1.3.1 Non confidential section

Overall summary of AIMS-2-TRIALS progress and impact

Autism is a heterogeneous neurodevelopmental condition, affecting approximately 1 in 58 individuals in Europe. Currently, there are no effective medical treatments for the core features of autism - difficulties in social communication and restricted/ repetitive behaviours (including sensory processing differences). In addition, there is a critical need for more effective treatments for frequently co-occurring medical (e.g. epilepsy) and mental health conditions (e.g. anxiety, depression) that impact quality of life and that can significantly reduce a person's life span.

The lack of effective therapies for autism results from a combination of factors, including substantial clinical and biological heterogeneity between autistic individuals (meaning there is likely no "one-size-fits-all" treatment) and a poor understanding of underpinning mechanisms. Consequently, prior clinical trials have been hampered by the inclusion of heterogeneous samples (despite the likelihood that only *some* autistic individuals will benefit from any particular treatment), high placebo response rates and a lack of objective, clinically relevant outcome measures to assess treatment efficacy.

Thus, the AIMS-2-TRIALS consortium has brought together experts in basic science, child development, psychiatry, neuroimaging, immune/ metabolic functions, genetics and autism to develop new 'personalised medicine' approaches. A key factor in these approaches is the identification of stratification biomarkers - objective tests or measures that enable us to identify more clinically relevant biological subgroups within autism and predict each individual's likely therapeutic needs, in order to better tailor treatments. Furthermore, the consortium aims to: develop new, objective outcome measures to assess the effectiveness of treatments that are acceptable to autistic people; and to create a sustainable clinical trials network across the EU to facilitate clinical trials and test new therapies.

Over the first two years of the project, AIMS-2-TRIALS has made significant progress in six key areas:

1. Creating a world-wide unique set of linked multidisciplinary longitudinal research studies from infancy to adulthood

Since 2018, the AIMS-2-TRIALS consortium has established a world-wide unique, multidisciplinary longitudinal research platform to identify and validate biomarkers for autism. The AIMS-2-TRIALS linked clinical cohorts comprise over 1,500 individuals from infancy to adulthood, comprehensively characterised by their clinical, cognitive and behavioural profiles, brain structure and function and genomics. This dataset significantly extends upon existing cohort studies set up in EU-AIMS - the STAARS project of early development in infants at increased familial likelihood of autism; and the Longitudinal European Autism Project (LEAP) of autistic and non-autistic individuals aged 6-30-years. We now also:

- Start at the earliest timepoint by studying fetal and neonatal brain development in those with elevated familial likelihood of autism.
- Include the first European multi-center MRI study of preschoolers with autism (Preschool Brain Imaging and Behaviour project) - directly responding to prior advice from the European Medicines Agency (EMA) to validate stratification biomarkers in young children.
- Study autism and related neurodevelopmental conditions cross-culturally in 4,500 South African children with increased environmental risk factors for social, emotional and cognitive difficulties.
- Compare two rare monogenic forms of autism – Phelan McDermid Syndrome and NRXN1 deletion – in the Synaptic Gene Project.

Through the unparalleled scale and depth of phenotyping in these linked clinical cohorts, we aim to improve understanding of individual differences in the mechanisms underpinning both core and associated autism features and translate these into clinical practice. This approach is crucial, since previous research results from EU-AIMS LEAP highlighted that there is no single behavioural, cognitive

or genetic characteristic shared by all autistic people and thus no single treatment approach that would be effective for every autistic person.

2. Progress in biomarker discovery and validation

Over the past year, the group has made significant progress in the identification and validation of stratification biomarkers for autism, based on data collected in EU-AIMS STAARS and LEAP. For example, we have shown that neonates and infants at elevated familial likelihood for autism exhibit differences in early brain development (increased functional connectivity in sensory/ face processing regions; cerebellum enlargement) and attenuated brain responses to motion and face stimuli, on average. Furthermore, over 36 LEAP analysis projects have been launched or completed, including markers based on cognitive profile, EEG, eye-tracking, resting state functional connectivity and structural MRI. From these projects, we have already discovered 11 candidate stratification or prognostic biomarkers, with validation steps in various stages of implementation.

