essential now.

The second speaker, **Erik Van der Eycken** shared the experience of Global Alliance of Mental Illness Advocacy Networks-Europe (GAMIAN-Europe), an umbrella organization of National Patient Organizations in Mental Health. He focused on the opportunities arising from patient involvement throughout the project and how GAMIAN-Europe has lead a broad range of activities aimed at collecting and integrating the patient perspectives in research. To follow, **Joke Jaarsma, President of the European Federation of Neurological Associations (EFNA),** emphasized the numerous challenges that prevent the realization of meaningful patient engagement, and provided a cross-section of the landscape facing patients with neurological diseases. The session ended with **Tsveta Schyns-Liharska** who shared her journey as a parent and driver of engaged patient communities for a rare genetic disease.

Session 2: Patient involvement: A beginner's guide

Getting patient involvement started – practical advice.

Dr. Heather Mortiboys (Sheffield Institute for Translational Neuroscience) shared practical information and insights into how to implement patient involvement for basic researchers. Working in the field of Parkinson's disease, she explained how she trains early career basic researchers on the value of PPI. This includes how to start, relationship and building the knowledge base and maintaining engagement.

Moderated panel discussion

Experts from various PPI-related organizations and initiatives (Maria Dutarte, Executive Director, European Patients' Academy - EUPATI; Richard M Ballerand, EUPATI training fellow; Nicholas Brooke, executive director, Patient Focused Medicine Development – PFMD - and founder of The Synergist; Valentina Strammiello, Head of Programmes, European Patients Forum - EPF) shared their perspectives in a panel discussion moderated by Donna Walsh, executive director EFNA. This included key learnings on:

1. How patient involvement in research is gaining momentum and is expected to increasingly transform the biomedical research landscape.

2. Lack of readiness and need for researchers' training

3. Treating patients as equal partners and reward their time investment and contribution.

4. How to identify the right people

5. How to incentivize researchers to embrace patient involvement

Session 3: Patient involvement in epilepsy research

The workshop ended with a spotlight on some case histories of patient involvement in epilepsy research. Four testimonies provided practical insights into what people with epilepsy and their organizations can contribute to research, and the reasons why patient involvement can be a game-changer for the epilepsy research. These were by **Isabella Brambilla**, mother of a boy with Dravet syndrome and active epilepsy advocate. She shared her experience of organizing multi-stakeholder meetings, raising funds and supporting research projects, and participating in the creation of a patient registry. EUPATI fellow **Bojana Mirosavljevic,** the founder of a patient organization for families with children affected by rare diseases in Serbia, further emphasized that people with epilepsy and their carers have not only their lived experience with the disease to contribute but are also increasingly equipping themselves with knowledge and skills to better understand and participate in research projects. **Simon R.W. Lees** brought the audience into the realm of digital health technologies and shared his experience as a patient advisor for the RADAR-CNS project (Remote Assessment of Disease And Relapse - Central Nervous System). Finally, the Patient Value Strategy at UCB was presented by **Alexandra Moutet** (Global Head of Patient Engagement at UCB). The initiative's goal is to build a cycle in the R&D process where everything starts from the patients and, ultimately, returns to the patient.

Shaping the future of epilepsy research in Europe, September 29th, 2022, hybrid

On September 29th, 2022, the final EPICLUSTER activity took place in Brussels and online. This meeting focused on the sustainability and the future of the EPICLUSTER and the European epilepsy researchers. What do they need/want next? The introduction and 4 sessions included presentations and discussions on (1) European perspective on priorities in basic, translational, and clinical epilepsy research, (2) patient priorities and patient involvement in epilepsy research, (3) industry priorities and cooperation, (4) Sustainability of projects, networks and infrastructures.

In total, 138 meeting participants signed up to join the meeting.

The agenda can be found here below.

8:50 – 9:00	**Welcome**
	David Henshall, RCSI/FutureNeuro, IE
9:00 – 9:15	**Opening address**
	Paul Boon, European Academy of Neurology/Ghent University, BE
9:15 – 9:45	**WHO Intersectoral Global Action Plan on Epilepsy and Other Neurological Disorders**
	Tarun Dua, Brain Health, Mental Health and Substance Use Department, World Health Organization, CH
Session 1	**Scientific objectives and priorities**
9:45 – 9:55	EPICARE, *Alexis Arzimanoglou, University Hospitals of Lyon, FR*
9:55 – 10:05	EPITARGET, M*erab Kokaia, Lund University, SE*
10:05 – 10:15	EPIXCHANGE, *Michele Simonato, University of Ferrara/ San Raffaele Hospital, IT*
10:15 – 10:25	EPImiRNA, *David Henshall, RCSI/FutureNeuro, IE*
10:25 – 10:35	DESIRE, *Renzo Guerrini, University of Florence, IT*
10:35 – 10:45	EPISTOP, *Sergiusz Jozwiak, University of Warsaw, PL*
10:45 – 10:55	EPIPGX, *Sanjay Sisodiya, University College London, UK*
10:55 – 11:05	EuroEPINOMICS, *Holger Lerche, University Hospital Tuebingen, DE*
11:05 – 11:15	EpiBioS4R, *Asla Pitkänen, University of Eastern Finland/Kuopio, FI*
11:15 – 11:45	**Coffee break**
Session 2	**Patient priorities: Shaping the research agenda**
11:45 – 11:50	Welcome: Why is PPI so important?
	Joke Jaarsma, European Federation of Neurological Associations (EFNA)
11:50 – 12:20	Shape Network: Building a PPI Community for Research into Epilepsy
	Caoimhe Bennett, Epilepsy Research UK
12:20 – 12:30	Starting PPI in Research: A case study
	Lorna Kerin, RCSI University, IE
12:30 – 13:30	**Lunch**
13:30 – 14:20	Participatory session on planning PPI in your research/work setting
	Caoimhe Bennett, Epilepsy Research UK
	Claire Nolan, International Bureau for Epilepsy
	Lorna Kerin, RCSI University, IE

	Sebastian Winter, International Bureau for Epilepsy
14:20 – 14:30	Future plans of the International Bureau for Epilepsy
	Sebastian Winter, International Bureau for Epilepsy
Session 3	**Industry trends, working with academia and priorities**
14:30 – 14:50	*Stefanie Dedeurwaerdere, UCB Pharma*
14:50 - 15:05	Experiences as an academic with a gene therapy start-up
	Merab Kokaia, Lund University, SE
Session 4	**Sustainability of projects, networks and infrastructures**
15:05 – 15:15:	EBRAINS, a sustained European Research Infrastructure with direct impact on epilepsy research
	Philippe Ryvlin, University of Lausanne/CHUV, CH
15:15 – 15:55	Roundtable with EPICLUSTER leadership
	Moderator: Frédéric Destrebecq, European Brain Council, BE
15:55 – 16:00	**Final comments and Close**
	David Henshall, RCSI/FutureNeuro, IE
16:00 – 17:30:	**Networking coffee**

The meeting outcomes will be published as a meeting report:

Henshall et all. (under preparation): Shaping the future of European epilepsy research: final meeting report from EPICLUSTER.

Abstract Collaboration is essential to the conduct of basic, applied and clinical research and translation into the technologies and treatments urgently needed to improve the lives of people living with brain diseases and the health professionals who care for them. EPICLUSTER was formed in 2019 by the European Brain Research Area (EBRA) to support the coordination of epilepsy research in Europe. A key objective was to provide a platform to discuss shared research priorities by bringing together scientists and clinicians with multiple stakeholders including patient organisations and industry and the networks and infrastructures that provide healthcare and support research. Additional objectives were to facilitate access and sharing of data and biosamples, working together to ensure epilepsy is a priority for research funding, and embedding a culture of public and patient involvement (PPI) among epilepsy researchers. In this meeting report, we summarise the shared research priorities discussed by the leadership of EPICLUSTER at the recent final meeting. We also briefly review the discussion on patient and industry priorities, guidance on starting PPI for epilepsy researchers, and the sustainability of funding and infrastructures needed to ensure a comprehensive stakeholder-embedded community for epilepsy research.

Keywords: Research agenda; Brain; Diagnosis; Epilepsy; Horizon Europe; Public Patient Involvement; Stakeholders; Therapeutics

2. Prevention of Severe Mental Disorders (PSMD) cluster

Overarching aims of the PSMD cluster include fostering collaboration and gathering of experts on a determinate topic, organising and promoting several Network meetings, providing administrative support, facilitating dialogue with the stakeholders, supporting grant applications and dissemination of the results of funded projects. The PSMD cluster responds to the European funding initiatives in the field of severe mental disorders. For example, it aligns with the European Commission's ROAMER (A Roadmap for Mental Health Research in Europe). The PSMD cluster is highly multidisciplinary and

includes basic researchers, psychiatrists, psychologists, and neuroscientists. Further multidisciplinary collaborations have been established with industrial agencies and charities.

The PSMD cluster articulates in two main sections: The area of prevention of severe mental disorders in general (with a specific focus on psychosis and depression), and the specific field of BD. Each section is composed of core institutions with an outstanding track record in the field of prevention of severe mental disorders, mental health promotion and research on BD in Europe. The members of the PSMD cluster are prominent researchers with specialists in genetics, neuroimaging, pharmacogenomics, neuropsychopharmacology, longitudinal clinical research, clinical prediction modelling, multisite and international research , experimental therapeutics, whose collaborative efforts have already provided the scientific community with advancements in the development of prevention models in severe mental disorders as well as in knowledge of the neurobiological underpinnings of psychosis, depression and BD. These experts are part of the ECNP funded Thematic Working Group on the Prevention of Mental Disorders and Mental Health Promotion (ECNP-PMD-MHP) as well as of the ECNP Bipolar Disorders Network (ECNP-BDN).

The European sites included in the PSMD are centres of excellence in the prevention of severe mental disorders, promotion of good mental health, with specific expertise in psychosis, depression and bipolar disorders research, and are part of this network with the following shared goals:

- Facilitate multidisciplinary collaboration, knowledge, and data sharing, building on existing ECNP Networks and Thematic Working Groups to support innovative translational research, from basic to clinical and public health research, for the benefit of patients, focusing on the transdiagnostic disease-modifying prevention of severe mental disorders and improved care for established bipolar disorders.
- Standardise core assessment, outcome measures and interventional research strategies for the promotion of good mental health in Europe.
- Create a common computerized research database enabling multinational data management on severe mental disorders.
- Use the available expertise to design and conduct research protocols on severe mental disorders.
- Promote clinical research partnerships across disciplines and sectors, including public-private partnerships, with pharmaceutical industries, charities and the public on severe mental disorders.
- Produce consensus papers and dissemination of clinical and basic research on severe mental disorders.
- Apply for European grant funding and produce research reports to disseminate the findings of the PSMD cluster in international journals.
- Disseminate a preventive culture in clinical psychiatry.
- Translate research into improved healthcare for severe mental disorders.

The members of the PSMD cluster are prominent researchers with specialist skills in genetics, neuroimaging, pharmacogenomics, neuropsychopharmacology, longitudinal clinical research, clinical prediction modelling, multisite and international research, experimental therapeutics, whose collaborative efforts have already provided the scientific community with advancements in the

development of prevention models for severe mental disorders as well as in knowledge of the neurobiological underpinnings of established bipolar disorders. These experts are part of the ECNP funded Prevention of Mental Disorders and Mental Health Promotion Network (ECNP-PMD-MHP, lead Paolo Fusar-Poli) as well as of the ECNP Bipolar Disorders Network (ECNP-BDN, lead Ole A. Andreassen).

