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RESEARCH PAPER

Individual consent in cluster randomised trials for non-pharmaceutical interventions: going beyond the Ottawa statement

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ABSTRACT

This paper discusses the issue of overriding the right of individual consent to participation in cluster randomised trials (CRTs). We focus on CRTs testing the efficacy of non-pharmaceutical interventions. As an example, we consider school closures during the COVID-19 pandemic. In Norway, a CRT was promoted as necessary for providing the best evidence to inform pandemic management policy. However, the proposal was rejected by the Norwegian Research Ethics Committee since it would violate the requirement for individual informed consent. This sparked debate about whether ethics stand in the way of evidence-based health policy, since the Norwegian Research Ethics law's strict requirements for individual consent make it practically impossible to carry out CRTs of public health interventions. We argue that, in the case of the school closure trial, the suggested CRT would not have eliminated an epistemic gap and thus would not have justified the violation of consent rights. First, we focus on the methodological challenges to estimating quantifiable effects of school closures in the specific case of an airborne infectious disease. Second, in line with Evidential Pluralism, we highlight the value of alternative lines of evidence for informing school closure policy in a pandemic. In general, we propose that a trial requiring the waiver of participants' consent rights must be highly likely to eliminate an epistemic gap. We elaborate on the practical aspects of this criterion and discuss the potential advantages of adding it to the *Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials.*

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Introduction

In this article, we discuss the question of whether and when overriding the right of individual consent to participate in trials of public health interventions, specifically cluster randomised trials (CRTs), should be considered ethically justified. As a case study, we use the controversy surrounding a Norwegian CRT,

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which was planned to test the effect of school closures on the spread of COVID-19 (Fretheim et al., 2020). The proposal was rejected by the Norwegian National Research Ethics Committees (Norwegian National Research Ethics Committees, 2020), provoking public debate involving researchers, decision makers, and other actors. The specific question we address concerns ethics and epistemology: when is the epistemic gain of a CRT large enough to justify a possible waiver of the requirement to individual informed consent? By referring to *The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials* (Weijer et al., 2012) and to current trends in the literature on the philosophy of evidence in medicine, we develop an approach based on Evidential Pluralism to address this question. We begin by providing an overview of our study case.

The Norwegian school closures trial

The Norwegian Knowledge Program (NKP) for COVID-19 was established in 2020 to strengthen the knowledge base for key decision making relating to the COVID-19 pandemic (Norwegian Institute of Public Health, 2021). The NKP was tasked to clarify the effect of school closures on the spread of infection. Fretheim et al. (2020) has argued that randomised trials are needed to inform policy decisions on whether to use school closures as a measure to stop the spread of infection. They proposed a cluster randomised trial (CRT) in which schools would be randomised to be re-opened or remain closed. There would be no opportunity for individuals to opt in or out of such a trial, however, which is ethically problematic since the trial would expose the participants to potential harms, including, for instance, a higher risk of infection in the open school group and mental health impacts in the closed school group. Possible adverse effects of school closure on pupils constituted the Ethical Board's main objection to the trial. This was in accordance with the research ethics principle that the safety of individuals should not be put at risk for the purpose of advancing knowledge (Norwegian National Research Ethics Committees, 2020). The risk of negative consequences of school closures on pupils was indeed later confirmed by evidence accumulated during the COVID-19 lockdown (Almeida et al., 2022; Hammerstein et al., 2021).

A broader range of ethical issues emerged during the debate, including the fact that a CRT design for public health interventions *generally* contravenes the Norwegian research ethics requirements for individual informed consent. The Norwegian research ethics law poses a nearly absolute requirement for consent to trial participation, with possible exceptions allowed only in clinical emergencies when the patient is unable to give consent (Health Research Act, 2009). Some scholars have argued that this regulation is obsolete in the face of newer experimental designs in which individual consent is often impossible, such as for a CRT for a public health intervention (Norwegian National Research Ethics Committees, 2021). The NKP, therefore, formally asked the Health Ministry to open up the possibility of exceptions to the requirement of individual consent in the case of studies that test interventions at a population level (Norwegian Institute of Public Health, 2020). In response, the Ministry did not agree that the situation would require a change of the law but did not exclude the possibility that a law change might happen in the future (Norwegian Institute of Public Health, 2020).

