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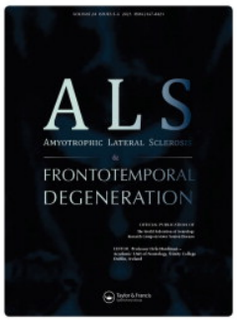

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RESEARCH ARTICLE

PRECISION ALS—an integrated pan European patient data platform for ALS

ROBERT MCFARLANE[1,2], MIRIAM GALVIN[1,2], MARK HEVERIN[1,2], ÉANNA MAC DOMHNAILL[1,2], DEIRDRE MURRAY[1,2], DARA MELDRUM[1,2], PETER BEDE[1,2], ANTHONY BOLGER[2], LUCY HEDERMAN[2], SINÉAD IMPEY[2], GAYE STEPHENS[2], CIARA O'MEARA[2], VINCENT WADE[2], AMMAR AL-CHALABI[3], ADRIANO CHIÒ[4], PHILLIPPE CORCIA[5], PHILIP VAN DAMME[6], CAROLINE INGRE[7], CHRISTOPHER MCDERMOTT[8], MONICA POVEDANOS[9], LEONARD VAN DEN BERG[10] & ORLA HARDIMAN[1,2,11]

[1]Academic Unit of Neurology, Trinity College Dublin, TRICALS Consortium, Dublin, Ireland, [2]ADAPT Centre Trinity College Dublin, Dublin, Ireland, [3]Kings College London, TRICALS Consortium, Dublin, Ireland, [4]University of Torino, TRICALS Consortium, Turin, Italy, [5]University of Tours, TRICALS Consortium, Tours, France, [6]Catholic University Leuven, TRICALS Consortium, Leuven, Belgium, [7]Karolinska University, TRICALS Consortium, Stockholm, Sweden, [8]Sheffield University United Kingdom, Sheffield, UK, [9]University of Barcelona, TRICALS Consortium, Barcelona, Spain, [10]University Medical Centre, Utrecht, TRICALS Consortium, Utrecht, The Netherlands, and [11]FutureNeuro Research Centre Trinity College Dublin, Dublin, Ireland

Abstract

Amyotrophic Lateral Sclerosis (ALS) is an incurable neurodegenerative condition. Despite significant advances in pre-clinical models that enhance understanding of disease pathobiology, translation of candidate drugs to effective human therapies has been disappointing. There is increasing recognition of the need for a precision medicine approach toward drug development, as many failures in translation can be attributed in part to disease heterogeneity in humans. PRECISION-ALS is an academic industry collaboration between clinicians, Computer Scientists, Information engineers, technologists, data scientists and industry partners that will address the key clinical, computational, data science and technology associated research questions to generate a sustainable precision medicine based approach toward new drug development. Using extant and prospectively collected population based clinical data across nine European sites, PRECISION-ALS provides a General Data Protection Regulation (GDPR) compliant framework that seamlessly collects, processes and analyses research-quality multimodal and multi-sourced clinical, patient and caregiver journey, digitally acquired data through remote monitoring, imaging, neuro-electric-signaling, genomic and biomarker datasets using machine learning and artificial intelligence. PRECISION-ALS represents a first-in-kind modular transferable pan-European ICT framework for ALS that can be easily adapted to other regions that face similar precision medicine related challenges in multimodal data collection and analysis.

Keywords: *Precision medicine, scientific collaboration, data science, amyotrophic lateral sclerosis*

Introduction

Amyotrophic Lateral Sclerosis (ALS) occurs in mid-life and is primarily associated with degeneration in motor pathways, but also affects cognition and behaviour (1) The lifetime risk of developing ALS in Europe is 1:400 for women, and 1:300 for men (2,3). The disease accounts for up to 10,000 deaths per year in Europe and costs over €600 million each

Correspondence: Orla Hardiman, Academic Unit of Neurology, Trinity College Dublin Academic Unit of Neurology, Ireland, Dublin. E-mail: hardimao@tcd.ie

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year in care, with multiples of this in loss of productivity of those affected and their families (4).

Once symptoms develop, ALS is rapidly progressive, with a mean life expectancy of less than 3 years. The neuropathology of ALS overlaps with other neurodegenerations, notably frontotemporal degeneration (FTD) with which it forms a clinical and pathological continuum, and the complex genomics of ALS overlap with other neurodegenerative conditions such as Huntingtons Disease and Parkinsonism, and neuropsychiatric conditions such as schizophrenia (5).