Norway: Ole A. Andreassen (Co-Chair), University of Oslo (ECNP-BDN); Gunnar Morken, Norwegian University of Science and Technology, Trondheim (ECNP-BDN); Trine V. Lagerberg, University of Oslo (ECNP-BDN);

Italy: Andrea Fagiolini, University of Siena (ECNP-BDN); Mirko Manchia, University of Cagliari (ECNP-BDN); Silvana Galderisi, University of Naples Luigi Vanvitelli (ECNP-PMD-MHP); Paolo Fusar-Poli (Co-Chair) Brain and Behavioral Sciences Department, University of Pavia (ECNP-PMD-MHP);

Germany: Michael Bauer, Technische Universität Dresden (ECNP-BDN and ECNP-PMD-MHP); Emanuel Severus, Technische Universität Dresden (ECNP-BDN); Phillip Ritter, Technische Universität Dresden (ECNP-BDN); Thomas G. Schulze, LMU University (ECNP-BDN); Andreas Reif, University of Frankfurt (ECNP-BDN); Marcella Rietschel, Heidelberg University, Mannheim (ECNP-BDN); Andreas Bechdolf, Charité University, Berlin (ECNP-BDN and ECNP-PMD-MHP); Christopher U. Correll, Charité University, Berlin (ECNP-BDN); Andreas Meyer-Lindenberg, University of Mannheim (ECNP-PMD-MHP); Nikolaos Koutsouleris, LMU Munich (ECNP-PMD-MHP); Katharina Domschke, University of Freiburg (ECNP-PMD-MHP); Andreas Pfennig, Technische Universität Dresden (ECNP-PMD-MHP);

France: Chantal Henry, Hospital Albert Chenevier, Creteil (ECNP-BDN); Frank Bellivier, INSERM, Paris (ECNP-BDN); Marie Odile Krebs, INSERM, Laboratoire de Physiopathologie des Maladies Psychiatriques, Université Paris Descartes, Paris (ECNP-PMD-MHP); Mark Millan, Servier Research Institute (ECNP-PMD-MHP);

The Netherlands: Ralph Kupka, VU University Medical Center Amsterdam (ECNP-BDN); Veerle Bergink, Erasmus Medical Center, Rotterdam (ECNP-BDN); D.H. Nieman, Department of Psychiatry, Academic Medical Center, University of Amsterdam (ECNP-PMD-MHP); Therese van Amelsvoort, Department of Psychiatry and Psychology, Maastricht University (ECNP-PMD-MHP);

Switzerland: Stefan Borgwardt, Basel Department of Psychiatry (UPK), University of Basel (ECNP-PMD-MHP); Kim Q. Do, Lausanne University Hospital (ECNP-PMD-MHP);

UK: John Geddes, University of Oxford (ECNP-BDN); Guy Goodwin, University of Oxford (ECNP-BDN); Jan Scott, University of Newcastle (ECNP-BDN); Philip McGuire, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London (ECNP-PMD-MHP); Belinda Lennox, University of Oxford (ECNP-PMD-MHP); Paolo Fusar-Poli (Co-Chair), Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London (ECNP-PMD-MHP);

Spain: Eduard Vieta, Fundació Clínic for the Biomedical Research, Barcelona (ECNP-BDN and ECNP PMD-MHP); Ana Gonzalez Pinto, Hospital Santiago Apostol, Vitoria (ECNP-BDN); Monica Martinez-Cengotitabengoa, Hospital Universitario Araba-Santiago, Madrid (ECNP-BDN); Celso Arango, Hospital General Universitario Gregorio Marañón de Madrid, Centro de Investigación Biomedica en Red de Salud Mental, CIBERSAM (ECNP-PMD-MHP);

Denmark: Lars Kessing, University of Copenhagen (ECNP-BDN and ECNP-PMD-MHP); Rasmus Licht, Aalborg University Hospital (ECNP-BDN); Rene E. Nielsen, Aalborg University Hospital (ECNP-BDN); Allan Wehnert, Lundbeck A/S (ECNP-PMD-MHP);

Czech Republic: Tomas Hajek, Charles University, Prague (ECNP-BDN);

Poland: Alexandra Suwalska, Poznan University (ECNP-BDN);

Turkey: Aysegul Yildiz, Dokuz Eylül University, Izmir (ECNP-BDN);

US: Michael Sand, Boehringer-Ingelheim (ECNP-PMD-MHP).

The PSMD cluster organised 3 activities of which the details can be found here below.

1. Ethics of precision and preventive psychiatry workshop, February 23rd and 24th, 2021, online
2. Strategy Planning Meeting with stakeholders, January 28th, 2021, online
3. Implementing precision and preventive psychiatry in Europe, September 21st, 2022, hybrid (Brussels and online)

Ethics of precision and preventive psychiatry workshop, February 23rd and 24th, 2021, online

Precision medicine offers new opportunities to improve mental health but also raises ethical tensions and challenges. The lack of an established ethics framework is one of the core barriers that impede the realization of predictive, preventive, personalized and participatory psychiatry in an ethically acceptable manner that optimizes benefits and minimizes harms. In this context, the European Brain Research Area (EBRA) cluster in Prevention of Severe Mental Disorders (PSMD), coordinated by Prof. Paolo Fusar-Poli and Prof. Ole A. Andreassen, undertook the important initiative of organizing a two-day workshop on the ethics of precision psychiatry (23 and 24 February 2021). The workshop involved key leaders from different professional backgrounds (day 1) and stakeholders (including individuals with lived experiences, day 2) and gathered consensus on a core blueprint to advance ethics of precision psychiatry.

In total, 27 participants joined this workshop.

Day 1, 23 February 2021

14:00-14:05	Welcome EBRA (*Frédéric Destrebecq*), Executive Director of the European Brain Council
14:05-14:15	PSMD introduction, goals and structure of meeting (*Prof. Paolo Fusar-Poli and Prof. Ole Andreassen, PSMD EBRA cluster*)
14:15-14:25	Session 1: Learning from oncology: precision medicine as a clinical reality *Prof. Le Torneau Christophe*, Oncologist and Head of the Department of Drug Development and Innovation (D3i), Institut Curie
14:25-14:40	Q&A
14:40-14:50	Session 2 Preventive and precision psychiatry have imprecise ethics *Prof. Christiane Woopen*, Chair of the European Group on Ethics in Science and New Technologies
14:50-15:05	Q&A
15:05-15:15	Session 3 Ethical challenges in artificial intelligence and mental health *Dr. Danielle Belgrave* Principal research manager in the Healthcare Intelligence group at Microsoft Research, Cambridge (UK)
15:15-15:30	**Q&A**
15:30-15:40	**Break**

15:40-15:50	Session 4 Ethical challenges of implementing personalised prognosis and treatment in psychiatry *Prof. Nikolaos Koutsouleris* Head of Workgroup for Neurodiagnostic Applications Max Plank Institute
15:50-16:05	Q&A
16:05-16:15	Session 5 Digital medicine and electronic healthcare records: ethical tensions and solutions *Dr. David Leslie* Ethics Theme Lead at the Alan Turing Institute
16:15-16:30	Q&A
16:30-16:40	Session 6 Novel methodological strategies for answering bioethical questions in mental health *Dr. Michael Dunn* Director of Medical Ethics and Law Education, Clinical School
16:40-16:55	Q&A
16:55-17:00	Conclusions

Panelists: Prof. Monica Calkins (UPENN), Prof. Daniel Stahl (Precision Medicine and Statistical Learning), Dr. Lucia Valmaggia (Past president of IEPA), Dr. Mirko Manchia (ECNP Bipolar Disorders Network), Prof. Eduard Vieta (ECNP PMD-MHP Network), Prof. Christoph Correll (ECNP PMD-MHP Network), Prof. Marcella Rietschel (ECNP Bipolar Disorders Network), Prof. Eva Reininghaus (ECNP Bipolar Disorders Network), Dr. Kristien Aarts (EBRA), Frédéric Destrebecq (EBRA)

Webinarists: All members of ECNP Bipolar Disorders Network and ECNP PMD-MHP Network

Day 2, 24 February 2021

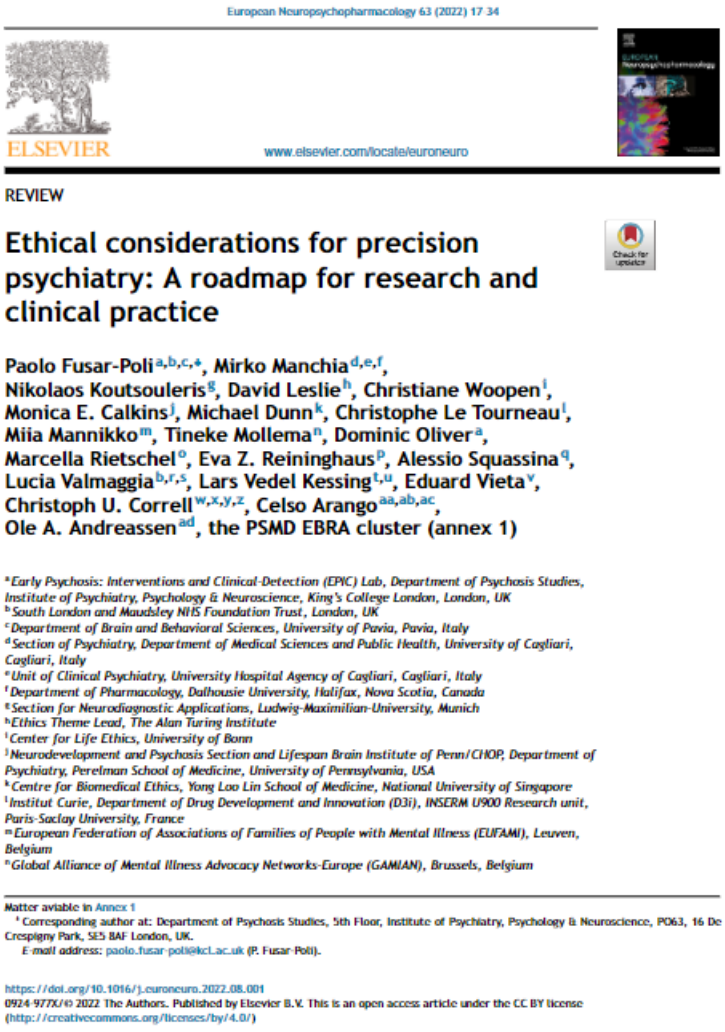
14:00-14:05	Welcome EBRA (*Frédéric Destrebecq*), Executive Director of the European Brain Council
14:05-14:15	PSMD introduction, goals and structure of meeting (Ole Andreassen and Paolo Fusar-Poli)
14:15-14:20	Session 1: How can precision psychiatry improve prognosis and lead to medication?
14:20-14:40	Q&A Stakeholders discussion *Jan Wise* European Psychiatric Association, *Florence Butlen* European Medicine Agency
14:40-14:45	Session 2: Fighting stigma with precision psychiatry opportunities
14:45-15:05	Q&A Stakeholders discussion *Tineke Mollema* Gamian-Europe, *Miia Männikkö* EUFAMI
15:05-15:10	Session 3 A complex lexicon: ethics and communication with patients and caregivers, lay people, and mass media
15:10-15:30	**Q&A** Stakeholders discussion *Tineke Mollema* Gamian-Europe, *Miia Männikkö* EUFAMI
15:30-15:40	**Break**
15:40-15:45	Session 4 Strengthening the alliance between users, families and mental healthcare services to overcome the ethical challenges of precision psychiatry
15:45-16:05	Q&A Stakeholders discussion *Tineke Mollema* Gamian-Europe, *Miia Männikkö* EUFAMI, *Jan Wise* European Psychiatric Association
16:05-16:10	Session 5 Confidentiality and privacy concerns: digital medicine, electronic healthcare records and biological data

16:10-16:30	Q&A Stakeholders discussion *Florence Butlen* European Medicine Agency
16:30-16:35	Session 6 Public mental health and policy ramifications
16:35-16:55	Q&A Stakeholders discussion *Sarah Shenow* MQ Mental Health, *Jan Wise* European Psychiatric Association
16:55-17:00	Conclusions and action plan

Panelists: Ms. Tineke Mollema - Gamian-Europe, Ms. Miia Männikkö - EUFAMI, Dr. Jan Wise - European Psychiatric Association, Dr. Sarah Shenow - MQ Mental Health, Dr. Florence Butlen - European Medicine Agency), Dr. Mirko Manchia (ECNP Bipolar Disorders Network), Prof. Eduard Vieta (ECNP PMD-MHP Network), Prof. Christoph Correll (ECNP PMD-MHP Network), Prof. Marcella Rietschel (ECNP Bipolar Disorders Network), Prof. Eva Reininghaus (ECNP Bipolar Disorders Network), Dr. Kristien Aarts (EBRA), Mr. Frédéric Destrebecq (EBRA)

The output of this workshop consists of a white paper presenting a critical review of the evidence and practical recommendations to manage ethical barriers to precision and preventive psychiatry:

Fusar-Poli P, Manchia M, Koutsouleris N, Leslie D, Woopen C, Calkins ME, Dunn M, Tourneau CL, Mannikko M, Mollema T, Oliver D, Rietschel M, Reininghaus EZ, Squassina A, Valmaggia L, Kessing LV, Vieta E, Correll CU, Arango C, Andreassen OA; PSMD EBRA cluster (annex 1). Ethical considerations for precision psychiatry: A roadmap for research and clinical practice. Eur Neuropsychopharmacol. 2022 Oct;63:17-34. doi: 10.1016/j.euroneuro.2022.08.001. Epub 2022 Aug 27. PMID: 36041245.