The prospect of changing the law in this direction triggers further questions, mainly concerning two issues: 1) Is there an absolute threshold of risk for participants at which a waiver cannot be granted? 2) if the risk is below this threshold or if there is no such threshold, does the expected knowledge gain of the trial(s) outweigh the expected negative consequences of granting the waiver?

When can CRTs be exempted from the requirement of individual consent?

As exemplified by the Norwegian case, the unique design of CRTs challenges the application and interpretation of standard research ethics regulations. International ethics guidelines are outlined in the *Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials* (Weijer et al., 2012). The Ottawa Statement says that an alteration to the individual consent requirement may be approved if: '(1) the research is not feasible without a waiver or alteration of consent, and (2) the

study interventions and data collection procedures pose no more than minimal risk' (Weijer et al., 2012, recommendation 6).

However, one consideration that is not included in the statement, and that emerged from the Norwegian discussion, is the need of a commonly agreed criterion to establish how large the expected epistemic gain of the experiment should be. This is a crucial point since the willingness to expose participants to even a small margin of risk, without their consent, must depend on the utility of the experiment. Although it is commonly agreed that any experiment is only justified when it is anticipated that the experiment will close an epistemic gap, in the case at hand there was no common agreement between stakeholders concerning the actual epistemic gain of a large-scale public health experiment. The Norwegian Ministry of Healthcare, for instance, argued that 'there is a relatively large scope for using other study methods' including 'already available data' (Norwegian Ministry of Healthcare, 2020, p1), while some researchers and politicians maintained that reliable answers to the research question cannot be arrived at without a large-scale experiment (Bjørnson Hagen, 2022).

Irrespective of the actual epistemic gap in the school closure case, there is a clear need for generally applicable guidance to establish whether waiving patients'/study participants' rights to individual consent is justified by the expected knowledge gain. Only with such guidance can an ethics committee be in a position to consider whether a trial that requires a waiver to consent is justified.

We propose the following condition for overriding an individual's right to consent, to be considered alongside conditions (1) and (2) of the Ottawa Statement outlined above:

> (3) Epistemic-Gap Condition: the study design must be highly likely to eliminate an epistemic gap. (See Appendix 1 for further discussion of this condition.)

The Epistemic-Gap Condition implies that one should consider the epistemic merits of the CRT *in the specific case*. On the other hand, it also requires a review of the *plurality* of currently available evidence to verify whether a new trial is really warranted. We propose that such evidence reviews should use the techniques of Evidential Pluralism, which provides a framework for assessing the full range of evidence. Evidential Pluralism is a philosophical theory of causal enquiry which holds that when assessing causality one should evaluate mechanistic studies (i.e. studies that shed light on the mechanisms that mediate between the putative cause and effect) alongside the experimental and observational studies that are the focus of orthodox systematic reviews (see the Assessing the Epistemic Gap section below).

We next consider how the Epistemic-Gap Condition might apply to the school-closure case.

Analysis of the Norwegian school closures trial

Potential knowledge gains

Randomised controlled trials (RCTs) are considered the gold standard to measure the effects of interventions, particularly pharmaceutical interventions (Howick, 2011). In the case of social interventions, which interact with local socio-political factors in ways that may be difficult to uncover or predict, the well-known issue of generalisability arises (Cartwright, 2012): while an RCT can inform whether an intervention works in the context in which the study was carried out, it can be difficult to predict the effect of the intervention in a different context. Despite this limitation, the scientific community assigns significant value to these experiments for example, in the field of economics (consider, for example, the 2019 Nobel Prize awarded to Abhijit Banerjee, Esther Duflo, and Michael Kremer, who applied experimental methods to the field of developmental economics). However, the issue of epistemic primacy of RCTs is still disputed in economics (Bédécarrats et al., 2020) even among Nobel laureates (Bédécarrats et al., 2020). Precisely because of the privileged epistemic role traditionally given to RCTs, however, there is a danger that the value of the evidence coming from an uninformative RCT is overestimated. Haber and colleagues, for instance, highlight this point while

expressing concern about the reliance on RCTs for measuring the effect of wearing masks for the spread of COVID-19 (Haber et al., 2021).