Although useful transgenic animal models have been developed, ALS remains a condition that is exclusive to humans. The human condition is best characterized as a heterogeneous syndrome comprising a wide range of clinical subtypes with various degrees of extra motor (cognitive/behavioural) involvement, differences in rates of progression, and in which a range of neuropsychiatric conditions occur within extended kindreds of up to 30% of probands (4).

At least 40 at-risk genes of major effect are associated with ALS, illustrating the heterogeneity in disease pathogenesis (6). Four of these genes (*SOD1, FUS C9orf72* and *ATXN2* have already been the target of a specific "precision medicine" -based approached toward therapy (7). However, for the forms of "sporadic" ALS (in which there is no clearly established singular genomic basis), clinical trials of over 100 compounds have either failed to demonstrate efficacy despite positive outcomes in animal models, or have reported efficacy, but require additional evidence for approval in Europe.

As a human disease, there is no complete animal model of ALS, and translation of pathogenic insights from pre-clinical models to human disease is at best limited. For example, and notwithstanding the success of rodent transgenics in elucidating pathways of neurodegeneration, the anatomy and physiology of the neuroaxis of non-primates differs from humans in many important aspects (8). Furthermore, preclinical studies are generally performed under strict laboratory conditions using inbred colonies, which limits our understanding of environmental exposures. Direct translation from laboratory models to humans is thus compromised both by the greater complexity of the human nervous system, and by poorly understood modifying factors in human disease including complex genomics, life events and environmental factors, all of which are likely to contribute to how the clinical disease develops and progresses in humans (8). Additional barriers in the clinical domain include the absence of robust clinical markers that can provide insights into heterogeneous pathogenic mechanisms, limitations in the ability of clinicians to fully characterize disease onset, an absence of robust quantitative markers of progression, and challenges in the design of informative clinical trials that can provide definitive conclusions (9).

To address these barriers, and to more fully understand and characterize human disease heterogeneity, large population-based datasets comprising multimodal clinical, imaging, genomic, transcriptomic and proteomic data are required. As ALS is a rare disease, a collaborative transnational approach is needed to generate sufficient scale, and to ensure that all aspects of the disease are captured. Moreover, given the limited capabilities of current clinical assessment, additional quantitative measures of disease onset and progression, and novel and appropriate data analytics that are grounded in meaningful clinical questions will be necessary to provide new knowledge that is applicable to clinical scenarios. To fully harness the capabilities of AI and machine learning technologies, collaborative engagement between clinicians and data scientists will be required. The ultimate goal will be to provide data-driven subcohorts of patients with shared biological characteristics and attributes that cannot be discerned by clinical evaluation alone.

To date, multiple challenges have impeded the ability to generate, manage and maintain such large and multimodal datasets, comprising clinical, genomic, transcriptomic, proteomic, imaging and neurophysiological data. Collection, integration and analysis of enriched multi sourced clinical datasets requires large-scale and long-term resourcing. Data privacy rights of subjects must be respected and protected. European general data protection regulations (GDPR) have demanded additional legally robust strategies to ensure transparent compliance with new and more stringent data governance requirements. Challenges of interoperability across data sources from different jurisdictions renders harmonized data collection expensive and time consuming.

Innovative solutions are required to address these and future problems inherent in the collection, harmonization and management of multimodal data and facilitate multinational cross-modal and multimodal data analytics.

PRECISION ALS

An innovative pan-European collaboration has been initiated to address these problems. The PRECISION ALS Consortium (www.precisionals.ie), is an academic/industry collaboration supported by Science Foundation Ireland (www.SFI.ie). The Consortium comprises international clinicians from the European ALS Research entity TRICALS (www.tricals.org) working closely with computational and data scientists based in the ADAPT center (https://www.adaptcentre.ie/) in

Ireland, and with key pharmaceutical and data science companies.

The aim of PRECISION-ALS is to capture the entire ALS patient and caregiver journey from diagnosis to include all clinical characteristics, health service engagements, imaging and "omic" characteristics of those diagnosed. The objective is to address the key clinical, computational, data science and technology associated research questions required to generate a sustainable precision medicine-based solution for ALS. This approach will collect and collate data at scale using a bespoke integrated, interactive platform that can be interrogated and analyzed in real time. Research insights will be generated from well characterized population-based cohorts that will address clinical and biological heterogeneity, and that will also provide important perspectives on the entire patient journey and interaction points within the healthcare ecosystems in Europe.