European Neuropsychopharmacology 63 (2022) 17–34

ELSEVIER www.elsevier.com/locate/euroneuro

REVIEW

Ethical considerations for precision psychiatry: A roadmap for research and clinical practice

Paolo Fusar-Poli[a,b,c,*], Mirko Manchia[d,e,f], Nikolaos Koutsouleris[g], David Leslie[h], Christiane Woopen[i], Monica E. Calkins[j], Michael Dunn[k], Christophe Le Tourneau[l], Miia Mannikko[m], Tineke Mollema[n], Dominic Oliver[a], Marcella Rietschel[o], Eva Z. Reininghaus[p], Alessio Squassina[q], Lucia Valmaggia[b,r,s], Lars Vedel Kessing[t,u], Eduard Vieta[v], Christoph U. Correll[w,x,y,z], Celso Arango[aa,ab,ac], Ole A. Andreassen[ad], the PSMD EBRA cluster (annex 1)

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[b] South London and Maudsley NHS Foundation Trust, London, UK
[c] Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy
[d] Section of Psychiatry, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy
[e] Unit of Clinical Psychiatry, University Hospital Agency of Cagliari, Cagliari, Italy
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[i] Center for Life Ethics, University of Bonn
[j] Neurodevelopment and Psychosis Section and Lifespan Brain Institute of Penn/CHOP, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, USA
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[l] Institut Curie, Department of Drug Development and Innovation (D3i), INSERM U900 Research unit, Paris-Saclay University, France
[m] European Federation of Associations of Families of People with Mental Illness (EUFAMI), Leuven, Belgium
[n] Global Alliance of Mental Illness Advocacy Networks-Europe (GAMIAN), Brussels, Belgium

Matter aviable in Annex 1

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https://doi.org/10.1016/j.euroneuro.2022.08.001

Strategy Planning Meeting with stakeholders, January 28th, 2021, online

To co-create the 3rd meeting of the PSMD cluster together with all important players in the precision psychiatry eco-system, the cluster coordinators organised a Strategy Planning Meeting with stakeholders.

In total, 7 different stakeholder groups (academia, patients, professional associations, pharmaceutical industry, regulators, funders, NGO's) were represented by 15 people:

The agenda included the following topics

- 12:00-12:05 Introductory remarks
- 12:05-12:10 EBRA-PSMD Background and Aims (Paolo Fusar-Poli)
- 12:10-12:20 Overview of White Paper (Mirko Manchia)
- 12-20-12:30 Q&A
- 12:30-12:40 Aims of Meeting (Ole A. Andreassen)
- 12:40-14:00 Discussion on strategic aspects of the workshop

The outcome of the meeting has been written down in a short internal meeting report.

Implementing precision and preventive psychiatry in Europe, September 21st, 2022, hybrid

This hybrid (Brussels and online) event was designed to highlight the urgent need to address the lack of parity between mental and physical health in European funding and to aid navigation of barriers to implementation of precision psychiatry. The programme highlights were:

- The importance of severe mental disorders research in Europe and globally
- Implementation of precision and preventive psychiatry
- Why is funding needed NOW in this field?

45 Participants signed up to join the meeting.

The agenda can be found here below.

12:00 - 13:00:	**Lunch**
13:00 - 13:15:	**Welcome and introduction to the PSMD cluster**
	Paolo Fusar-Poli, Kings College London, PSMD cluster
	Ole Andreassen, University of Oslo, PSMD cluster
SESSION 1:	**The importance of precision psychiatry**
	Chair : Ole Andreassen
13:15 - 13:30:	Opportunities for brain research under Horizon Europe
	Tim Raemaekers, European Commission-Directorate General Research and Innovation
13:30 - 13:50:	Industry perspective on precision psychiatry
	Cornelia Dorner-Ciossek, Boehringer- Ingelheim
13:50 - 14:10:	Ethical considerations for precision psychiatry

	Mirko Manchia, Università Degli Studi di Cagliari, PSMD cluster
14:10 - 14: 45:	Panel discussion moderated by *Frédéric Destrebecq, European Brain Council*
	Tineke Mollema, Gamian-Europe
	Jan Wise, European Psychiatric Association
	Paolo Fusar-Poli, PSMD cluster
14:45 - 15:00	Questions from the audience
15:00 - 15:20:	**Coffee break**
SESSION 2:	**Implementation of precision and preventive psychiatry**
	Chair: Paolo Fusar-Poli
15:20 - 15:35:	How to navigate the current and existing legal and data protection frameworks to implement precision psychiatry?
	Damian Okaibedi Eke, The Montfort University, Leicester
15:35 - 15:50:	Regulator perspective on precision psychiatry: Guideline development, stratification and regulation of biomarker qualification
	Interview with Florence Butlen, European Medicine Agency
15:50 - 16:00:	Questions from the audience
SESSION 3:	**Why is funding needed NOW in this field?**
	Chair: Ole Andreassen
16:00 - 16:15:	Private organisations and philanthropic perspective
	Niall Boyce, Wellcome
16:15 - 16:30:	NIH perspective on precision psychiatry
	Joshua Gordon, NIH
16:30 - 17:25:	Roundtable with speakers and the audience
	Moderator: Frédéric Destrebecq, European Brain Council
17:25 - 17:30:	**Closing remarks**
	Paolo Fusar-Poli, Kings College London, PSMD cluster
	Ole Andreassen, University of Oslo, PSMD cluster
17:30 - 19:00:	**Networking reception**

The outcome of the meeting has been written down in a summary document (see here below).

Summary document

This event was organised by the **European Brain Research Area Prevention of Severe Mental Disorders (EBRA-PSMD) Cluster**, co-chaired by **Ole Andreassen** (University of Oslo) and **Paolo Fusar-Poli** (King's College London & University of Pavia), to highlight the urgent need to address the lack of parity between mental and physical health in European funding and aid navigation of barriers to implementation of precision and preventive psychiatry.

In **Session 1**, **Tim Raemaekers** (European Commission) and **Cornelia Dorner-Ciossek** (Boehringer Ingelheim) discussed the relative importance of precision and preventive psychiatry in the European funding landscape and in industry. **Mirko Manchia** summarised the recently published white paper on ethics in precision psychiatry (https://doi.org/10.1016/j.euroneuro.2022.08.001) that followed the EBRA-PSMD workshop in February 2021. This led into an informative panel discussion, moderated by **Frédéric Destrebecq** (executive director of EBC) where **Paolo Fusar-Poli**,

Tineke Mollema (GAMIAN-Europe) and **Jan Wise** (European Psychiatric Association) discussed how to advance the field while prioritising service user wellbeing and equity of access to mental healthcare, and how funders can best support this effort.

In **Session 2**, **Damian Okaibedi Eke** (De Montfort University) elaborated on his work in the EU Human Brain Project, how legal and regulatory frameworks are essential for good quality, ethical research, and how best to navigate them. **Florence Butlen-Ducuing** (European Medicines Agency) informed us of the regulatory, scientific and qualification processes at EMA and how they apply to precision and preventive psychiatry. There was particular focus on biomarkers and digital health tools. For more information on these topics, please see the following links:

https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development-0

https://www.ema.europa.eu/en/documents/other/questions-answers-qualification-digital-technology-based-methodologies-support-approval-medicinal_en.pdf

https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-efficacy-safety/clinical-efficacy-safety-nervous-system

https://www.icmra.info/drupal/sites/default/files/2021-08/horizon_scanning_report_artificial_intelligence.pdf

In **Session 3**, **Niall Boyce** (Wellcome Trust) and **Joshua Gordon** (National Institute of Health) discussed current and future initiatives within their organisations to advance precision and preventive psychiatry. To finish, a productive roundtable discussion summarised research priorities within the field and how to ensure any progress results in inclusive and equitable improvements in mental healthcare.

There may be scope for a white paper to be produced from the content of the meeting. We will be in contact with attendees and cluster members with further details once we have reviewed the event transcript. We will also explore opportunities for a follow-up meeting in the near future.

3. TRISOMY21 cluster

The primary objective the Trisomy 21 cluster is to establish a collaborative framework for the coordinated actions of Down syndrome research in Europe. Through EBRA cluster, the TRISOMY21 cluster wishes to expand existing European networks to promote coordination and collaboration among European scientists belonging to these research networks and share common projects with the goal of understanding disorders of the developing brain leading to intellectual disabilities such as DS.

The TRISOMY 21 CLUSTER aims at:

- Expand the network of DS researchers and initiate collaborative research on other intellectual disabilities and Alzheimer's disease.
- Harmonize and standardize protocols for DS (pre)clinical research, enabling better comparisons among studies.
- Co-ordinate efforts with research strategies across European and global brain initiatives.
- Enhance resource-sharing (experimental models, IPSc, clinical protocols, etc.).
- Develop a preclinical network and enhance clinical trial structures.
- Increase engagement in research of persons with Down syndrome and their representatives.
- Promote research on Down syndrome and Intellectual Disabilities by developing a funding initiative across agencies.
- Increase the visibility of the Down syndrome research community.

The Trisomy 21 EBRA cluster is composed of centres of excellence in Neuroscience in seven different European countries (Belgium, France, Italy, Spain, Switzerland, The Netherlands and UK) with 20 scientists and the exact gender balance. Members will be both senior and mid-carrier researchers and clinicians.

Coordinator: Prof. Mara Dierssen, Genomic Regulation Center, Barcelona, Spain

Co-coordinator: Prof. Marie-Claude Potier, Hôpital de la Pitié-Salpêtrière, Paris, France

Name	**Institute, City, Country**
Antonarakis, S	University of Geneva Medical School, Geneva, SW
Bartesaghi, R	Bologna University, Bologna, IT
Contestabile, A	The Italian Institute of Technology (IIT), Genoa, IT
Coppus, T	Radboud University Medical Center Nijmegen, NL
De Deyn, P	University of Antwerp Institute Born-Bunge, Antwerp, BE
de la Torre, R	Hospital del Mar Medical Research Institute, Barcelona, ES
Dekker, A	University Medical Center Groningen (UMCG), Groningen, NL
Delabar, JM	Institut du Cerveau et de la Moelle, Paris, FR
Dierssen, M	Genomic Regulation Center, Barcelona, ES
Fisher, L	University College London, London, UK
Herault, Y	Institut de Génétique et de Biologie Moléculaire et Cellulaire Illkirch Cedex, FR
Martinez-Cue, C	University Cantabria, Santander, ES
Potier, MC	Hôpital de la Pitié-Salpêtrière, Paris, FR
Strydom, A	Kings College London, London, UK
Fortea, J	Hospital de Sant Pau Alzheimer Down Unit, Barcelona, ES
Guidi, S	Bologna University, Bologna, IT
Lio, P	Cambridge University, Cambridge, UK
Perluigi, M	University “La Sapienza”, Roma, IT
Puig, V	Hospital del Mar Medical Research Institute, Barcelona, ES
Stagni, F	Bologna University, Bologna, IT

The TRISOMY21 cluster organised 4 activities of which the details can be found here below.

1. Consensus meeting, November 12th, 2020, online
2. Thematic Workgroup on Down syndrome research priorities: Research infrastructures and biocollections, November 29th, 2021, hybrid (Barcelona and online)
3. Science and Society Symposium at T21RS conference 2022 : June 11th, 2022, in-person (Long Beach, US)

4. Patient Involvement in European Down Syndrome research, October 10th 2022, hybrid (Brussels and online)

Consensus meeting, November 12th, 2020, online

On November 12th, 2020, TRISOMY21-CLUSTER held the first meeting. The focus of the meeting was to bring together the leadership of the TRISOMY21-cluster and several relevant stakeholders including patient organizations, basic and clinical researchers, clinicians, industry, funders research infrastructures and data experts (see Table 7 for list of institutions and organisations). During this meeting, they discussed priorities and opportunities for Down syndrome research and consensus was built on research needs in the short and long term, and on main objectives and priorities for action.

The research and coordinating objectives and priorities of TRISOMY21 cluster were discussed before and during the meeting with the invited stakeholders, identifying opportunities and challenges to go beyond the current limits of Down syndrome research and elaborating a European Research Strategy. These include:

(1) Facilitating data and bio sample availability and sharing.

(2) Increasing translation of basic science to clinical practices.

(3) Creating European and International joint funding initiatives.

(4) Supporting a multi-stakeholder Down syndrome research community.

24 participants joined the meeting.

The agenda can be found here below.

10:00 Welcome (Mara Dierssen)

10:05 Introduction to EBRA (Monica Di Luca)

10:10 Introduction to TRISOMY21-cluster (Marie Claude Potier/Mara Dierssen)

10:15 Q&A about TRISOMY21-cluster

10:20 Tour the table

10:40 Results of the TRISOMY-21 EBRA cluster survey (Mara Dierssen)

10:50 Priorities and opportunities for TRISOMY21 research in Europe

- Marzia Perluigi/Eugenio Barone: Thematic Workgroup on Down syndrome research priorities (5 min)
- Andre Strydom/Jean Delabar: Thematic Workgroup on strategy to link with policy makers and other relevant stakeholders (5 min)
- Q&A

11:10 Short break

11:15 Views of the European Down syndrome Association (Pat Clarke/James Larkin)

11:25 Views of Funding agencies (5 min each) and Q&A

- Monica Ensini, DG Research & Innovation at European Commission
- Philippe Amouyel, EU Joint Programme – Neurodegenerative Disease Research (JPND)
- Marlies Dorlöchter, ERANET-NEURON
- Catherine Lemmonier, Jérôme Lejeune Foundation
- Georgina MacKenzie, Wellcome trust
- Amy Halls, National Institute for Health Research (NIHR, UK)
- Magda Chlebus, Innovative Medicines Initiative (IMI)
- Laurent Meijer, PERHA Pharmaceuticals
- Richard Oakley, Alzheimer's Society
- Hanna Churchill, Alzheimer's Society

12:05 TRISOMY21 stakeholder discussion
Discussants: Andre Strydom, Jean Maurice Delabar, Marzia Perluigi, Eugenio Barone

12:35 Refining and discussion about the working plan for proposed priorities and consensus building

12:50 Conclusion and next steps

13:00 END

The outcome of this meeting was written down in a consensus document which can be found here below.

