Project Title

Unlocking the potential of precision mental health – a pilot investigation focused on schizophrenia

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Introduction

Precision medicine has brought healthcare into a new era in pursuit of highly specific diagnoses and treatment tailored to patients' characteristics. This challenges conventional paradigm of clinical translation, which relies on one-size-fits-all approaches to develop therapeutic interventions for 'average' patients only. Statistical designs for precision medicine clinical trials feature stratification of patients into small subgroups, defined using biomarkers, genetic, phenotypic or psychosocial characteristics. Inherently, clinical benefit of a new treatment can vary among distinct patient subgroups. This is noted to be the heterogeneity of treatment effect.

Mental health disorders are well recognised as heterogeneous for the wide variation in how symptoms of illness manifest and are experienced by individuals. Developing effective treatments for mental health disorders under the conventional paradigm can be especially challenging, partly because the averaged treatment effect is inevitably modest. One way out of the conundrum is to design clinical trials acknowledging the heterogeneity of treatment, as well as to set the goal as evaluating subgroup-specific treatment effects instead. However, methodology development for precision medicine clinical trials in mental health disorders lags behind other fields such as oncology.

Objectives

This project aims to

- identify opportunities and barriers of designing precision mental health trials,
- raise public and patients' awareness of the advantages of innovative statistical designs, especially those allowing realisation of precision mental health trials.

Progress

Schizophrenia is a chronic mental health disorder affecting 24 million people worldwide. While there is no cure for schizophrenia, ongoing research is leading to the development of innovative, safe and effective treatments. At the outset, we reviewed a few randomised controlled trials in schizophrenia (namely, NCT00615433, NCT00549718, NCT00790192, NCT02074319) and the associated publications to gain understanding about

a) how therapeutic options are typically developed,
b) how disease severity is measured,
c) how efficacy of a candidate treatment is demonstrated.

The inherent heterogeneity of schizophrenia is two-fold. Firstly, schizophrenia can manifest in a wide range of symptoms including

- psychotic symptoms, e.g., hallucinations and delusions,
- negative symptoms, e.g., reduced motivation and social withdrawal,
- cognitive deficits, e.g., impaired memory, attention, and reasoning.

Secondly, individuals live with a combination of such symptoms, with variability in how their symptoms present and impact functioning with self-care, hygiene, and decision making.

Treatments for Schizophrenia and New Insights

Current treatments often provide only partial relief of symptoms. Following the diagnosis of major symptoms, patients can be treated with

- anti-psychotic medications to reduce the psychotic symptoms present in the acute phase of the illness,
- cognitive behavioural therapies to manage persistent symptoms like stress, anxiety and depression,
- combination therapies when monotherapy proves insufficient.

Advancements in schizophrenia genomics have pinpointed specific genes and pathways involved in schizophrenia, with about 300 common genetic variants and over 20 rare variants identified as contributing risk factors [1,2]. Generally, schizophrenia is thought of as consequence of an ensemble of genes than a single genetic factor [3].

Many specific genes and loci have begun to point towards formulating new targeted therapies [4]. Specifically, a genome-wide association study identified 108 genetic loci, which represent genes expressed in the brain and immune cells involved in adaptive immunity, are associated with schizophrenia [5]. Emerging immunological evidence on diverse immune endophenotypes provides further insight into the development of distinct anti-inflammatory therapies for schizophrenia [6,7]. Some studies have explored the use of immunomodulatory agents, such as methotrexate, in randomised controlled trials (NCT02074319).

Innovative Proposals

While treatments for schizophrenia are often evaluated one at a time in clinical trials, it would be possible to plan and carry out a *master protocol* by allowing simultaneous evaluation of a number of treatments in potentially heterogeneous patient subgroups.

