JPND Final SRA Workshop: Rome, 20 June 2011

Report – Key Outputs

1. Background and aim of workshop

The EU Joint Programme on Neurodegenerative Disease Research (JPND) has been established by 23 European countries to address the growing societal challenge presented by age-related neurodegeneration. This initiative spans the biomedical, healthcare and social science agendas, and seeks to improve the scientific understanding of neurodegenerative disorders, provide new approaches for their prevention, diagnosis and treatment, and ensure effective provision of health and social care and support so that individuals can receive optimum care at all stages of their illness.

The first goal of the initiative is to establish a joint 'Strategic Research Agenda' to guide research activity and investment over the coming decade. To provide a basis for this, three thematic meetings were held with academic opinion leaders in neurodegeneration research followed by consultation with key stakeholder groups from industry and organisations representing patient/carer groups and healthcare professionals. The aim of this workshop was to integrate the findings of the previous meetings and provide a holistic view of the research landscape and a roadmap for future research activity. This report provides an overview of the key outputs highlighting research opportunities and key requirements as well as potential barriers to progress. These recommendations will be considered under the JPND strategic research agenda which will be published at the end of 2011 following further consultation with stakeholder groups and policy makers.

2. Overview

The workshop confirmed that there was considerable common ground in the priority areas highlighted by the various stakeholder groups; academia, patient groups, carers, and industry. Several themes were highlighted as being of fundamental importance when considering any future JPND actions:

- Any overarching strategy should be open-minded to novel (bottom-up) approaches.
- Funding mechanisms should be flexible enough to be able to support collaborative effort across groups and borders where this will increase impact.
- There should be wider availability and easier access to data and materials, as well as active dissemination of outputs.
- Methodologies should be harmonised and technology platforms standardised wherever possible.
- Education and awareness of neurodegenerative disorders (NDD) should be promoted across groups.
- The ethical issues in this area need to be more systematically addressed.
- Regulators should be involved at all levels of the research agenda to ensure effective translation of research for patient benefit.
- There will be a continuing need for a regular forum or fora to build a common way forward across the various stakeholders in this area.

- The initiative will need to look for early gains and at the same time build long term sustainability.

3. Key needs/opportunities in terms of scientific research

The following areas of consensus emerged from the discussions, building on the outputs from the previous thematic JPND workshops:

Disease aetiology

- Large pan-European population-based studies and longitudinal studies of high-risk populations should be established and/or existing cohorts expanded and further strengthened. Ideally such studies should be multidimensional, multimodal, and span multiple NDD, and be open access to ensure data can be mined to its full potential. Their design should also be geared to potentially enroll subjects into clinical trials. Statistical power could be gained through using a pan-European population base and with deep phenotyping and biomarker-based selection.
- There is a continued need to elucidate the importance of existing and novel genetic and environmental risk factors, and probe the effect of gene-environment interactions. Total genetic variation needs to be understood and correlated with the risk of NDD in different environments/with different lifestyles. A fuller understanding of the genetic 'entry points' to NDD should be established, and the relevance of early disease markers determined. Nutritional factors as causes of disease remain poorly understood and need to be addressed.
- It was apparent that more research is needed into ageing including the relationship between ND pathology and 'normal' ageing. We need to know what determines the basis of resilience, and what is the impact of comorbidity.

Disease mechanisms and models

- In order to develop new therapeutic approaches and understand the optimal time-window for intervention, a more complete understanding of disease mechanisms is required, with cross-reference across the various NDD which were increasingly seen to share common features. For example, studies should address:
    - cell non-autonomous mechanisms
    - role of inflammation
    - mechanisms of neuronal death/dysfunction
    - the biological basis of behavioural and psychological symptoms.
- More effective disease modelling is needed, using innovative animal models and human-derived cells, for example using induced pluripotent stem cell technology.
- There should also be a focus on modelling defined rare genetic variants and diseases, which might then be progressed to address subsets of common sporadic diseases.

Diagnosis, disease definitions and outcome measures

- The standard clinical diagnoses were increasingly seen as uninformative and effort should be placed on redefining and standardising definitions/parameters for disease and diagnosis/diagnostic procedures taking into account traits and biomarkers. This would help improve the validity of diagnosis, enable disease stratification and ultimately lead to better and earlier diagnosis. There is also a need for standardised assessment batteries.
- The cost-effectiveness of different diagnostic pathways should be determined.
- There is a pressing need to develop and validate new and improved biomarkers (biological, cognitive or imaging-based), that:
    - link to the mechanism of disease as well as functional endpoints;
    - link to treatment responses;
    - are sensitive to disease progression;
    - are commercially viable, for example by having utility at the population level.