TRISOMY21 CLUSTER EBRA CONSENSUS STATEMENT

Dierssen, M; Potier, MC; Herault, Y; Perluigi, M; Fisher, L; Barone, E; Delabar, JM; Strydom, A.

Overview TRISOMY21-CLUSTER was funded by EBRA in 2020 as a two-year networking action to enhance Down syndrome research in Europe.

Mission Establish a collaborative framework of coordinated actions of Down syndrome research in Europe.

Strategic objectives

- Expand existing and create new European Down syndrome research networks.
- Promote coordination and collaborations at both European and global level and contribute to European Policy.
- Increase translation of Down syndrome research into health interventions.
- Increase participation of industrial partners.
- Improve access to and optimise the use of research infrastructures and data.
- Explore funding possibilities for broader scale cooperation at global level.

Activities

- Consensus workshop.
- Thematic Workgroup on Down syndrome research priorities.
- Thematic Workgroup on strategy to link with policy makers and other relevant stakeholders.
- Public Forum of the EBRA Trisomy 21 cluster.

The first event was a meeting of TRISOMY21-cluster members with external stakeholders with the intention to reach consensus on the priorities, gaps and enabling actions.

TRISOMY21 consensus meeting

On November 12th, 2020, TRISOMY21- CLUSTER held the first meeting. The focus of the meeting was to bring together the leadership of the TRISOMY21-cluster and a number of relevant stakeholders, from funding agencies to patient's organisations and industry, to discuss priorities and opportunities for Down syndrome research and liaise with industry partners and patient representatives. During the meeting, consensus was built on research needs in the short and long term, and main objectives and priorities for action.

Meeting attendees The following TRISOMY21 stakeholder groups were represented during the meeting: Patient organizations, basic and clinical researchers, clinicians, industry, funders research infrastructures and data experts.

TRISOMY21 cluster: Mara Dierssen, Chair (Center for Genomic Regulation, Barcelona); Marie Claude Potier, Co-Chair (Institut du Cerveau et de la Moelle, Paris); Andre Strydom (King's College London); Jean Maurice Delabar (Institut du Cerveau et de la Moelle, Paris); Marzia Perluigi (University "La Sapienza", Roma); Eugenio Barone (University "La Sapienza", Roma); Elizabeth Fisher (University College London); Yann Herault (IGBMC, Strasbourg).

From EBRA: Kristien Aarts, Project manager EBRA, European Brain Council ; Fréderic Destrebecq, Executive director, European Brain Council

Stakeholders group: Philippe Amouyel, EU Joint Programme – Neurodegenerative Disease Research (JPND); Pat Clarke, Chair European Down syndrome Association; Marlies Dorlöchter, ERANET-NEURON; Monica Ensini, DG Research & Innovation at European Commission; Catherine Lemmonier, Jérôme Lejeune Foundation; Georgina MacKenzie, Wellcome trust; James Larkin, Innovative Medicines Initiative (IMI); Magda Chlebus, Executive Director, Science Policy and Regulatory (EFPIA and IMI); Bettina Ryll, Innovative Medicines Initiative (IMI); Amy Halls, National Institute for Health Research (NIHR, UK); Richard Oakley, Alzheimer's Society; Laurent Meijer, PERHA Pharmaceuticals; Hanna Churchill, Alzheimer's Society

Toward consensus

The research and coordinating objectives and priorities of TRISOMY21 cluster were discussed before and during the meeting with the invited stakeholders, identifying opportunities and challenges to go beyond the current limits of Down syndrome research and elaborating an **European Research Strategy**. These include (1) facilitating data and biosample availability and sharing, (2) increasing translation of basic science to clinical practices, (3) creating European and International joint funding initiatives and (4) supporting a multi-stakeholder Down syndrome research community.

The TRISOMY21 cluster aims to represent the research priorities of the entire Down syndrome research community. **The specific actions to achieve these general priorities will be discussed through two working groups**, the Thematic Workgroup on Down syndrome research priorities and the Thematic Workgroup on strategy to link with policy makers and other relevant stakeholders.

As part of the preparation for these specific actions, consensus aspects are acknowledged below and have been written by the leadership:

Basic Research in Down Syndrome

Research in the field of DS has generated new knowledge on disease mechanisms, leading to the discovery of druggable targets, compounds and procedures for treatment and has increased the quality of science in this field. This has opened unprecedented opportunities for individuals with DS and will provide many benefits for the general population and other conditions.

There is a need to continue reinforcing basic and pre-clinical research opportunities to increase our understanding of DS from the unknown molecular origin of the trisomy 21 aneuploidy to the pathophysiological mechanisms and preclinical proof-of-concept for therapies. We anticipate that those could also be beneficial in other intellectual disabilities, neurodevelopmental and neurodegenerative disorders.

Challenges for the future include (i) developing new experimental and theoretical approaches; (ii) increasing the pace of adoption of technologies such as iPSC, organoids, multi-omics, connectomics, computational neuroscience, single cell, molecular imaging, gene therapy etc.; (iii) attracting and retaining talented students, researchers and clinicians; (iv)

accelerating the translation of novel therapies and biomarkers from the laboratory to the clinic; and (v) increase transversal and translational training efforts in complex diseases.

Clinical Research in Down Syndrome

Clinical research in the Down syndrome field needs reinforcement in three major research areas:

The lifelong nature of the disorder settles an important research need of extensive characterization from birth to adult life. This requires to define a more detailed clinical evaluation along lifespan, attached to a DS registry with a direct connection to a bioresource infrastructure to support longitudinal epidemiologic research and cross sectional studies.

Clinical trials on new age-specific drug treatments and neurotherapies are needed

Down syndrome is a complex disorder characterized by several comorbidities (psychiatric disorders, epilepsy and autism spectrum disorders, blood disorders, diabetes, obesity Alzheimer's disease etc.). These comorbidities settle another important research area and may enlighten the role of genes with pleiotropic function in DS and other conditions.

Studies for accurate stratification of patient populations to pave the way for personalized and precision medicine. Without an accurate and precise patient stratification model, researchers struggle to maximize the impact of their health intervention.

Challenges for the future: (i) the development of harmonised clinical evaluation protocols and dedicated ontology leading to the definition of a clinical path for DS; (ii) the creation of an European Down syndrome registry and a Down syndrome Clinical Trial Network (EU_DSCTN), given the uniqueness of Down syndrome and the recruitment complexity; (iii) the identification and incorporation in clinical practice of relevant disease and target engagement biomarkers; (iv) increasing the path to personalised and precision medicine; (v) increasing the pace of data and biosample sharing; (vi) adoption of technologies such as neurotherapies, eHealth and mHealth, gamification and cognitive training systems; (vii) bioethical aspects; (viii) primary care training

Innovation and infrastructures

Infrastructures

The size and complexity of the biosamples and data needed to promote translational research extends far beyond the scope of individual research projects.

1. There is a need of funding for dedicated Down syndrome bioresource infrastructure, with associated data (medical/epidemiological, social), and databases independent of physical samples, and other biomolecular and bioinformatics research tools. including animal and cellular models repositories.

2. Given the recruitment complexity enforces the need of a Down syndrome specific registry including individuals of all ages, with a direct connection to the bioresource infrastructure.

3. Deeper insights into clinical and preclinical data (multilevel including multi-omic, brain imaging, behavioural phenotyping) that may generate findings on lifetime evolution, drug mechanisms, novel targets for therapy, comorbidities, prognosis and outcome require developing long-term biomedical digital data preservation strategy for Down syndrome is very important to improve data quality, provide traceability and support reproducibility.

We need agreement between funding agencies and the Down syndrome scientific community to accommodate "bottom-up" integration and "top-down" financing of databases and biorepositories on an international scale.

Innovation

Delivery of medical care is changing, requiring transition to care facilitated by eHealth/mHealth platforms and digital healthcare. Creation of virtual Down syndrome centres to optimize and deliver care but also to collect useful clinical information across time.

Challenges for the future: (i) EU research infrastructures to support Down syndrome research; (ii) create a Down syndrome registry extending on existing registries including all ages, with a direct connection to a bioresource infrastructure; (iii) Create bioresource infrastructures; (iv) long-term preservation of Down syndrome biomedical research data and secure virtual workspaces to integrate and manipulate data, with shared software programs (e.g., bioinformatics tools), to facilitate the FAIR (Findable, Accessible, Interoperable and Reusable) use of data for near- and long-term research needs; (v) develop incentives to support and promote bioresources and data sharing

Down Syndrome Research Networks

The Down syndrome field needs to build a highly connected research community. A first initiative to create this interactive group has been the creation of the European local chapter among members of the Trisomy 21 Research Society to promote collaboration among institutions and investigators.

The establishment of cooperating networks of preclinical laboratories and clinical research centres could help integrate preclinical findings using clinical samples for biomarker analysis, integrate molecular characterization, pharmacology, biology, and imaging into clinical trials and create a pipeline for drug development and validation.

The European Research Networks would offer a unique opportunity to bridge hospitals and clinics with experts of DS, to perform academic clinical trials (phase 1) with innovative therapies, share data acquired during routine clinical work for data analytic sciences and homogenize the "rare disease" status for DS to leverage orphan drug designations and patent protection for increased investment.

Challenges for the future: (i) support the development of translational research networks at the European and global level; (ii) create an integrated preclinical-clinical program promoting cooperative agreements for research into preclinical and clinical aspects; (iii) funding opportunities to participate in global initiatives inside and outside the Down syndrome field (complex disorders; rare diseases; developmental diseases etc.)

Patients and Industry Involvement

Down syndrome organisations are major stakeholders that have a key role in advocacy and awareness. The Trisomy 21 Research Society (www.t21rs.org) as already built strong means for engagement and involvement of persons with Down syndrome and their families, but they should be strongly involved in the process of research prioritisation and design.

Down syndrome is a new extremely attractive field for investment by industry and new technology companies. Industry is recognizing the need to focus more on disease-modifying therapies that target specific mechanisms of disease and the underlying pathophysiology, which is very strong in the Down syndrome field already leading to promising therapeutic targets. This should be promoted through dedicated funding programs.

Challenges for the future: (i) involvement of Down syndrome organisations in research prioritisation through participation in funding decisions; (ii) involvement of persons with Down syndrome and their families as partners to researchers, clinicians and industry; (iii) implementation of adequate tools for co-creation research; (iv) increasing SMEs and biotechnology companies entering the field, allowing truly innovative approaches through specific funding programs (IMI); (v) means to promote access of industry to preclinical trial capabilities and expertise distributed throughout the TRISOMY21 network and to support the participation of industry to translational initiatives; (vi) educate on path to industry (spin-off, start-up); (vii) Involvement of regulatory agencies (EMA).

Thematic Workgroup on Down syndrome research priorities: Research infrastructures and biocollections, November 29th, 2021, hybrid

On November 29th, 2021, the TRISOMY21-cluster came together in Barcelona (Spain) and online with representatives from EU research infrastructures, networks, cohorts, repositories, biobanks, patient associations, and relevant stakeholders, from funding agencies to industry. They discussed European infrastructures for DS research and biocollections.

In the morning, several EU Cohorts and Registries presented their work including Horizon 21 Consortium, the independent cohorts/bio sampling initiatives la Princessa Madrid, PoliClinico Gemelli Rome, French DS cohort Lyon, Defeating Dementia in Down Syndrome(DIDS) Cambridge, Down Alzheimer Barcelona Neuroimaging Initiative (DABNI), Genetic Forms of Intellectual Disability and Autism Spectrum Disorders (GENIDA), and the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT). This was followed by presentation from the EU Biobanks: BioJEL Jerome Lejeune Foundation, LonDowns, European Bank for induced pluripotent stem cells (EBiSC), Telethon and Askion. Finally, they discussed together 1. How to structure registries/repositories/biocollections for DS research; 2. How to incorporate all existing cohorts/samples in large efforts such as Horizon 21; 3. Issues with regards to collection and storage of relevant samples for DS research and 4. The need for harmonization and guidelines for biobanking in DS research.