PRECISION partners

PRECISION ALS is a partnership of TRICALS sites (www.TRICALS.org) in Ireland (Trinity College Dublin), the UK (King's College London, University of Sheffield), France (University of Tours), the Netherlands (University Medical Center Utrecht), Italy (University to Torino), Sweden (Karolinska Insitutet), Belgium (Katholic University Leuven) and Spain (Bellvitge Hospital, University of Barcelona). Industry partners include; large pharma (Biogen, Novartis, Takeda); clinical research organizations (IQVIA); technology companies (Aural Analytics, Cumulus); and data science companies (Accenture). With co-funding from Science Foundation Ireland, partners have worked together in a pre-competitive environment to define research questions that target integration and analysis of quality longitudinal multimodal patient data from multiple European ALS research centers to progress data science and clinical research toward a precision medicine approach to treatment.

Data sources

Strengths of PRECISION ALS include the existing infrastructure within Europe that can identify and collect well-phenotyped population-based patient cohorts with associated granular datasets for ALS The participating centres have established excellence in genomics, deep phenotyping, cognitive profiling, neuro-electrical signaling and imaging analysis. Clinical partners in PRECISION ALS are also expert in design-science, systems thinking ethnography, and in integrating data sets (phenotype, clinical, genomic) to support clinical care, continuous quality improvement, research, and innovation.

Under GDPR compliant data sharing agreements, data collected from previously funded collaborations including FP7 (Euromotor https://www.euromotorproject.eu/), JPND funded projects (SOPHIA, STRENGTH, ALSCARE, BRAINM END, (https://neurodegenerationresearch.eu/supported-projects/) and large scale genomic projects (Project MinE (www.projectmine.com) have been harmonized and collated for additional analyses.

Extant data analyses

PRECISION ALS has already collated data from 21,000 patients with ALS from 9 participating sites pertaining to incidence, prevalence, clinical phenotype, genomic signatures, engagement with health services and disease trajectories. Ongoing analysis of these datasets will provide a detailed perspective of the landscape of ALS in Europe, with particular emphasis on the prevalence of known gene variants, impact of specific gene variants on disease progression, the utilization of services and equipment, and cross-cultural differences that might exist, and will provide new predictive models of disease progression. These ongoing analyses will continue to inform the prospective data collection, which is scheduled to commence in quarter 2 of 2023.

The collation and harmonization of these extant data have also informed and supported the development of a customized electronic data collection tool for prospective data capture and prototype bespoke ICT patient data platform.

Data collection instrument

Existing infrastructure across the nine participating sites supports population-based capture of all patients. The customized electronic data collection instrument has been designed to capture all disease relevant data from each site, with the aim of including at least 50% of all incident patients providing an estimated inclusion of up to 2000 consenting ALS patients per annum. Additional data will be collected through telehealth devices and remote monitoring of consenting patients and caregivers. A digital application linked to a web-based administrative server platform and bespoke tablet devices have already been supplied to each participating site. Following extensive consultation, the application has been custom designed to collect demographic details, clinical and cognitive phenotype, co-morbidities, concomitant medications, family history, socioeconomic details, and details of service utilization. Through iterative user-centered design cycles, the suite of data collection instruments will be refined to enable capture of all relevant data at source efficiently, providing novel interfaces to enable integration with preexisting electronic resources. The population-based and inclusive nature of the data collected will represent the entire disease course as it occurs and as it is experienced by people living with the disease, providing research-

quality multi-sourced clinical patient and caregiver journey information.

Patient data platform

The data collected will link directly with a customized design ICT Patient data platform (PDP). The platform will be structured to manage multi-source, multi-format, multi-modal and longitudinal data in a manner that is easily accessible to clinician scientists for research purposes. The ICT data platform is subject to appropriate data governance and metadata evolution. The platform will harness data from multiple sources, including imaging, neuro-electric-signaling, genomic and biomarker datasets. The underlying design of the Platform will enable a centralized store of structured patient data, while simultaneously indexing into bulky, specialist, sensitive or protected data that are collected locally at each site (e.g., genomic or imaging data.)

As PRECISION ALS is an interdisciplinary project involving continuous discovery, identification, validation, and use of integrated multimodal P-ALS information, the ICT platform will be designed to provide an information pipeline that seeks to identify data sources and concludes with facilitation of well governed clinical research. To achieve this the platform will build, deploy, and evaluate innovative semantic modeling approaches that support quality data governance. This work will advance processes and information models for generalizable clinical research, data curation and management. Semantic modeling will identify important components such as management strategies that integrate clinical research data, support quality of governance and multimodal integration. The platform will also advance sociotechnical processes to support manual and automatic tasks along the information pipelines to facilitate clinical research.