In our view, basket trials [8] and umbrella trials [9] are two most relevant approaches (visualised in Figure 1) for designing future schizophrenia clinical trials. More specifically, schizophrenia basket trials can evaluate a new targeted therapy (e.g., anti-inflammatory therapy alone or as adjuncts to anti-psychotics) in several subtypes of schizophrenia characterised by, for instance, disease stage or genetics. By contrast, schizophrenia umbrella trials can assess multiple therapies tailored to respective subgroups defined by symptom domains. Provisionally, anti-psychotic medications, cognitive behavioural therapies, and the combination, can be given to treat patients with corresponding predominant symptoms in a schizophrenia umbrella trial.

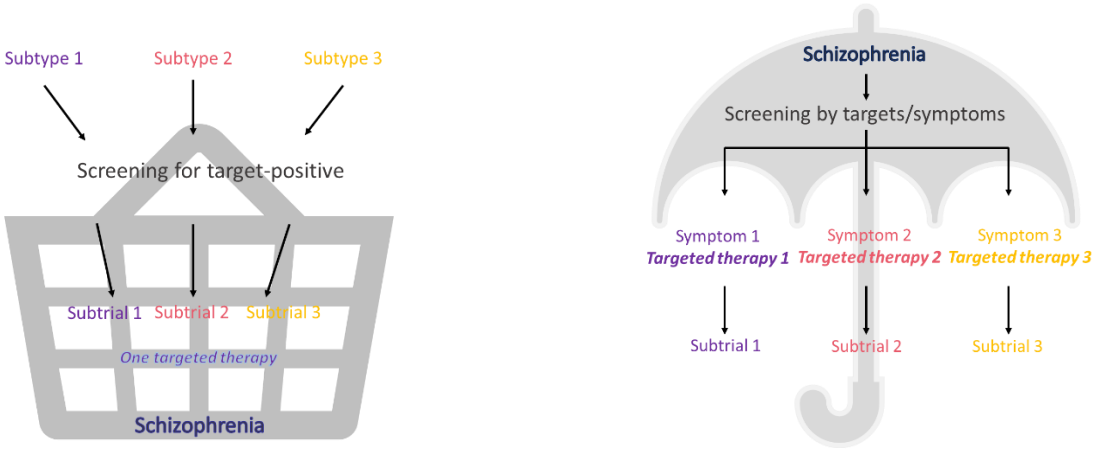

Figure 1. Schematics for basket trials and umbrella trials.
Each subtrial involves a single targeted therapy or random assignment of patients to the therapy or control.

Outcome Complexity

The severity of symptoms is measured using a test called the Positive and Negative Syndrome Scale (PANSS). Each symptom is recorded on a regular basis, for instance, biweekly. A total PANSS score that adds together the itemised ratings would typically be used in the trial analysis, with a higher score indicating more severe symptoms. Current practice uses change in PANSS score from baseline as the primary outcome in schizophrenia trials, whereas trajectory of PANSS over time often displays nonlinearity.

Opportunities for Statistical Methodology Development

To realise the potential of schizophrenia basket or umbrella trials, we believe that the feature of nonlinearity in PANSS score measured over time, alongside the potential heterogeneity in baseline measurements, should ideally be accommodated in the modelling strategy to estimate the subgroup-specific treatment effects.

From December 2024, we began to develop statistical methods for schizophrenia basket trials, with an emphasis on establishing random-effects model to enable sharing of information across subtrials that display similar treatment effects. This is part of our series research on statistical designs for basket trials [10-12].

Figure 2 visualises a simulated dataset of patient-level total PANSS scores measured over nine weeks. This was generated from a hypothetical, schizophrenia basket trial in three heterogeneous patient subgroups. A new targeted therapy (T) was compared against control (C) simultaneously in the subtrials.