In the afternoon, similar initiatives in the US (i.e., Alzheimer's biomarker consortium for Down syndrome (ABC-DS), The Alzheimer's Clinical Trial Consortium-Down Syndrome (ACTC-DS), the INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndrome (INCLUDE) Project and the Data Management and Portal for INCLUDE (DAPI) project shared their knowledge and experience on how to set up, contribute to and use registries/repositories/biobanks. Then, the European Strategy Forum on Research Infrastructures (ESFRI) and Biobanking and BioMolecular Resources Research Infrastructure-European Research Infrastructure Consortium (BBMRI-ERIC) presented services and support they can offer to the Down Syndrome research community. The day finished with a round table open to all participants.

The meeting provided a clear view on the European landscape of research infrastructures in Europe. A lot of work has already been done but there is still too much fragmentation and the accompanying challenges. A roadmap has been created on how to move forward but we can capitalize on what has already been done for Down Syndrome research in the US. We need to start building Down Syndrome Research Infrastructures across the borders and coordinate the work in Europe and globally. The TRISOMY21 cluster will play a very important umbrella role in this effort.

41 in-person and online participants joined the meeting.

The agenda can be found here below.

10:00 – 10:05: Welcome – *M. Dierssen*, Chair of the EBRA TRISOMY 21 cluster; *K. Aarts*, Project Manager at EBRA

SESSION 1: State of the art: EU cohorts/repositories/biobanks for DS research
Moderators: *Mara Dierssen, Marzia Perluigi, Marie-Claude Potier, Eugenio Barone*

10:05 – 10:10 **Introduction** – *Marie-Claude Potier*

10:10-11:25 **EU Cohorts and Registries**

10:10-10:20 **Horizon 21 Consortium** *Anne-Sophie Rebillat (TriAL21)*

10:20-11:15 **Other independent cohorts/biosampling**: *Diego Real de Asua, Angelo Carfì, Damien Sanlaville, Rafa de la Torre, Johannes Levin, Shahid Zaman, Isabel Barroeta, Pauline Burger*

11:15-11:25 **Eurocat:** *Joan Morris*

Coffee break: 11:25 – 11:45

11:45 – 12:15 **EU Biobanks**

BioJEL Jerome Lejeune Foundation *Sophie Durand*
LonDowns *Andre Strydom*
EBiSC *Julia Neubauer*
Telethon: *Luca Sangiorgi*
Askion *Stefan* Chabierski

12:15 – 13:15 **Round Table open to participants**
Chairs: *Marie-Claude Potier & Andre Strydom*
Ségolène Aymé, Angelo Carfì, Sophie Durand, Joan Morris, Anne-Sophie Rebillat, Luca Sangiorgi,

- How to *structure* registries/repositories/biocollections for DS research? How to incorporate all existing cohorts/samples in large efforts such as Horizon 21?
- Issues with regards to *collection and storage* of relevant samples for DS research
- The need for *harmonization and guidelines* for biobanking in DS research

13:15 – 14:30: Lunch

SESSION 2:How to set up, contribute to and use registries/repositories/biobanks. Learning from existing infrastructures

Moderators: *Mara Dierssen, Marzia Perluigi, Marie-Claude Potier, Eugenio Barone*

14:30-14:35 **Introduction -** *Eugenio Barone*

14:35-15:15 **The USA experience**

14:35-14:45 **ABC-DS** Laurie Ryan

14:45-14:55 **The Alzheimer's Clinical Trial Consortium-Down Syndrome (ACTC-DS)** *Lotta Granholm*

14:55-15:05 **The INCLUDE Project** (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE). *Melissa Parisi*

15:05-15:15 **The DAPI Project** (Data Management and Portal for INCLUDE (DAPI)) *Joaquin M Espinosa*

15:15- 15:35 **European Infrastructures**

15:15- 15:25 **ESFRI** Radislav Sedlacek

15:25- 15:35 **BBMRI-ERIC**: Jens K. Habermann

15:35 – 16.35 **Round Table open to participants**
Chairs *Marzia Perluigi and Juan Fortea*
Moderators *Pat Clark, Melissa Parisi, Tim Raemaekers, Hella Lichtenberg, Sylianos Antonorakis, Andre Strydom, Stephanie Sherman, Philippe Amouyel*

16:35 Closing remarks

The outcomes of this meeting have been written down in a minutes report.

Science and Society Symposium at T21RS conference 2022: June 11th, 2022, Long Beach, US

The 3rd activity of the TRISOMY21 cluster took place at the 4th T21RS biennial International Conference: https://www.t21rs.org/t21rs-meetings/. This conference is instrumental in promoting scientific exchanges, maximizing resource use and defining the most promising research at the basic, translational and clinical levels. The rapid pace of progress that has taken place in the last few years demands effective communication between scientists and clinicians working in the field. The 4th T21RS International conference was held in Long Beach, California on June 9-12, 2022. A dialog was established between researchers and the families and Down syndrome associations. The agenda can be found here below.

8:30 AM - 10:00 Science and Society (I)

8h30- 8h35- **Introduction**
Anne-Sophie Rebillat and María Carmona-Iragui, *co-chairs S&S Committee T21RS*

8h35- 8h40- **Opening**
Theresa Mabie

8h40- 9h10- **Presentations**

DS and Covid-19, including psychosocial impact
Dr. Sujay Ghosh, *University of Calcutta, India*

Therapeutics: IVIG treatment for regression
Dr. Jonathan Santoro, *Childrens Hospital Los Angeles, USA*

9h10- 10:00- **Panel discussion on research participation: Why families' participation in Down syndrome research is key and how you can get involved**

On the importance of research participation
Hampus Hillerstrom, *President & CEO, LuMind IDSC*

Introduction of the clinical trial networks
Hampus Hillerstrom, *President & CEO, LuMind IDSC*
Dr. Andre Strydom, *King's College, London, UK*
Dr. Michael Rafii, *University Southern California, USA*

Importance of Brain Biobank and how it works
Dr. Lotta Granholm, *University of Colorado, USA*

EBRA T21 cluster (European Brain Research Area)
Dr. Mara Dierssen, *Centre for Genomic Regulation- CRG, Barcelona, Spain*
Dr. Marie-Claude Potier, *Institut du Cerveau - Paris Brain Institute, France*

Testimonials from research participants in Europe and the USA
Coordinated by Dr. Isabel Barroeta, *Hospital Sant Pau, Barcelona, Spain*

Panel discussion with all the speakers
Moderated by Hampus Hillerstrom and Isabel Barroeta

10h00- 10h30- **Coffee break**

10:30 AM - 12:00 Science and Society (II)

10h30- 11h00 - **Presentations**

Physical activity and impact of exercise on cognition
Dr. Sarah Pape, *King's College, London, UK*

Innovative treatments for sleep apnea disease. Presentation of DSC2U
Dr. Brian Skotko, *Massachusetts General Hospital*

11h00- 11h30- **Hollywood panel**
Moderated by Eric Rubenstein
Guests: Cole Sibus, actor, Los Anteles, CA, USA.
Blair Williamson, actor, Los Angeles, CA, USA.
Gail Williamson, talent agent, Los Angeles, CA, USA.

11h30- 11h40- **Cultural program: Music show**
Sujeet Desai, *Musician & Motivational speaker, Williamsville, NY, USA*

11h40 – 11h55- **Video with highlights of the conference**

11:55- 12:00- **Closing**
Anne-Sophie Rebillat and María Carmona-Iragui, *co-chairs S&S Committee T21RS*

Patient Involvement in European Down Syndrome research, October 10th, 2022, hybrid

During the final hybrid (Brussels and online) meeting of the TRISOMY21 cluster, the newest advances in Down syndrome research were discussed as well as the engagement of people with Down syndrome and their families in research. The aim was to share the news on science and to better understand the needs people with Down syndrome that should drive further projects. 30 participants joined the meeting.

The agenda can be found here below.

11:30 – 11:35:	Welcome and introduction
	Mara Dierssen, Centre for Genomic Regulation (CRG), Barcelona, Spain
11:35 – 11:45:	Recent Advances in Down Syndrome and European Health Data Space
	Mara Dierssen, Centre for Genomic Regulation (CRG), Barcelona, Spain
11:45 – 11:55:	Data Sharing: The Federated European Genome-Phenome Archive

	Babita Singh, Centre for Genomic Regulation (CRG), Barcelona, Spain
11:55 – 12:10:	Patient Involvement in Brain Research
	Joke Jaarsma, European Federation for Neurological Associations
12:10 – 12:20	A central European Registry for Neurology
	Joke Jaarsma, European Federation for Neurological Associations
Open Discussion:	**What can patients do and how?**
	With patient representatives and TRISOMY21 cluster members
12:20 – 12:25:	Advancing brain health: cognitive activation with non-pharmacological methods
	Jo Lebeer, University of Antwerp, Belgium
12:25 – 12:30:	Registries: what are the problems, and opportunities.
	Andre Strydom, Kings College London, UK
12:30 – 12:35:	Bio samples: opportunities and benefits. Are we yet there?
	Eugenio Barone, Sapienza University of Rome, Italy
12:35 – 12:40:	Patient involvement. Advocacy groups, guidelines
	Pat Clarke, European Down Syndrome Association
12:40 – 13:15:	Roundtable
13:15 – 13:30:	Next steps and actions
	Mara Dierssen, Centre for Genomic Regulation (CRG), Barcelona, Spain
13:30 – 14:30:	**Networking finger lunch**

The outcomes of this meeting will be published in a high level peer review journal:

Potier et al. (submitted). Improving research for advancing treatments in Down syndrome. Lancet Neurology.

4. BRAINFOOD cluster

The overarching objective of the BRAINFOOD cluster is to ultimately positively impact on brain health by improving nutrition of European citizens based upon fundamental insights in the bidirectional links between brain health and nutrition. In line with the EBRA concept, it is our mission to work together, synergistically and in a coordinated and non-fragmented manner, to specifically identify knowledge gaps and priorities in ways that can impact on the societal challenge of improving brain health through nutrition. At all levels, and where possible, gender will be taken into account.

Many of the members of our cluster are (or have been) involved in EU-funded or European-wide projects specifically dedicated to understanding the neurobiological processes linking nutrition and brain health (e.g., by metabolic, endocrine, and gut microbiota signalling) and the role of genes and environment in shaping this outcome. BRAINFOOD, established in 2017 as the ECNP Nutrition Network, includes experts from academia and industry, mainly neuroscientists, nutritionists, psychiatrists, psychologists, or geneticists with an interest in the impact of nutrition on mental health. We have key experts in gut-brain signalling (hormones, vagal afferents, gut microbiota, inflammatory signals), neuroendocrine regulations, metabolites/nutrients, and the neural systems involved

(revealed through genetics, epidemiology, functional brain imaging, behavioural models in rodents and morphological, biochemical, and molecular neuroscience tools).

Coordinator: Prof. Roger Adan, University Medical School Utrecht, The Netherlands

Co-coordinator: Prof. Suzanne Dickson, University of Gothenburg, Sweden

Partners	Institute	Country
Prof Roger Adan	University Medical School Utrecht	The Netherlands
Prof Suzanne Dickson	University of Gothenburg	Sweden
Dr Francesca Cirulli	Instituto Superiore di Sanita, Rome	Italy
Prof Jan Buitelaar	Radbound University Nijmegen	The Netherlands
Dr Tony Goldstone	Imperial College London	UK
Prof Beate Herpertz- Dahlmann	University of Aachen	Germany
Prof John Cryan	University of Cork	Ireland
Prof Louise Dye	University of Leeds	UK
Prof Gary Frost.	University College London	UK
Prof Philip Gorwood	Paris Descartes University	France
Dr Odile Viltart	Paris Descartes University	France
Prof Suzanne Higgs	University of Birmingham	UK
Prof Johannes Hebebrand and	University of Duisburg-Essen	Germany
Prof Lars Libuda	University of Duisburg-Essen	Germany
Prof Ute Nothlings	University of Bonn	Germany
Prof Jannus Harro	University of Tartu	Estonia
Dr Jose Manuel Fernandez-Real	University of Girona	Spain
Prof Eline Van der Beek	Danone Nutricia Research Utrecht & University of Groningen	The Netherlands
Prof Lora Heisler	University of Aberdeen	UK
Dr Aniko Korosi	University of Amsterdam	The Netherlands
Prof Alex Johnstone	University of Aberdeen	UK
Prof Lucia Reisch	Copenhagen Business School	Denmark

BRAINFOOD aims to:

- Stimulate the development of novel concepts that support design of foods/beverages for brain health.
- Provide new opportunities and incentives for scientists to bridge the gap in knowledge of how nutrition impacts on brain health.