We propose therefore that the epistemic value of a CRT must be carefully evaluated for the specific research question at hand. In the case of school closures, the following specific considerations concern the use of a CRT to address a research question about an airborne infectious disease.

A pharmaceutical intervention, for example a novel cancer treatment, can typically be applied at the individual level, and while baseline (pre-treatment) dependencies may be present, the treatment of one individual can typically be assumed not to affect the outcome for other individuals. In contrast, for an infectious disease, the outcome of one individual depends on the treatment and outcomes of other individuals. This must be considered in the design of vaccine trials, for example, since vaccines can provide both direct protection to the vaccinated and indirect protection to the unvaccinated by reducing transmission. The World Health Organization provides extensive guidelines on the design of vaccine trials, including possible quantifiable treatment effects, or estimands (World Health Organisation, 2019).

Testing the effect of school closures in an ongoing pandemic encounters these challenges too, because school closures, just like vaccines, are interventions applied in an infectious disease setting. But this is not all. There are in this specific case additional challenges to bear in mind. School closures, unlike vaccines, are a type of non-pharmaceutical intervention (NPI), aimed at modifying social networks and contact rates in a certain community. They are thus a type of NPI that necessarily must be applied at a community level, unlike vaccines and other NPIs such as wearing masks, which are instead applied at the individual level.

Estimating the quantifiable effects of school closures, using a clustered randomized trial design, faces specific challenges:

(1) Complex effect modification: The effect of school closures on social networks and contacts will be modified by several factors that are only partially foreseeable, such as other pandemic management policies, the attitudes and behaviour of the population and other unknowns. While effect modification in an RCT is usually calculated through stratified statistical analyses, the accuracy of this calculation depends on the possibility of collecting data on the relevant baseline parameters that will be used to stratify the participants in groups (e.g. age, sex, medical history, etc.) (Rocca, 2018). This task is particularly difficult in the case at hand, given the social character of the intervention and given that effect modification is expected to be non-linear and unstable and to change over time.
(2) Blinding is impossible: Blinding, a hallmark of the gold standard RCT in the ideal pharmaceutical setting, is not possible when testing school closures, increasing the risk of bias. The risk of bias must be considered case by case. In this specific case, failing to blind can work as a powerful behaviour modifier for instance, by increasing precautionary behaviour in the open-school group because of feeling more exposed.
(3) Problems inherent to the CRT design in pandemics: the assumption that during a pandemic the outcome is independent among clusters (of schools) is doubtful, given the many other occasions for contact between children and their families and other members of the population. The intra-cluster correlation (ICC), measuring the strength of clustering of outcomes within a cluster, is not a stable parameter during a pandemic, since it depends on infection prevalence which is not a stable parameter during a pandemic, since it depends on the prevalence of infection (Gulliford et al., 2005).
(4) External validity: The external validity of school closure trials, as with other NPI trials, is limited, due to a number of factors that are prone to frequent changes over time and may also vary geographically: vaccination status (infectability); infection prevalence; pathogen variants; availability (price) and quality of (self-) testing for the pathogen; weather (and even climate); isolation and quarantine laws and how strictly they are followed;

transmissibility (SARS-CoV-2 variants thrive differently in the upper and lower airways) (Hou et al., 2020); availability and quality of protective equipment (air purifiers, masks, and gloves) and their proper uses. So, even if one could design an NPI RCT with good internal validity, it is hard to imagine how these results could be used to inform future pandemic management policy decisions.

These considerations underscore the complexities inherent in utilizing a clinical trial to assess the impact of school closures on COVID-19 transmissions, for the purpose of informing public health policy decisions. It is important to note that these complexities are not exclusive to this scenario, but also extend, with varying degrees, to trials of other social interventions – both in pandemic contexts and otherwise. The applicability of these considerations to other trials necessitates a case-by-case evaluation.

Assessing the epistemic gap

When the CRTs were suggested, a sizeable body of evidence on SARS-CoV-2 was already available. In particular, there was plenty of relevant mechanistic evidence, as well as observational studies and surveillance data (e.g. Lorig et al., 2021).

