EUAN MACDONALD CENTRE
Vital research into motor neuron disease

MND–SMART

Collaborative Approach to Meta Analysis and Review of Animal Data from Experimental Studies
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Developing a data-driven framework to identify, evaluate and prioritise candidate drugs for motor neuron disease clinical trials

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Introduction

Motor neuron disease (MND) is a **progressive, disabling** and **fatal** neurological disease

1 in 300 people develop MND in their lifetime

5000 adults are affected by MND at any one time in the UK

1 in 2 people with MND die within 2 years of diagnosis

mndassociation.org

Between 2008 and 2019, **125 phase II and III trials** recruiting **15647 people with MND** tested **76 drugs** in motor neuron disease. Yet, **NO new disease-modifying drugs** have been approved in Europe.

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We need to rethink how drugs are selected and evaluated in MND clinical trials

Aim

data → ? → drugs

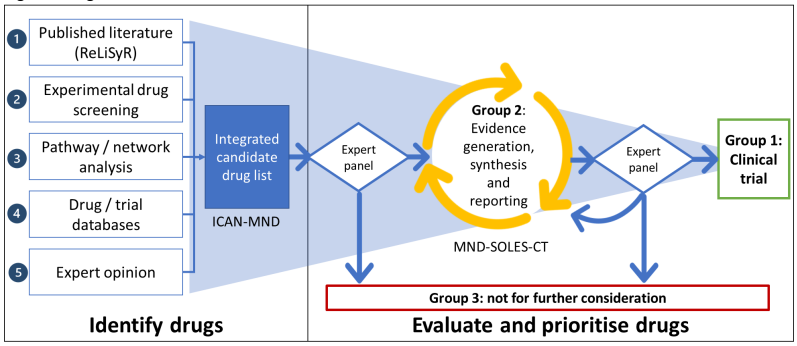
- identify suitable data domains
- systematic data gathering
- robust evaluation and weighting of data
- efficient workflows for pooling, synthesising and reporting data

- ☑ efficacy
- ☑ safety
- ☑ feasibility
- ☑ pharmacology

We aim to develop a systematic and structured data-driven framework to identify, evaluate and prioritise candidate drugs for evaluation in Motor Neuron Disease - Systematic Multi-Arm Adaptive Randomised Trial (MND-SMART; NCT04302870).

A data-driven framework for drug selection

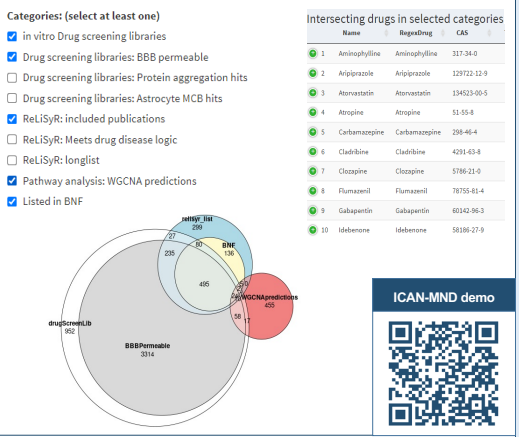
Figure 1: Drug selection framework



In our framework (Fig. 1), we take into consideration emerging data in different domains, the interplay between these domains and expert opinion.
The current domains of data include:

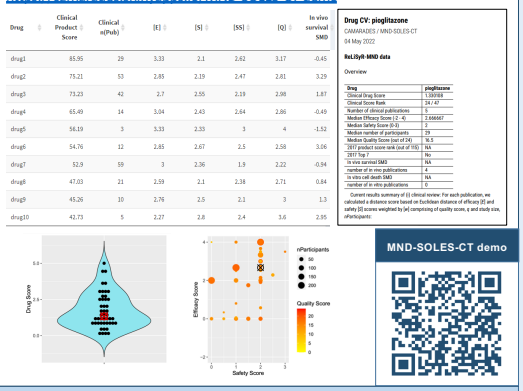
1. **Repurposing Living Systematic Review – Motor Neuron Disease (ReLiSyR-MND),** a three-part machine learning-assisted systematic review of:
   i. clinical literature of MND and other neurodegenerative diseases of interest which may share similar pathways
   ii. MND animal *in vivo* studies
   iii. MND *in vitro* studies
   For the clinical review, we score and rank drugs using a metric based on efficacy, safety, study size, study quality and number of studies.
2. **Experimental drug screening** including validated in-house high throughput drug screening assays (such as protein aggregation and oxidation) on human induced pluripotent stem cell derived motor neurons and astrocytes.
3. **Pathway and network analysis** using a ranked drug list from 1, 2, and Target ALS post-mortem RNAseq data to identify pathways and networks of interest. Where targets are implicated but not amenable to drug treatment in humans due to safety, pharmacological or feasibility issues, we will identify potential upstream or downstream targets and candidate drugs acting on these.
4. **Drug and trial databases**: We will mine ChemBL, British National Formulary, admetSAR and ClinicalTrials.gov to obtain data on pharmacology, chemical and physical properties, mechanism of action, prescribing information, predictions on blood brain barrier (BBB) penetrance, and clinical trials.
5. **Expert opinion**: We will gather opinion from our panel consisting of MND triallists, clinicians, scientists, and experts in drug screening, pharmacology, and systematic reviews.

Figure 2: Identifying candidate drugs
https://camarades.shinyapps.io/ICAN-MND-demo



ICAN-MND demo

Figure 3: Evaluating and prioritising candidate drugs. Demo ranked drug list and excerpts from example drug CV including violin plot of drug scores and bubble plot of clinical subscores, with selected drug highlighted.
https://camarades.shinyapps.io/MND-SOLES-CT-demo



MND-SOLES-CT demo

Identifying candidate drugs (Fig. 2)
Integrated CANdidate drug list (ICAN-MND) is an interactive web app reporting candidate drugs identified from different data domains. On selecting categories of interest, the app will render a Euler plot showing numbers of drugs in each category, and tabulate drugs meeting all criteria selected.

Evaluating and prioritising candidate drugs (Fig. 3)
We compile drugs described in ≥1 clinical publication, drug screening positive hits, and drugs targeting pathways and networks of interest. The expert panel prioritise drugs suitable for imminent repurposing, considering BBB penetrance, availability in oral formulation, safety and feasibility. We further identify, evaluate, and synthesise evidence across different domains for prioritised drugs and report these using automated workflows as interactive living evidence summaries. These summaries can be used to inform expert panel discussions on drug selection for future arms of MND-SMART at trial adaptation epochs.

Future considerations:

Our framework is modular with flexibility to add other suitable data domains. The systematic reviews incorporate automation tools for living searches, citation screening and drug and disease annotation. Development of automation tools for annotation of other items can further improve efficiency. ReLiSyR can be used in other neurodegenerative diseases, with existing applications in progressive multiple sclerosis. The overall framework could be adapted and implemented in other diseases, especially in adaptive platform trials.

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