- Stimulate the interest of funders (including industry) in supporting development of specific nutritions for target life stage groups (elderly, new-born, people at risk to develop mood (and other mental) disorders.
- Provide an exchange platform (knowledge and know-how) on how to address key questions and foster new collaborations based on the collective expertise of our group.
- Provide a knowledge base that can be used not only by the scientific community but also for all stakeholders that seek precise knowledge (separating fact from fiction) about the evidence base on how foods impact on brain health. These include the Food industry, Health care professionals, journalists, Public Health institutions, academia (seek funding for PhD students), policy makers and patient organizations. Social media will be exploited to develop targeted information that could reach all the above-mentioned categories, in addition to the general public (this could be achieved, e.g., by having an ad hoc twitter account that could be used as a platform to disseminate results and key messages on nutrition and health).

The BRAINFOOD cluster organised 3 activities of which the details can be found here below.

1. BRAINFOOD-cluster core group meeting, September 30, 2020, online
2. Stakeholder workshop, October 18-19, 2021, hybrid (Brussels and online)
3. Policy meeting, September 22nd, 2022, hybrid (Brussels and online)

BRAINFOOD-cluster core group meeting, September 30, 2020, online

The BRAINFOOD-cluster established a core group of external experts that aims to influence the EU agenda to improve brain health via nutrition and better understand the relationship between nutrition and brain health. The following organisations are part of this core group:

- Associations : ILSI Europe ; EAN ; EFNA ; GAMIAN ; EPA
- Industry: Danone
- Research: University of Leeds Human Appetite Research Unit; ISS · Center for Behavioral Sciences and Mental Health
- The core group members will be involved in the preparation for the 2 BRAINFOOD meetings and define the agenda. During these meetings, the strategy will be discussed, an agenda defined for the meetings and a list of stakeholders to invite for these meetings will be completed.

12 participants joined the meeting.

The agenda can be found here below.

11:00: Welcome and introduction to BRAINFOOD (Roger Adan)

11:05: Tour the table of core members (All)

11:15: Presentation of BRAINFOOD general objectives (Roger Adan/Suzanne Dickson)

11:20: Presentation of the BRAINFOOD consensus workshop agenda: Priorities, enabling actions and expected outcome (Roger Adan/Suzanne Dickson)

11:30: Feedback and discussion on the proposed objectives, consensus workshop agenda and stakeholders to invite (All)

11:55: Wrap up and next steps

The outcome of this meeting was written down in a short internal meeting report.

Stakeholder workshop, October 18-19, 2021, hybrid

On 18 and 19 October, the BRAINFOOD leadership came together in Brussels and online with relevant stakeholders from patient organisations, industry, etc. The aim was to reach consensus on problems and (knowledge) gaps in the field and to hear the different perspectives (i.e., researcher, clinician, patient, industry, health economy, etc).

16 participants joined the meeting.

The agenda can be found here below.

Day 1, 18 October 2021, 12:00 - 17:00 CET

12:00 - 13:00: Lunch

13:00 - 13:05: **Welcome**

Roger Adan, University Medical Center (UMC) Utrecht, NL

Suzanne Dickson, University of Gothenburg, SE

13:05 - 13:10: **The European Brain Research Area (EBRA)**

Frédéric Destrebecq (EBC, Brussels, BE))

13:10 - 13:25: **Introduction to BRAINFOOD cluster**

Roger Adan UMC Utrecht, NL

Suzanne Dickson, University of Gothenburg, SE

13:25 - 13:30: Q & A

13:30 - 14:15: **State of the art of the BRAINFOOD field**

- Nutrition and Cognitive Function

  Louise Dye, University of Leeds, UK

  Followed by discussion

- (14.00h) Gut-brain axis - What are the limits in our understanding?

  John Cryan, University of Cork, IR

14:15 - 14:30: **Discussion** around the problems and gaps in the BRAINFOOD field

Chairs: Suzanne Higgs, University of Birmingham, UK; Roger Adan UMC Utrecht, NL

14:30 - 14:50: Break

14:50 - 15:20: **Clinician perspective**

- Nutrition and psychiatry: neurodevelopmental disorders

  Jan Buitelaar, Radboud University, Nijmegen, NL

- Nutrition and Neurology: neurodegenerative disorders

  Tobias Hartmann, Deutsches Institut für Demenzpräventio, Homburg, Germany

15:20 - 15:50: **Discussion** around the problems and gaps in knowledge for food for mental health

Chairs: Francesca Cirulli, Istituto Superiore di Sanità, Rome, IT; Louise Dye, University of Leeds, UK

15:50-16:00: Break

16:00-16:30: **Patient/consumer perspective, prevention and how to communicate about nutrition**

- Patients' considerations on nutrition and mental health: how to influence?

  Erik Van der Eycken, GAMIAN-Europe, a patient-driven pan-European organisation, Brussels, BE

- Responding to consumers demand for evidence-based nutritional science affecting brain health

  Lucie Geurts, International Life Sciences Institute – ILSI, Brussels, BE

16:30-17:00: **Discussion on proving the potential**

Chairs: Suzanne Dickson, UGOT, SE; Suzanne Higgs, University of Birmingham, UK

19:00 – 22:00: Dinner

Day 2, 19 October 2021, 9:00 - 12:00 CET

9:00- 9:30: **The proof of the pudding is in the eating:**

Evaluating ways to improve dietary choices: a health economics perspective

Stephanie von Hinke, University of Bristol (UK) and Erasmus University Rotterdam (NL)

- 'Effects of nutritional interventions to support brain health: the industry perspective' *Eline van der Beek, Nestlé Institute for Health Sciences, Nestlé Research, Lausanne, CH*

9:30-12:00: **Discussion and writing consensus**

Chairs: Francesca Cirulli, Istituto Superiore di Sanità, Rome, IT; Suzanne Dickson, UGOT, SE

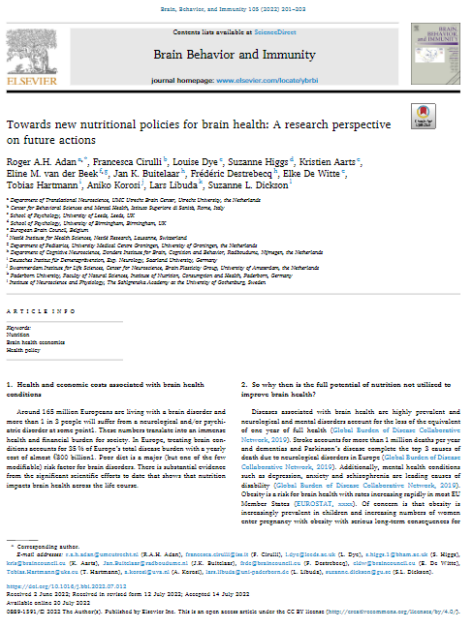
END

13:00 – 15:00: **Writing of the report with smaller group**

Aarts, Dickson, Cirulli, Higgs, Dye, Adan

And others who are interested to help

The discussions and insights gained were written down in publication:


Brain, Behavior, and Immunity 105 (2022) 201–203

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Towards new nutritional policies for brain health: A research perspective on future actions

Roger A.H. Adan, Francesca Cirulli, Louise Dye, Suzanne Higgs, Kristien Aarts, Eline M. van der Beek, Jan K. Buitelaar, Frédéric Destrebecq, Elke De Witte, Tobias Hartmann, Aniko Korosi, Lars Libuda, Suzanne L. Dickson

ARTICLE INFO

Keywords:
Nutrition
Brain health economics
Health policy

1. Health and economic costs associated with brain health conditions

Around 165 million Europeans are living with a brain disorder and more than 1 in 3 people will suffer from a neurological and/or psychiatric disorder at some point1. These numbers translate into an immense health and financial burden for society. In Europe, treating brain conditions accounts for 28 % of Europe's total disease burden with a yearly cost of almost €800 billion1. Poor diet is a major (but one of the few modifiable) risk factor for brain disorders. There is substantial evidence from the significant scientific efforts to date that shows that nutrition impacts brain health across the life course.

2. So why then is the full potential of nutrition not utilized to improve brain health?

Diseases associated with brain health are highly prevalent and neurological and mental disorders account for the loss of the equivalent of one year of full health (Global Burden of Disease Collaborative Network, 2019). Stroke accounts for more than 1 million deaths per year and dementias and Parkinson's disease complete the top 3 causes of death due to neurological disorders in Europe (Global Burden of Disease Collaborative Network, 2019). Additionally, mental health conditions such as depression, anxiety and schizophrenia are leading causes of disability (Global Burden of Disease Collaborative Network, 2019). Obesity is a risk for brain health with rates increasing rapidly in most EU Member States (EUROSTAT, xxxx). Of concern is that obesity is increasingly prevalent in children and increasing numbers of women enter pregnancy with obesity with serious long-term consequences for

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https://doi.org/10.1016/j.bbi.2022.07.012
Received 2 June 2022; Received in revised form 12 July 2022; Accepted 14 July 2022
Available online 20 July 2022
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Adan RAH, Cirulli F, Dye L, Higgs S, Aarts K, van der Beek EM, Buitelaar JK, Destrebecq F, De Witte E, Hartmann T, Korosi A, Libuda L, Dickson SL. Towards new nutritional policies for brain health: A research perspective on future actions. Brain Behav Immun. 2022 Jul 20;105:201-203. doi: 10.1016/j.bbi.2022.07.012. Epub ahead of print. PMID: 35868600.

Policy meeting, September 22nd, 2022, hybrid

During the final meeting of the BRAINFOOD cluster in Brussels and online, the outcomes of their previous meetings were communicated to the broader brain and nutrition community including policy makers.

88 participants signed up to join the meeting.

The agenda can be found here below.

12:00 - 13:00:	**Lunch**
13:00 - 13:15:	**Welcome and introduction to the BRAINFOOD cluster**
	Prof. Roger Adan, University Medical Center (UMC) Utrecht, NL
	Prof. Suzanne Dickson, University of Gothenburg, SE
13:15 - 13:40:	**Opening talk**
	Prof. Felice Jacka, International Society for Nutritional Psychiatry Research
13:40 – 14:15	**Towards new nutritional policies for brain health: A research perspective on future actions.**
	Prof. Eline Vanderbeek, Nestlé Research, CH / University of Groningen, NL
	Prof. Louise Dye, University of Leeds, UK
14:15 – 14:55	**Round table**
	Prof. Tobias Hartmann, Deutsches Institut für Demenzprävention, Homburg, DE
	Dr. Isabelle Guelinckx, International Life Sciences Institute – ILSI, Brussels, BE
	Prof. Felice Jacka, International Society for Nutritional Psychiatry Research, AU
	Prof. Eline Vanderbeek, Nestlé Research, CH / University of Groningen, NL
	Prof. Louise Dye, University of Leeds, UK
	Prof. Jochen Seitz, University Hospital RWTH Aachen, DE

Chair: Prof. Suzanne Higgs, University of Birmingham, UK

14:55 – 15:00 **Closing remarks**

Prof. Roger Adan, University Medical Center (UMC) Utrecht, NL

Prof. Suzanne Dickson, University of Gothenburg, SE

15:00 – 16:30: **Networking coffee**

The outcome of the meeting was written down in a report (see below).

Meeting report

On 22 September 2022 a final meeting was held in Brussels of the EBRA BRAINFOOD cluster with the title: What actions improve nutrition for brain health for European citizens? The meeting was attended by 90 stakeholders ranging from scientists and clinicians to patient organizations and consultants. The meeting started with introductions of Prof Felice Jacka (Australia, Food and Mood center), Prof Eline van der Beek (Nutricia Research, Lausanne) and Prof Louise Dye (Health psychologist, Leeds). It was shown that nutritional interventions for brain health are cost effective and improve mental health of people suffering from depression. The full potential of nutrition for brain health has not been utilized. This was the topic of a panel discussion.

It was concluded that healthy nutrition for brain health is a responsibility of policy. For the food industry/private sector there is little or no return on investment for research in this area, except for specific food components, where an application for a health claim is possible. Therefore, the responsibility to generate the scientific evidence relies on public funding from the European Commission and the member states.

Healthy nutrition for the brain requires access to safe, nutritious and affordable diets throughout life for all citizens. What a healthy diet is, depends on life stage (infancy, pregnancy, adolescence and elderly) and it is not a matter of losing weight because the mechanisms underlying obesity and mental disease differ.

Most citizens report they would change their diet if it is proven that is better for their mental health. In order for better education for promotion of healthier eating we first need more evidence to show the link between diet and brain health. To eat healthy is not your own responsibility! Money devaluation for instance results in poorer diets.

Further reading:

Nutritional psychiatry: Towards improving mental health by what you eat. Adan RAH, van der Beek EM, Buitelaar JK, Cryan JF, Hebebrand J, Higgs S, Schellekens H, Dickson SL. Eur Neuropsychopharmacol. 2019 Dec;29(12):1321-1332.

