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## Redesigning phase 3 and 4 trials to adopt shared decision making

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this dangerous time, we must equip them with comprehensive mental health care, including suicide-specific assessments and treatments, regardless of the circumstances of OAT cessation.

This study does leave a few questions unanswered. The median treatment period of 84 days in this cohort is less than what is generally recommended,<sup>7</sup> leading us to question whether longer treatment duration might be associated with lower suicide risk after treatment discontinuation. Future studies might compare OAT treatment settings, distinguish the risks associated with methadone cessation from that of buprenorphine, and determine the effect of comorbid mental illnesses or the potential benefits of a slower taper off treatment or protective adjunctive treatments. It would also be helpful to assess the roles of social determinants of health, including poverty, racism, and access to care. Would access to better-resourced treatment centres result in less risk after OAT cessation? These findings might look different if adjusted for ethnicity, as they were for age and sex, given that minority populations face discrimination and have distinct risk factors for suicide as well as reduced access to quality treatments like OAT.

Most of all, further study is needed to test potential suicide prevention interventions in the period after treatment cessation. As with OAT, the period immediately following cessation of psychiatric inpatient care has been identified as a high-risk period for suicide.<sup>8</sup> Might the evidence-based interventions that are recommended following inpatient discharge, such as safety planning, caring contacts, and lethal means counselling,<sup>9</sup> be as effective in the period of vulnerability after stopping OAT?

Although there are always further directions to explore, the study by Padmanathan and colleagues adds to the evidence of the ability of OAT to prevent suicide and non-fatal self-harm, and illustrates the overlap and interplay between the two main fatal outcomes in psychiatric illness. It is a reminder that the benefits of opioid agonist therapies are not limited to the prevention of cravings and relapse, but are in some cases essential to maintaining our patients' fundamental desire to live.

We declare no competing interests.

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## Redesigning phase 3 and 4 trials to adopt shared decision making



There has been an ongoing debate about different types of medical trial design.<sup>1</sup> The classic double-blind, randomised, controlled trial (RCT) has superior internal validity and has been considered the gold standard for proving biological efficacy in medical science. Other designs, such as pragmatic trials, are increasingly popular because of their strong external

validity: the design and outcome variables better reflect daily clinical practice. The impact of changing health-care ethics and the rise of shared decision making as an essential part of treatment are not well accommodated in RCTs. In this Comment, we propose how to adopt principles of user-centred health care in medical trials.

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Detailed specification	
Allocate on the basis of choice	Inclusion should not be the result of randomisation but a constructive dialogue between people with mental illness, informal caregivers, and care teams, and should result in a wholehearted choice for a particular study treatment group; consider partially randomised preference trial designs <sup>9</sup>
Stop double-blinding and respect trial participants' unblinded opinion	Consider single-blinded designs with objective outcome measures, obtained by a blinded research team
Use outcome measures that are relevant for trial participants	Consult patient organisations in the choice of outcome measures; include patient preference (before and afterwards) and a reflection on the initial treatment decision
Minimise the number of exclusion criteria	Set the inclusion criteria so as to include most people with the mental illness under study
Use statistics that reflect the clinical complexity	Instrumental variable analyses can better accommodate non-dichotomous events; including more people enables proper post-hoc subgroup analyses (eg, gender or age)
Give tailored and user-friendly information before inclusion	Use plain language (considering different literacy levels) with simple statistics and visual information; create choice awareness and consider the use of decision aids; offer time to think and discuss the participation with caregivers

**Table: Recommendations to adopt shared decision making in phase 3 and 4 trials**

Key elements of shared decision making are tailored and user-friendly information, choice awareness, attention for values and preferences, and a decision process in which users and clinicians co-interact.<sup>2,3</sup> Shared decision making helps to change the traditional power asymmetry in mental health care by strengthening the decisional position of service users, and paves the way for personalised and deliberate decisions, a strong coalition between users and mental health-care professionals, and better treatment adherence.<sup>2,3</sup>

Therefore, it is not only a practical arrangement, but also a conceptual change in how people with mental health problems, their caregivers, and care teams should collaborate in a triad. This arrangement is radically different from the more authoritative style clinicians employed in the past.<sup>4</sup> In principle, the ownership of medical decisions is shared between service users, informal caregivers, psychiatrists, and other (mental) health-care professionals.