Most notably, in collaboration with industry partners, we have achieved significant progress working to obtain regulatory approval for a stratification biomarker based on EEG measurement of brain response to faces. The EEG signal to faces marker has been independently replicated in a US cohort by the National Institute of Health Autism Biomarker Consortium-Clinical Trials (NIH ABC-CT), becoming the first ever biomarker in autism to be accepted into the Food and Drug Administration (FDA) biomarker development programme. We have also engaged with the EMA to obtain qualification advice on this biomarker and received supportive feedback.

In addition, we identified robust evidence for altered resting-state functional connectivity in autism, in a study of over 1,500 individuals from across three independent cohorts. To further develop upon these analyses, we have published standardised methodological protocols for conducting 'normative modelling' to assess how each autistic *individual* in a given sample diverges from age (and/ or sex) expected norms, in terms of their brain development, social or cognitive function. These innovative methods have allowed us to move from predictions at the group level to making individual predictions about a particular person with autism - crucial for precision medicine approaches.

We (**RUMC, KCL, INSERM, IP, BC, KI, UGENT, APHP**) also secured independent Horizon 2020 funding to ascertain whether the panel of stratification biomarkers identified from AIMS-2-TRIALS cohort studies are autism-specific or shared with other neurodevelopmental conditions, such as attention-deficit/ hyperactivity disorder (CANDY project). The CANDY database will be built on the same principles as AIMS-2-TRIALS and will share overlapping measures and data analytic strategies to promote optimal cross-talk between projects.

These advances will support industry partners in reducing the time and cost of clinical trials in neurodevelopmental conditions, through facilitating regulatory alignment between Europe and the US and minimising placebo effects (by incorporating stratification biomarkers to balance treatment and placebo trial arms).

3. Launching innovative clinical trials, enhanced by biomarkers

AIMS-2-TRIALS is the first neuropsychiatric consortium in Europe to incorporate candidate biomarkers in clinical trials of autism. For instance, this year we launched a randomised-controlled trial of arbaclofen, targeting social functioning. The arbaclofen trial incorporates EEG assessment and 'wearable' measures (e.g. smart watches) of physiology in everyday life, to ascertain whether treatment may be more effective in particular autism subgroups and/ or whether physiological responses are a valid, objective measure of treatment effects.

Demonstrating the value of the CTN, many of our centres were selected by industry (and provided with additional resources by them) to take on extra trials in ASD. Also, the PI (Murphy) acted as EU lead for one trial (Balovaptan) of our industrial partners (Roche). Specifically, we have already been given extra support by industry partners to deliver three multicentre clinical trials - a phase 3 trial of balovaptan for adults, a phase 1 trial of balovaptan in children and a phase 3 trial of bumetanide for autistic young people. None of these trials compromised our own trial. We further worked with industry partners to develop robust clinical outcome measures for restricted and repetitive behaviours, ensuring the highest

standards for assessing the efficacy of clinical trials in autism, including those run as part of AIMS-2-TRIALS, Work Package 4.

We will extend this work in Part 2 of the project to accelerate more innovative clinical trial designs, also taking forward the most promising of eight candidate compounds (as identified by our new 'Trial Advisory Board', comprised of experts in academia, industry, charities, regulatory bodies and the autism community) for the next clinical trial in Part 2.

4. Identifying and testing novel treatment targets

To identify and test novel treatment targets in neurodevelopmental conditions, we have overseen the translation of preclinical work in cellular and rodent models to advances in human studies. For instance, we discovered signalling dysfunction in the ventral tegmental area (associated with social/ reward processing) of Nlgn3 mutant mice, providing a mechanism-based rationale for testing the effectiveness of arbaclofen for modifying brain responses in mouse models. This work links to both the arbaclofen trial (outlined above) and promising preliminary findings from our proof of concept studies, of arbaclofen and tianeptine, which provide the first evidence that: 1) differences in visual sensory processing in autistic, as compared to non-autistic, adults can be 'shifted' using arbaclofen; and 2) differences in brain activation during executive function can be shifted by targeting the serotonin system with tianeptine.