Towards new nutritional policies for brain health: A research perspective on future actions. Adan RAH, Cirulli F, Dye L, Higgs S, Aarts K, van der Beek EM, Buitelaar JK, Destrebecq F, De Witte E, Hartmann T, Korosi A, Libuda L, Dickson SL. Brain Behav Immun. 2022 Oct;105:201-203

5. Predictive Model Systems (PREMOS) cluster

The primary objective of the PREDICTIVE MODEL SYSTEMS (PREMOS) cluster is to enhance the alignment of EU disease model development resources and preclinical research expertise with clinical and brain research community needs across academia and industry.

The proposed Predictive Model Systems Cluster is formed based on several large networks and current EU funded consortia, which join forces to propel disease modelling capacities and expertise for neuroscience research in Europe and beyond.

The International Mouse Phenotyping Consortium (IMPC) is an international effort of 20 globally distributed research institutions to identify the function of every protein-coding gene in the mouse genome.

- INFRAFRONTIER Research Infrastructure
- PRISM – Psychiatric Ratings using Intermediate Stratified Markers brings together academic experts, SMEs, patient and family organisations, regulators, ECNP and EFPIA partners.
- EQIPD – European Quality in Preclinical Data

Coordinator: Prof. Sabine Hölter-Koch, Helmholtz Zentrum München, Germany

Co-coordinator: Prof. Yann Hérault, Institute of Genetics and Molecular and Cellular Biology, Strasbourg, France

Surname	**First name**	**Organisation**	**Consortium**	**PREMOS relevant role**	**City/ Country**
MacLeod	Malcolm	University of Edinburgh	EQIPD	EQIPD project coordinator	Edinburgh, UK
Steckler	Thomas	Janssen Pharmaceutica	EQIPD	EQIPD project leader	Beerse, Belgium
Bespalov	Anton	PAASP	EQIPD	EQIPD WP leader	Heidelberg, Germany
Kas	Martien	University of Groningen	EQIPD PRISM	PRISM project coordinator	Groningen, Netherlands
Hengerer	Bastian	Boehringer Ingelheim	PRISM	PRISM preclinical WP lead	Biberach, Germany
Hölter	Sabine	Helmholtz Zentrum München	INFRAFRONTIER IMPC	PREMOS cluster coordinator	Munich, Germany
Hrabé de Angelis	Martin	Helmholtz Zentrum München	INFRAFRONTIER IMPC	INFRAFRONTIER project coordinator, GMC director	Munich, Germany
Wurst	Wolfgang	Helmholtz Zentrum München	INFRAFRONTIER IMPC	EuMMCR director	Munich, Germany
Sedlacek	Radislav	Czech Centre for Phenogenomics	INFRAFRONTIER IMPC	CCP director	Prague, Czech Republic
Herault	Yann	Institute of Genetics and Molecular and Cellular Biology	INFRAFRONTIER IMPC	PHENOMIN-ICS director	Strasbourg, France
Wells	Sara	MRC Harwell	INFRAFRONTIER IMPC	Mary Lyon Centre director	Harwell, UK
Brown	Stephen	MRC Harwell	INFRAFRONTIER IMPC	MRC Harwell director	Harwell, UK

Specific objectives are to:

- Improve communication (channels) between disease modelling and brain research communities.
- Develop shared research priorities aligned to brain research and biopharmaceutical innovation community needs.
- Enhance resource and data sharing using European Research Infrastructures.
- Enhance data integration between high dimensional clinical and model data.
- Prioritise resource development needs (predictive rodent preclinical models).
- Develop joint back-translation strategies informing preclinical model development.
- Harmonise/standardize protocols for preclinical research (phenotyping assessments).
- Expand network of disease modelling experts with focus on brain research (across model systems and integrating in-vivo, in-vitro and in-silico approaches).
- Robust, rigorous, and reliable CNS preclinical science and data inform R&D decision-making.

The PREMOS cluster organised 3 activities of which the details can be found here below.

1. 1st PREMOS cluster event: 3 working groups on the translational Models of Animal Models
    - Working Group 1, March 19th, 2021, online
    - Working Group 2, July 1st, 2021, online
    - Working Group 3, October 11th, 2021, in-person (Brussels)
2. Stakeholder meeting on translational value of animal models, April 1st, 2022, online
3. Policy meeting, September 22nd, 2022, hybrid (Brussels and online)

3 working groups on the Translational Models of Animal Models

Working Group 1, March 19th, 2021, online

As part of its first activity, the PREMOS EBRA cluster held its first working group meeting on the translational value of animal models on 19th March 2021. In preparation for the meeting, a survey had been conducted among cluster members about the most important translational gaps. During the meeting, the coordinators of the 3 main large networks INFRAFRONTIER, PRISM and EQIPD discussed the priorities of their networks with respect to the identified translational gaps. This included a detailed discussion on "**Humanization" of mouse models,** the contexts in which this is helpful and where the limitations are. A consensus was reached that considering the **environment and epigenetic signatures of life history and events** is important to improve the translational value of models. **Cross disorder relevance of phenotypes** was considered another important aspect requiring further attention, as well as what is defined as "animal model".

19 participants attended this working group.

The agenda can be found here below.

11:00 – 11:05	Welcome and introduction to EBRA
	European Brain Council

11:05 – 11:15	Tour de table
11:15 – 11:25	Presentation of survey results *Dr. Sabine Hölter*
11:25 – 11:40	Presentation of PRISM perspective: The reverse translation of a quantitative neuropsychiatric framework into preclinical studies *Prof. Martien Kas*
11:40 – 12:10	Discussion about neurobiology-related gaps Moderated by *Dr. Sabine Hölter*
12:10 – 12:20	*Break*
12:20- 12:35	Presentation of INFRAFRONTIER perspective *Dr. Michael Raess*
12:35 – 13:05	Discussion of Infrafrontier topic page Moderated by *Dr. Sabine Hölter*
13:05 – 13:20	Presentation of EQIPD perspective Dr. *Thomas Steckler*
13:20- 13:35	Discussion about data quality-related gaps Moderated by *Dr. Sabine Hölter*
13:35 – 14:00	Preparation of working group activities 2 and 3, next steps. *Dr. Sabine Hölter*

Minutes were taken during this meeting and shared with the working group.

Working Group 2, July 1st, 2021, online

In the 2nd WG meeting clinicians were asked about their requirements for animal models to be considered clinically relevant and having predictive value. The main answers were: “symptom similarity” and „similar responses to drugs” between the models used and humans. The attending clinicians and industry partners also considered the investigation of genetic contributions to neuropsychiatric diseases a valuable approach, and they advocated for a staggered use of different model systems to optimize the predictive validity of preclinical studies.

19 participants attended this working group.

The agenda can be found here below.

13:00 – 13:05	Welcome *Dr. Sabine Hölter*
13:05 – 13:15	Tour de table
13:15 – 13:20	Introduction to PREMOS *Dr. Sabine Hölter*
13:20 – 13:30	Results of first workgroup meeting *Prof. Yann Herault*

13:30 – 14:50	Discussion about requirements for clinical relevance of preclinical models
	Moderated by Dr. Sabine Hölter
14:50 – 15:00	Break
15:00- 15:30	Wrap up and further discussion points
	Moderated by Prof. Martien Kas
15:30 – 15:55	Next steps, plans for 3. WG meeting in Brussels
	Dr. Michael Raess
15:55 – 16:00	Closing remarks
	Dr. Sabine Hölter

Minutes were taken during this meeting and shared with the working group.

Working Group 3, October 11th, 2021, Brussels

The 3rd WG meeting picks up on previous discussion points and primarily work on a consensus within the cluster on the way forward to present to the stakeholders in our following activity, the stakeholder meeting. The stakeholder meeting will also include patient groups, and their views and feedback will need to be included for the last activity, the consensus meeting. 12 participants attended this working group. The agenda can be found here below.

14:00 – 14:05	Welcome
	Dr. Sabine Hölter
14:05 – 14:15	EBC/EBRA welcome
	Dr. Kristien Aarts
14:15 – 14:30	Goals of 3rd WG meeting
	Dr. Sabine Hölter
14:30 – 15:00	Predictive validity of animal models in PRIME
	Dr. Simone Macri
15:00 – 15:30	Advancing Neuropsychiatric Targets through integrative human and preclinical disease models
	Dr. Magali Haas
15:30 – 16:00	*Break*
16:00 – 16:20	Discussion about European Parliament resolution on animal experiments
	Moderated by *Dr. Jan Rozman*
16:20 – 16:45	Discussion on 3 key messages, preparation of stakeholder meeting
	Moderated by *Dr. Yann Herault*
16:45 – 17:00	Wrap-up and Closing remarks
	Dr. Sabine Hölter

Minutes were taken during this meeting and shared with the working group.

Stakeholder meeting on translational value of animal models, April 1st, 2022, online

During this meeting, the PREMOS cluster liaised with the PERMIT (PERsonalised Medicine Trials) project. First, the results of previous PREMOS cluster working group meetings and the results of the PERMIT (PERsonalised Medicine Trials) project were presented. After, the meeting attendees discussed about the suggestions on how to increase the predictive value of model systems for clinical trials resulting from this previous work of PREMOS and PERMIT. 25 participants attended this meeting. The agenda can be found here below.

9:00 – 9:05	Welcome *Dr. Sabine Hölter*
9:05 – 9:20	Tour de table
9:20 – 9:30	EBC/EBRA welcome *Frédéric Destrebecq/Dr. Kristien Aarts/Dr. Elke de Witte*
9:30 – 9:45	Introduction to PREMOS aims and goals of the meeting *Dr. Sabine Hölter*
9:45 – 10:00	Lessons learnt from PERMIT project - Recommendations for robust and reproducible preclinical research in personalised medicine *Dr. Vibeke Fosse/Dr. Emanuela Oldoni*
10:00 – 10:30	Feedback discussion on first 3 positions/questions Moderated by *Dr. Sabine Hölter*
10:30 – 10:45	*Break*
10:45 – 11:45	Continuation of feedback discussion on further positions/questions, preparation of consensus meeting Moderated by *Dr. Sabine Hölter*
11:45 – 12:00	Wrap-up and Closing remarks *Dr. Sabine Hölter*

The meeting outcomes were written down in an executive summary which can be found here below.

Executive summary

The stakeholder meeting was Activity 2 of the PREMOS cluster, conducted as online meeting on April 1st, 2022, 9-12 am CEST. Because both projects have similar goals, the attendees were first informed about: • Results of previous PREMOS cluster working group meetings, including the identification of translational gaps in a survey among cluster members and the discussion with clinicians about prerequisites for clinical relevance of model systems • Results of the PERMIT (PERsonalised Medicine Trials) project, in particular their recommendations for robust and reproducible preclinical research in personalized medicine The main part of the PREMOS stakeholder meeting was the following discussion about the suggestions how to increase the predictive value of model systems for clinical trials resulting from this previous work of PREMOS and PERMIT. The open and critical discussion resulted in the following conclusions:

It is important to invite patient organisations into preclinical research discussions because we need their input to make models relevant, as patients and clinicians do not always concur on what is a priority focus.

1. To achieve this, the language must be more accessible and common to non-experts in the field, and relationships with patient organisations must be nurtured.
2. We need to communicate openly and transparency to normalize the role of animal models in scientific research within the public consciousness.

3. It was consensus among participants that animal studies can test for causality of human clinical findings and that they can expand our knowledge at the mechanistic level.

4. There was agreement that animal models contribute significantly to proving genetic causality in rare neurodevelopmental or neurodegenerative diseases.

5. As the majority of psychiatric disorders are complex, a suggestion also needs to be developed for complex disorders until the PREMOS consensus meeting.

6. Access to existing animal models and their detailed information, including negative results as e.g. available for IMPC models, through national, European and global repositories needs to be reinforced. The extent and regulation of the access, including a grace period for the provider, need to be further debated.

7. To ensure clinical relevance, the biological mechanisms and functions studied in a model must be similar to humans, taking into account species specificity. The use of literature to establish that a model is clinically relevant for the question asked should be reinforced. Symptom, target and drug response similarity are important aspects for clinicians. Preclinical evidence justifying clinical trials should be based on the use of multiple models, not only one, to increase the predictive value of the preclinical evidence for translational success.

8. To enable the provision of clinically relevant model systems, it should be mandatory that human studies provide quantitative and biological data to optimize back-translation of human clinical findings. Closer interactions between preclinical scientists and clinicians need to be fostered on a larger scale to reduce the number of animal studies with irrelevant outcomes.

9. Further discussion is needed on the question if primary endpoints for clinical trials should be based on the indicated quantitative biological and translational parameters used for back translation. Changing of primary endpoints would hamper meta-analyses, and there may be primary endpoints that are relevant for patients but not apt to back-translation.

10. In the position paper resulting from the PREMOS cluster activities, it would be useful to address and respond to the EU goal to eliminate animal research.

Consensus meeting on translational value of animal models, July 1st, 2022, hybrid

On July 1st, 2022, the importance of animal research in neuroscience as well as the outcomes from the previous PREMOS cluster meetings was presented to the broader audience including funders, policymakers, industry, researchers, clinicians, patients, etc. In total, 18 participants attended the meeting in Brussels and 67 online.