Social inclusion and respect for personal values and preferences in the centre of the clinical decision making process are increasingly becoming policy in many countries.<sup>5</sup> However, medical research has not yet developed accordingly. We believe that, in many cases, there are practical, ethical, and scientific reasons to favour pragmatic trials over double-blind RCTs.

The movement of user-centred care, with active and responsible service users and caregivers, might be at odds with the more passive role of RCT participants in the decision process for entering a study group: they are randomly assigned, included or excluded, and masked for the intervention. In addition, trial participants are still called subjects in many research papers. This

nomenclature is in sharp contrast to the position and level of ownership we, as clinicians, would like them, as patients, to adopt in clinical practice, where they actively decide in the choice of treatment.

Extrapolating the role of shared decision making in clinical practice to clinical trials, we believe trial participants should be considered as co-investigators. The changing attitude of service users and their caregivers towards power symmetry might be partly reflected in the high rates of refusal to participate in RCTs.<sup>6</sup> The preference not to be randomly allocated was the most prominent reason for refusing trial participation in a study of 90 individuals with non-affective psychosis.<sup>7</sup> This barrier might make large RCTs in mental health care increasingly difficult. A decline of inclusion in studies not only introduces bias but also results in failed studies and an increased risk of type II errors.

Admitting only people who are willing to give up deliberate choice for a particular treatment group raises the question of who wants to be randomly allocated nowadays. Moreover, we introduce a new form of bias: study participation bias for the subgroup of patients who are willing to be study participants. It is a combination of values and socioeconomic factors that determines whether one chooses to do so or not. Personality characteristics that determine whether someone wants to participate in a blinded trial, such as sensitivity to stress, and levels of anxiety, suspicion, and apathy, are critical factors for many medical outcomes and therefore introduce an important selection bias.

Let us reflect on the exact comparisons made in RCTs. Double-blind placebo comparison is a highly suitable way to establish treatment effect in phase 1

and 2 studies designed for efficacy (eg, experimental therapeutics and mechanistic studies). The outcome of a treatment in clinical practice, however, is dependent on both medication-specific aspects and non-specific (ie, psychological) aspects. These non-specific aspects entail the trust and hopes placed on a treatment, the conviction that improvement is possible, the chance that the treatment is continued, and the strength of the therapeutic alliance between patient and doctor. In an RCT setting, these non-specific factors are very different, as trial participants and clinicians have not actively chosen to start a specific treatment. The effect of non-specific factors might be much larger than that of specific factors, as shown in the seminal study on an antidepressant compound prescribed by nine different psychiatrists,<sup>7</sup> in which the allocation to a particular psychiatrist had more effect on the outcome variance than allocation to either placebo or antidepressant.<sup>8</sup>

Furthermore, if patient preference is a key factor in a participative intervention study, it is also possible to use a partially randomised preference trial design, combining allocation by choice and randomisation only for participants without a strong preference.<sup>7,9</sup>

As the positive effects of shared decision making on recovery emerge, the fundamental question arises of whether we should compare treatments or treatment decisions as a whole in phase 3 and 4 trials. The ownership of the decisions has become a fundamental part of the treatment that should not be left out in study comparisons, and personal decisions cannot be randomised or blinded.

Where do we go from here? The term pragmatic is not synonymous with *laissez faire*, and creativity

is needed from researchers to develop effectiveness studies with an optimum between internal and external validity. We first need to develop framework conditions for pragmatic phase 3 and 4 trials (table). We should be careful not to introduce selection bias if we stop randomly assigning people, but study designs that include wholehearted treatment decisions better respect the clinical reality.

Taken together, modern user-centred health care, with shared decision making at its heart, could and should also be applied in clinical research. We—researchers, people with mental illness, and care givers—should rethink our medical trial designs.

We declare no competing interests.

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## Addressing fentanyl use disorder with fentanyl-assisted treatment



The opioid overdose crisis has evolved into one of the worst public health emergencies in North America, with mortality rates having skyrocketed since 2015.<sup>1,2</sup> The current political and public health responses have not done much to change the trajectory of the crisis. Moreover, neither the free distribution of psychotropic substances in a non-therapeutic context (safe supply), nor the available opioid agonist treatments (OAT),

which are largely based on buprenorphine as first-line medication, have helped slow down the accumulating death toll.<sup>3</sup> A similar critical situation is also unfolding in two Baltic states, Lithuania and Latvia.<sup>4</sup> This crisis is having a direct effect on life expectancy, and is challenging the field of psychiatry, which is failing in the treatment of substance use and concurrent disorders.<sup>5</sup>

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