- A better appreciation of the approach of regulatory agencies to the use and development of biomarkers and surrogates is needed.
- The endpoints/outcomes of studies should be redefined and harmonised, with more attention paid to the incorporation of functionality, carer situation, patient dignity, and quality of life (QoL).

Drug discovery and development

- Develop better translation between animal models and the clinic - the lack of common biomarkers to facilitate 'back translation' was seen as a significant barrier to progress, and hampered preclinical drug development programmes in particular.
- Animal models might be brought to better use if defined as 'animal assays', to recognise that they mimic discrete mechanistic pathways rather than human diseases.
- Stem cell (iPSC)-based assays should be developed in an attempt to ensure more predictive modelling and drug screening.
- The heterogeneity of responses to interventions needs to be taken into consideration, and stratification of treatment groups based around risk-factors or traits should be used to improve the signal to noise ratio.
- A new approach is needed to promote the repositioning and combinatorial use of marketed drugs for NDD.
- The high level of attrition in drug development in NDD was well recognised, and there is a real risk that continued failure could lead to complete withdrawal of industry from the NDD sector.
- Nevertheless, multi-centre primary prevention studies should be conducted in population-based cohorts and based on existing knowledge. These should encompass methodologically-appropriate (i.e. randomised, well-powered) approaches.
- The efficacy of new treatments might be easier to demonstrate by ensuring (better) patient selection/stratification for intervention studies.
- Improved understanding of the various stages of the disease process is required, and effort should be focussed on determining how QoL can be improved especially at the mid-stage.
- Patient/carer organisations have a key role to play in improving the involvement of their members in research - currently relatively small numbers of patients with NDD are enrolled in studies or on brain-donation registers.
- Preventative/curative interventions are not currently possible, and therefore more emphasis should be placed on developing non-pharmacological interventions directed at QoL. Psychosocial interventions, promoting social inclusion, should be promoted, alongside person-centred care to improve health-related QoL and dignity. However, improved methodology to assess psychosocial interventions needs to be developed.

Health and Social Care

- As a starting point there needs to be agreement as to what is meant by the term 'care'.
- Given the uncertainties of care standards and provision across Europe, a survey of the arrangements for long-term care could provide a valuable platform for comparative studies to investigate:
    - the effectiveness of different European health and social care systems;
    - the economics and social effects of different living arrangements, i.e. the impact of home environment versus institutionalisation.
- The cost-effectiveness of pathways to diagnosis, intervention, care and support should be determined and the results factored into healthcare system approaches
- There is a need to better understand the causes of (comorbid) behavioural problems/manifestations, ensure there is better recognition of the effect of cognitive decline on the outcome of comorbidities, and investigate treatment strategies.

- There is a lack of research into the effects of poor nutrition and frailty, while there needs to be a systematic assessment of research care and decision making in relation to end of life.
- The needs of carers are often overlooked and research is needed to ensure effective support can be provided to this group.

4. Key needs in terms of policy, organisation and infrastructure

The workshop participants considered that an initiative such as JPND could make real progress through ensuring cooperation and harmonisation across national research infrastructures and policy. To do this it would be essential to understand what information exists and implement what is known, and develop an integrative approach across basic, clinical and social dimensions. It was repeatedly emphasised that methodologies should be harmonised and technology platforms standardised wherever possible, while there must be a concerted effort to improve sharing of resources/data and develop/ensure a common language across all sectors.