The agenda can be found here below.

10:00 – 10:10	Welcome and introduction
	Dr. Sabine Hölter-Koch, PREMOS Cluster Coordinator
10:10 – 10:20	Relevance of animal models in scientific research
	Kirk Leech, EARA Executive Director
10:20 – 10:30	Patient perspective
	Dr. Orla Galvin, EFNA Executive Director
10:30 – 10:40:	The role of animal models for brain research
	Prof. Jean-Antoine Girault, FENS president
10:40 – 10:55:	Testimonies from fundamental and preclinical brain research
	Ass. prof. Tomas Ryan, Trinity College Dublin
	Ass. prof. Thomas McWilliams, University of Helsinki
10:55 – 11:10:	PREMOS cluster issues and challenges

Prof. Yann Hérault, PREMOS Cluster Co-coordinator

11:10 – 11:25: Recommendations for increasing translational value of animal models

Dr. Sabine Hölter-Koch, PREMOS Cluster Coordinator

11:25 – 11:55 Panel Q&A with the audience

Moderated by Frédéric Destrebecq, EBC executive director

Dr. Orla Galvin, EFNA Executive Director

Dr. Sabine Hölter-Koch, PREMOS Cluster Coordinator

Prof. Jean-Antoine Girault, FENS president

Kirk Leech, EARA Executive Director

11:55 – 12:00 Closing remarks

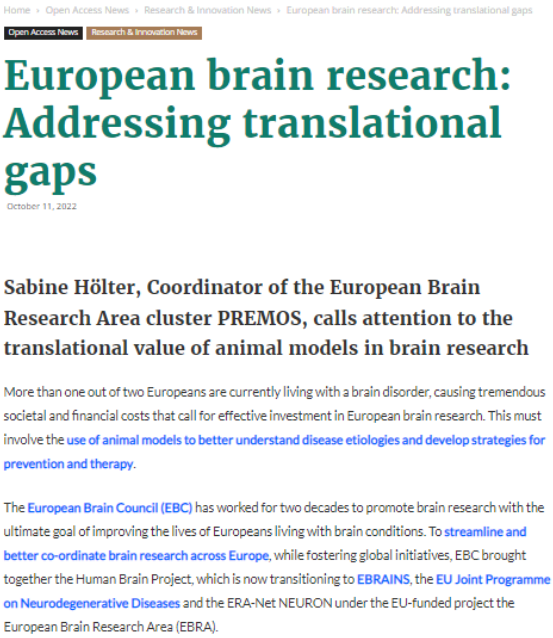
Dr. Sabine Hölter-Koch, PREMOS Cluster Coordinator

12:00 – 13:00 Networking lunch

The outcome of this meeting has been published in the October edition of the Open Access Government journal:

Hölter, S. (2022). European brain research: Addressing translational gaps. Open Access Government.

https://www.openaccessgovernment.org/european-brain-research-addressing-translational-gaps/145399/



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European brain research: Addressing translational gaps

October 11, 2022

Sabine Hölter, Coordinator of the European Brain Research Area cluster PREMOS, calls attention to the translational value of animal models in brain research

More than one out of two Europeans are currently living with a brain disorder, causing tremendous societal and financial costs that call for effective investment in European brain research. This must involve the use of animal models to better understand disease etiologies and develop strategies for prevention and therapy.

The European Brain Council (EBC) has worked for two decades to promote brain research with the ultimate goal of improving the lives of Europeans living with brain conditions. To streamline and better co-ordinate brain research across Europe, while fostering global initiatives, EBC brought together the Human Brain Project, which is now transitioning to EBRAINS, the EU Joint Programme on Neurodegenerative Diseases and the ERA-Net NEURON under the EU-funded project the European Brain Research Area (EBRA).

6. European Cluster for Imaging Biomarkers (ECIB)

The European Cluster for Imaging Biomarkers (ECIB) forges a complementary and synergetic harmonization alliance across major European consortia, networks and platforms engaged in multicentric collection, curation, transfer, and analysis of “big-imaging-data”. The ECIB ambition is to achieve transformative leaps in the translation of “big-imaging-data”-research into scientific and medical innovations by creating critical synergies between neuroimaging projects at both European

and global level. In the big picture, we aspire to become instrumental in unlocking the full potential of new tools, technologies, and digital solutions for a healthy society.

ECIB has formed a highly inclusive Cluster of “big-imaging-data” projects from JPND, Horizon2020, and IMI. These projects are supplemented by National Neuroimaging Platforms of France, Italy and Germany and one of the largest national multicentric imaging biomarker consortium, the Swedish BioFINDER Study. This Cluster will weave together large European projects of different entities (Consortia, Networks, and Platforms) for a common greater goal: deploying latest advances in data science, computing, and imaging technologies to develop imaging biomarkers supporting personalized diagnostics and treatments in brain disorders.

Coordinator: Thilo van Eimeren, MD, University of Cologne, Germany

Co-Coordinator: Stefano Cappa, MD, University of Pavia, Italy

- Hartwig Siebner, Copenhagen University Hospital Hvidovre Denmark
- Emrah Düzel University of Magdeburg Germany
- Oliver Speck University of Magdeburg Germany
- Arfan Ikram Erasmus MC, Rotterdam Netherlands
- Andreas H. Jacobs University Muenster Germany
- Daniela Perani San Raffaele University Italy
- Gaelle Chetelat INSERM, Caen France
- Laura Wisse Lund University Sweden
- Giovanni B. Frisoni University of Geneva Switzerland
- Jorge Jovicich University of Trento Italy
- Dag Aarsland Stavanger University Hospital Norway
- Silvia Morbelli University of Genoa Italy
- Frederik Barkhof VU University Medical Center - Amsterdam Netherlands
- Bertrand Thirion Institut National de Recherche en Informatique et en Automatique France
- Svenja Caspers University of Dusseldorf Germany
- Petra Ritter Charite Berlin Germany
- Stephane Lehéricy Sorbonne France
- Oskar Hansson Lund University Sweden
- Fabrizio Tagliavini Istituto Neurologico "Carlo Besta" Milan Italy

The ECIB organised 2 activities of which the details can be found here below.

1. Leadership meeting to develop a survey on the sharing of brain imaging data, May 10th, 2021, online
2. Consensus meeting, April 7-8, 2022, hybrid (Brussels and online)

Meeting to develop a survey on the sharing of brain imaging data, May 10th, 2021, online

On May 10th, 2021, the ECIB leadership came together online for a structured examination and recording of viewpoints, positions and approaches with regard to chances, challenges and limitations on sharing brain imaging data in online data repositories, particularly considering open access under the requirements of EU data protection laws from an investigator's perspective.

In total, 21 participants attended the meeting.

The following points were on the agenda:

1. Introduction of ECIB and aims of the project
2. Presentation of survey activity (aims, target audience, methods)
3. Discussion of survey content (categories, questions, answer categories)
4. Next steps and timeline

Minutes were taken during this meeting and shared with the ECIB leadership.

Consensus meeting, April 7-8, 2022, hybrid

The aim was to reach consensus on a statement including positions and recommendations on sharing brain imaging data in the context of Open Science. The consensus meeting consisted of members of the ECIB cluster with representatives from EU research infrastructures, funding agencies, regulators, and legal centres. In total, 8 participants joined in Brussels and 13 online. The agenda can be found here below.

Day 1, 7 April 2022, 12:00 - 17:30 CET

12:00 - 13:00	Lunch
13:00 - 13:05	**Welcome by the European Brain Council (EBC)**
	Prof. Wolfgang Oertel, EBC president
13:05 - 13:10	**Welcome by the European Cluster for Imaging Biomarkers**
	Prof. Thilo van Eimeren, MD, University of Cologne, Germany
	Prof. Stefano Cappa, MD, University Institute for Advanced Studies and IRCCS Mondino Foundation, Pavia, Italy
13:10 - 13:15	**Introduction to the European Brain Research Area (EBRA)**
	Kristien Aarts, PhD, European Brain Council
13:15 - 13:25	**Introduction to ECIB cluster**
	Prof. Stefano Cappa, MD, University Institute for Advanced Studies and IRCCS Mondino Foundation, Pavia, Italy
13:25 - 13:30	Q & A

13:30- 13:50	**Open science in future funding calls** *Konstantinos Repanas, Policy officer at the Open Science Unit, EC Directorate-General Research and Innovation (DG RTD)*
13:50 - 14:00	Q & A
14:00 - 14:20	**Presentation of the ECIB survey: Aim, methodology and results** *Kathrin Giehl, PhD, University of Cologne, Germany*
14:20 – 15:00	**Discussion of the survey results** *All*
15:00 – 15:30	**Coffee break**
15:30 – 15:40	**Why should I share my data with everyone? The need for a new scientific currency** *Prof. Thilo van Eimeren, MD, University of Cologne, Germany*
15:40 – 16:10	**Discussion and positions around the need for incentives** *All*
16:10-16:20	**How can I share my data with others? Current challenges and options for sharing brain imaging data** *Prof. Stefano Cappa, MD, University Institute for Advanced Studies and IRCCS Mondino Foundation, Pavia, Italy*
16:20-16:50	**Discussion and positions around data sharing** *All*
16:50-17:00	**Summary and wrap up**
19:00 – 22:00	Dinner
Day 2, 8 April 2022, 9:00 - 12:00 CET	
09:00- 10:00	**Consensus 1: Main obstacles of sharing brain imaging data**
10:00-10:40	Coffee break
10:40-12:00	**Consensus 2: Recommendations for the future**
12:00-13:00	Lunch break
13:00 – 15:00	**Writing of the final report on positions and recommendations regarding sharing brain imaging data in online repositories report with a smaller group** *Prof. Thilo van Eimeren, Prof. Stefano Cappa, Kathrin Giehl, PhD* *And others who are interested to help*

The outcomes of this meeting will be published in a high-level peer review journal: Kathrin Giehl, Henk Mutsaerts, Kristien Aarts, Frederik Barkhof, Svenja Caspers, Gaëlle Chetelat, Marie-Elisabeth Colin, Emrah Düzel, Giovanni Frisoni, Arfan Ikram, Jorge Jovicich, Silvia Morbelli, Wolfgang Oertel, Christian Paret, Daniela Perani, Konstantinos Repanas, Petra Ritter, Bàrbara Segura, Laura Wisse, Elke de Witte, Stefano Cappa, Thilo van Eimeren (under preparation). Sharing brain imaging data in the Open Science era. How and why?

7. Conclusions

The cluster meetings led to the following outcomes.

EPICLUSTER

Henshall DC, Guerrini R, Jozwiak S, Kokaia M, Pitkanen A, Sisodiya S, Simonato M, Cross JH, Ryvlin P, Brodie MJ, Trinka E, Sofia F. Meeting report: EpiXchange II brings together European epilepsy research projects to discuss latest advances. Epilepsy Res. 2021 Dec;178:106811. doi: 10.1016/j.eplepsyres.2021.106811. Epub 2021 Nov 14. PMID: 34814066.

Henshall et all. (under preparation): Shaping the future of European epilepsy research: final meeting report from EPICLUSTER**.**

PSMD

Fusar-Poli P, Manchia M, Koutsouleris N, Leslie D, Woopen C, Calkins ME, Dunn M, Tourneau CL, Mannikko M, Mollema T, Oliver D, Rietschel M, Reininghaus EZ, Squassina A, Valmaggia L, Kessing LV, Vieta E, Correll CU, Arango C, Andreassen OA. Ethical considerations for precision psychiatry: A roadmap for research and clinical practice. Eur Neuropsychopharmacol. 2022 Oct;63:17-34. doi: 10.1016/j.euroneuro.2022.08.001. Epub 2022 Aug 27. PMID: 36041245.

TRISOMY21

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Adan RAH, Cirulli F, Dye L, Higgs S, Aarts K, van der Beek EM, Buitelaar JK, Destrebecq F, De Witte E, Hartmann T, Korosi A, Libuda L, Dickson SL. Towards new nutritional policies for brain health: A research perspective on future actions. Brain Behav Immun. 2022 Jul 20;105:201-203. doi: 10.1016/j.bbi.2022.07.012. Epub ahead of print. PMID: 35868600.

PREMOS

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ECIB

Kathrin Giehl, Henk Mutsaerts, Kristien Aarts, Frederik Barkhof, Svenja Caspers, Gaëlle Chetelat, Marie-Elisabeth Colin, Emrah Düzel, Giovanni Frisoni, Arfan Ikram, Jorge Jovicich, Silvia Morbelli, Wolfgang Oertel, Christian Paret, Daniela Perani, Konstantinos Repanas, Petra Ritter, Bàrbara Segura, Laura Wisse, Elke De Witte, Stefano Cappa, Thilo van Eimeren (under preparation). Sharing brain imaging data in the Open Science era. How and why?