A central aim of PRECISION ALS is to facilitate the identification of subcohorts of patients that cannot be currently identified using clinical evaluation alone. The advanced analytic work will take an algorithmic perspective, to focus on enabling content to flow freely across different languages and modalities. The application of sequencing and advanced machine learning and artificial intelligence to multimodal patient data will ultimately deliver better patient categorization and stratification in trial design, power calculations, cost analyses and health economic modeling required by the pharma industry, and will provide the opportunity, where appropriate for selection of a virtual control population to enhance clinical trial delivery.

Legal and data protection considerations

PRECISION ALS is governed by an extensive legal framework. This includes a partnership agreement within the TRICALS group, a series of cross-institutional agreements in the Irish University sector and project level agreements with industry partners.

PRECISION ALS also works within the framework of European GDPR legislation which came into force in 2016. This requires that all data pertaining to clinical research is considered sensitive and subject to stringent regulation regarding transfer and utilization for research purposes. All Universities and health care facilities across the EU and UK have incorporated strict data protection protocols that must be observed to permit data sharing. PRECISION ALS has already developed an extensive set of GDPR compliant protocols that map both data flow and governance, commencing with the recruitment and consenting of the patient through to the collation of their data on the ICT platform. Access to data is governed by Consortium and Project level agreements subject to approval of a Scientific Executive, representing the participating centers with additional oversight from independent scientific data protection and ethical expertise.

Projected outcomes

PRECISION ALS is an innovative collaboration between clinicians, computer scientists, Information engineers, technologists, and data scientists. The patient data platform will enable representation of the entire disease course as it occurs, is experienced by patients and caregivers, and analyzed by researchers.

The Platform design is modular, and as such will enable the addition of new variables and data fields and facilitate nested studies. It will expedite the integration of device technology and telemedicine into clinical practice (10). The ICT analytics research solutions will meet the need for selection and execution of appropriate machine learning algorithms and user-friendly approaches to support clinician scientists.

This true precision-medicine solution will address the problems of seamlessly gathering new multimodal data at scale in a timely and cost-effective manner across multiple international sites and ensure that the data are available in real time to clinical scientists. The programme will provide urgently needed clinical insights into disease heterogeneity by providing novel outcomes, refined subcohorts of patients generated by integrated multimodal analyses, better monitoring devices and new approaches to understanding and measuring clinic al meaningfulness. All of these outcomes will be invaluable to future clinical trial design and for health technology assessment.

Once established, PRECISION ALS will be self-sustainable, as the combination of high-quality

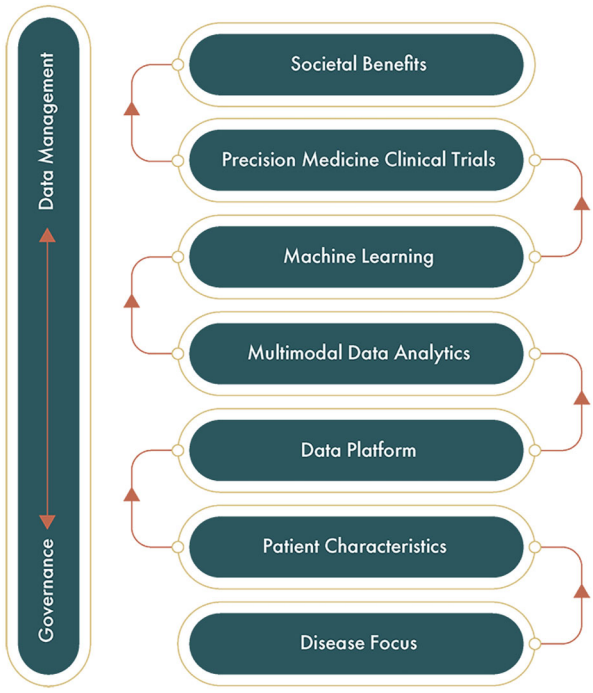

Figure 1. Schematic showing the overview of the PRECISION ALS project structure including the incorporation of machine learning and data science in an iterative and informative way to directly better and improve patient outcome.

data and analytic capabilities continue to inform both clinical researchers and industry.

The developed approaches intrinsic to PRECISION-ALS will also be suited to address extant barriers to collating and analyzing datasets from multiple sources across multiple jurisdictions, providing an invaluable resource to future multi-national and cross-continent collaborative research, including harmonization with other cognate world-wide initiatives such as the Accelerating Medicine Partnership Programme, supported by FNIH in the US (https://fnih.org/our-programs/AMP) (Figure 1).

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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ORCID

Christopher McDermott http://orcid.org/0000-0002-1269-9053

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