Policy, regulation and legislation

- Evidence-based policy towards the provision of healthcare and prevention should be promoted wherever possible. To support research and enable relevant data to be collated and analysed, NDD-focused 'observatories' should be developed or existing observatory data better exploited to ensure public health is appropriately monitored.
- Insufficient research is currently conducted within formal and national healthcare structures such as care homes and the NHS in the UK. To overcome existing barriers and improve research engagement policy structures need to be put in place. For example, access to (patient) data held by care homes could be gained by providing financial incentives.
- Engagement with regulators needs to be improved to ensure greater, and earlier, input to reduce late stage problems and failures and remove (unnecessary) barriers or impediments to conducting research.
- Industry representatives identified patent lifetime as a problem area for commercial drug development in ND. Trials in NDD tend to have a long time course which reduces commercial viability and limits financial return. System(s) for conducting joint public-private clinical trials, potentially utilising public money if trials extend beyond patent life, may encourage companies to remain in this area. Further obstacles in some countries are political barriers that prevent health professionals from becoming involved in commercial studies. Lastly, some attendees expressed the view that drug development might be best served by encouraging industry to adopt a pre-competitive approach to research.
- Legislation has an important role in protecting the rights of the individual; however, particularly where laws are outdated this can impact on research. For example, ethical and legal restrictions can prevent the release of information from clinical trials particularly after death of participants. Similarly, issues surrounding obtaining and giving consent need to be researched and addressed. Accordingly, there is a need to review and potentially update legislation relating to privacy and data disclosure taking into consideration the needs and wants of patients and carers. Secondly, effective treatment of NDD most likely requires intervention to occur at as early a stage as possible. This can only occur if the ethics of treating asymptomatic, at risk, or early stage individuals are explored and appropriate legislation developed.

Education, training and collaboration

- Broadly there is a need to understand how best to educate the various stakeholder groups affected by NDD and to base future education strategies on proven research and facts (evidence-based education). Effort should be directed towards the destigmatisation of dementia, as well as to improve awareness and knowledge of

research and research participation. Investing in the education of the younger generation would have long-term benefits and could, for example, improve involvement in care. Education and training of health professionals with respect to patient needs and available healthcare options also needs improving.

- Capacity building is required especially in some disciplines, for example, health economics and bioinformatics. More should be done to facilitate recruitment of good post-doctoral researchers, potentially by improving funding, and cross-disciplinary working should be promoted. Furthermore, the training of translational and clinician-scientists would provide clear benefit in terms of developing appropriate diagnostic tools and interventions and should be promoted.

Funding and funding mechanisms

- Funding and funding mechanisms should maintain capacity for, and potentially promote, bottom-up and innovative research including 'unknown unknowns' (novel or unaccounted for ideas). For example, stimulating innovative basic research might lead to identification of new targets. Translational research also needs to be promoted.
- Emphasis should be placed on systematically improving networking across disciplines and countries, ensuring that they are inclusive and involve statisticians and health economists amongst others.
- Funding for collaborative studies should be linked to a requirement to develop procedures for open-access sharing of data and materials.
- To facilitate development of new interventions, funding models to bring industry and academia together (beyond IMI) should be considered.
- Patient and carer groups indicated support for high-risk projects with potential benefits for the individual and studies investigating neuroregeneration.
- Academic researchers felt that European funding application systems need to be simplified, perhaps to mirror, or improve on, the NIH system in the USA.

Repositories and centres

- Concentrating resources in specific sites without negatively impacting on the wider research community was seen as a way of improving research quality and output. Centres of excellence combining research, treatment and education, and dedicated translational research centres could help drive the research agenda forward in key areas. For example, a network of clinical research centres could facilitate running of trials, help maintain interaction with industry and potentially promote related clinical and research training.
- More broadly, better access to, and sharing of, infrastructure and resources was seen vitally important across stakeholder groups particularly for:
    - clinical and preclinical imaging equipment;
    - good quality brain and tissue samples.

Data and registries

- To underpin better and more effective research, collection of patient data and samples must be improved. Collection should employ a common methodology, which may need developing, and provision for sharing.
- A (pan-European) register of a cognitively-impaired population with comprehensive phenotyping and longitudinal follow-up was suggested as a research requirement.
- Issues surrounding sharing and utilisation of exiting data were identified as limiting factors in a number of sectors. Industrial research is currently hampered by lack of access to patients, patient samples and data; accordingly, industry would like greater access. Conversely, better access to industry data, particularly trial results, would inform and influence research in the academic sector. Lastly, individuals with NDD, their carers and the general public would like disclosure and dissemination of information to improve. For example, transparency of clinical trials and disclosure of results could be improved and information on the positives and negatives of trial involvement more widely and better disseminated. Patient-focused organisations could help bridge the gap and facilitate disclosure of research results in 'lay' terms.

Care

- To overcome existing problems that will only be exacerbated by increasing use due to the aging population, a fundamental rethink of care approaches and infrastructures was proposed. Systems should aim to minimise the burden on family and carers; providing innovative care at home and implementing assisted-living technologies were considered important and could help reduce strain on individuals. Planning for new or revised care systems should factor in a requirement for research to ensure policies are evidence-based.

Annex - List of Participants

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