5. Creating a sustainable infrastructure for future clinical trials of autism across Europe

We conducted meta-analyses to determine reasons for failure of previous clinical trials in autism (e.g. placebo effects, use of caregiver vs. clinician symptom ratings, heterogeneous samples) and delivered a white paper on innovative clinical trial designs to overcome these challenges. We have also further expanded our European clinical trials network to include 120 sites across 38 countries, with access to >28,000 newly diagnosed autistic individuals each year and trained to Good Clinical Practice standards.

6. Establishing a scientific legacy

We have developed a secure, centralised database that includes measures obtained from all AIMS-2-TRIALS cohort studies, clinical trials and cellular/ animal studies, to ensure efficient exploitation of data and establish a scientific legacy. We formulated a core set of data sharing principles that will support the release of project data to the wider scientific community, from early 2021. In partnership with charity **Autism Speaks**, we have led the development of one of the richest phenotypic and genomic autism databases worldwide for accelerating breakthrough discoveries – the 'Autism Sharing Initiative' – which was chosen as a 2019 Global Alliance for Genomics and Health driver project. These advances will promote international collaborations, ensure scientific rigour and improved replicability and enable researchers worldwide to conduct experiments with higher likelihood of gaining regulatory approval.

Utilising the rich AIMS-2-TRIALS dataset, over 43 scientific papers are under review/ have been accepted for publication in less than one year; and since the launch of the project our network has published over 100 scientific papers, including in very high impact journals (e.g. Nature, Nature Reviews Drug Discovery, Science Translational Medicine). We have also advanced our communication, outreach and education strategies - achieving >77,919 website views and 133,464 impressions on Twitter, as well as hosting several researchers- and industry-led conferences and workshops and overseeing the launch of an AIMS-2-TRIALS webinar series.

We continue to develop sustainability models and strategies, notably establishing the Early Career Researcher Autism Network of over 120 individuals across 23 European countries to facilitate cross-sector, international research collaborations and deliver high quality clinical trials training to the next generation of future leaders. We also launched a new initiative linking to North America that will underpin a platform trial approach for designing proof-of-concept clinical studies of autism (via the Autism Spectrum Proof Of Concept Initiative; ASPI) that can be conducted through a public–private partnership, with the aim of finding effective treatments in the most expeditious manner.

7. Impact for the autism community

Further to the progress reported above, we have enhanced research collaborations with autistic people and their families to ensure that AIMS-2-TRIALS outputs respond to priorities identified by the autism community and deliver real-world impact for clinical practice and policy. Over the past year, there have been over 35 research engagement activities with a panel of AIMS-2-TRIALS autism representatives across Europe, including: 1) collaboration and co-production on key policy research projects regarding health and social care access for autistic people (e.g. the 'ACCESS-EU' study); 2) co-design and development of measures and protocols for cohort studies; and 3) advice on clinical endpoints and sharing of expertise in dedicated project and analysis working groups.

Last, in response to the unprecedented global COVID-19 pandemic, the AIMS-2-TRIALS consortium and collaborators have provided support and resources for the autism community. Examples include the provision of telephone consultations and email contact seven days a week for autistic people needing support; comprehensive online toolkits to support families; and regular expert webinars on topics like mental health and coping with uncertainty. We have also initiated and/ or are supporting several novel COVID-19 projects to better understand (and respond to) the impact of global pandemics on the autism community. For instance, Institut Pasteur are developing a COVID-19 database to support global data sharing initiatives (e.g. through data standardisation/ accessibility). In addition, we launched one of the first ever prospective studies of prenatal exposure to maternal immune activation (COVID-19 infection in pregnancy) on early brain development and conducted a large-scale policy review of access to COVID-19 health and social care services for autistic people and those with intellectual disabilities.