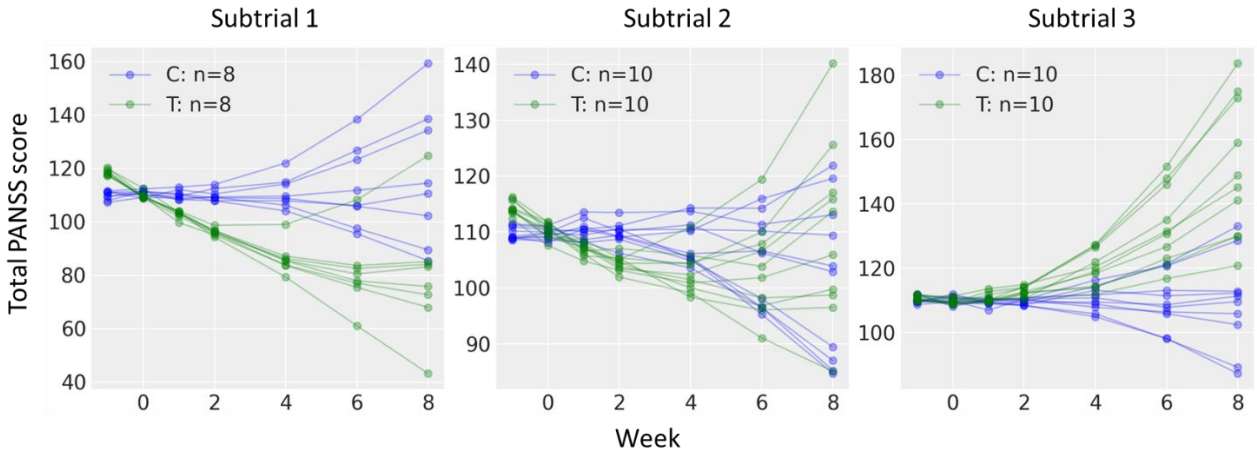

Figure 2. Simulated dataset of patient-level total PANSS scores over nine weeks from a hypothetical basket trial.

On schizophrenia umbrella trials, we developed a research proposal for a new 36-month project, focused on added flexibility by adaptive designs to simultaneously evaluate multiple treatments that target the respective symptom domains.

Going Beyond Schizophrenia

We have also delved into data characteristics of anxiety and depression, which are among the most common mental health disorders. A synthetic dataset was obtained to explore the repeated measurements, as well as the level of heterogeneity in the baseline. The underlying study was a randomised controlled trial that evaluated the efficacy of an inhibitor to improve on anxiety and depression. As these symptoms can often co-occur with schizophrenia [13], our investigation would potentially encourage the design of precision mental health trials for antidepressants, possibly in combination of other therapies, involving not only schizophrenia, but also other mental health disorders. We are currently preparing to write a perspective paper, targeting a psychiatrist's audience, on design options for a precision mental health trial.

The PPIE Meeting

A focus group zoom meeting was held on 8 January 2024, followed a pre-event survey to understand priorities of schizophrenia patients and carers. The survey had been broadly circulated through the NIHR People in Research, a Facebook support group, and the Mental Health Research for Innovation Centre (M-RIC) emailing list. A total of 25 patients and carers expressed interest in being involved further; 4 of them were eventually invited to attend the meeting. Key discussion points included: process of precision schizophrenia trials in contrast to conventional ones, patients' experiences living with schizophrenia, prioritising outcomes, recruitment and participation, ethical concerns.

A YouTube video and a plain English summary were created and distributed broadly. Both can be accessed at https://www.zhengh-stats.co.uk/projects/precision-mental-health

Outputs

- 1 technical report on the analysis of anxiety and depression synthetic dataset.
- 1 outreach activity to facilitate discussion with patients and carers on precision schizophrenia trials.
- 1 research proposal for a 36-month project on adaptive designs for schizophrenia umbrella trials.
- 1 perspective paper (in progress) on how future precision mental health trials are to be designed.
- 1 research paper (in preparation) on efficient statistical designs for schizophrenia basket trials.

Future plans

In the next ten months, we aim to (1) complete the work on Bayesian design and analysis of schizophrenia basket trials, and (2) submit the perspective paper to a respected psychiatric journal for publication. The research proposal of schizophrenia umbrella trials is currently under review by a funding body. We hope to kick off the project within one year or two.

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