In the case of controlling the spread of infection, there already exists a considerable amount of relevant mechanistic evidence. For infectious diseases, reducing contact rates will reduce transmission, and school closures are an intervention that aims to reduce contact rates at schools, but could also have unintended consequences on contact rates outside of schools. It has been established that in the case of SARS-CoV-2 the dominant mode of transmission is airborne, with the virus able to survive for over 3 hours in aerosols (Van Doremalen et al., 2020). It is also well established that airborne transmission occurs particularly indoors, including in classrooms (Leclerc et al., 2020). Transmission also occurs via direct contact, contact with surfaces (Van Doremalen et al., 2020), and via animal vectors. These are the only means of transmission.

Observation studies and surveillance data have shown that policy measures greatly reduce mobility (Kamineni et al., 2023) and thus contact rates.

This evidence was already available prior to the demand for CRTs, and we would argue that the full diversity of the available evidence should be considered here. One approach to engaging with diversity of evidence is to consider observational studies alongside RCTs; see Verde (2020) for a theoretical development. It has also been argued that mechanistic evidence should be considered alongside observational and experimental studies and that this would have been particularly helpful during the pandemic (Aronson et al., 2021; Greenhalgh et al., 2022). The motivation for this 'EBM+' view of evidence appraisal can be found in the theory of Evidential Pluralism (Parkkinen et al., 2018; Shan & Williamson, 2023). Evidential Pluralism emphasises the importance of evidence of the mechanism of action of the intervention, of the mechanisms of the underlying health problem, and of any mechanisms that counteract or reinforce the action of the intervention. These mechanisms may have social and behavioural as well as biomedical aspects. Evidence of mechanisms should be considered because confirming the presence of key features of hypothesised mechanisms (such as mediating variables or entities or activities involved in the mechanisms) can lend confidence to the claim that an observed correlation is genuinely causal, rather than attributable to unknown confounding factors. On the other hand, evidence that key features of the purported mechanism of action are absent, or that there are mechanisms that can counteract the mechanism of action, can undermine confidence in causation. Either way, evidence of mechanisms is an informative part of the evidence base and should be systematically considered alongside experimental and observational studies (Williamson, 2019a). Evidential Pluralism provides a detailed account of how these streams of evidence should be integrated

(Parkkinen et al., 2018; Shan & Williamson, 2023). Evidential Pluralism thus provides a suitable framework for assessing whether there is an epistemic gap.[1]

Would the CRTs have eliminated an epistemic gap?

According to our Epistemic-Gap Condition, we must now take into account whether the proposed CRT would be sufficiently likely to eliminate an epistemic gap. Given the methodological challenges facing CRTs of public health policy interventions (see above) and given the other available pertinent evidence (see also above), we suggest that the potential knowledge gains of the proposed CRT to study the effects of school closures on the spread of the COVID-19 infection were limited. Therefore, exposing individuals to any risk, without their consent, would have not been epistemically worthwhile in this case.

Notice, however, that if all this evidence had *not* been available – if there were only a hypothesis of a possible mechanism by which social distancing might affect transmission and by which school closure might affect social distancing, and such a hypothesis were not supported by the evidence we mentioned above – the relative potential value of the CRT would be higher.

In general, therefore, we claim that the existing evidence, in all its diversity, needs to be systematically scrutinised and evaluated, using the framework of Evidential Pluralism, before any case can be made for a waiver of individual consent for the purpose of CRTs.

Conclusions

CRTs have a particular design that poses not only methodological but also ethical challenges, and therefore specific ethical guidelines are needed. The Norwegian proposal of a CRT to test the effect of school closures of the spread of COVID-19 was rejected by the national ethics committee based on current research ethics laws. This opened up the question whether Norwegian legislation might need to modify the requirement of individual consent to make CRTs feasible. Whether or not the law needs changing is still a matter of debate, and it is beyond the scope of this paper to take any particular stance on this issue. However, the prospect of a possible change in the law motivates the need to think carefully through the available ethical guidelines for CRTs – a need that goes beyond the Norway's borders.

Infringing an individual's right to consent to the risks of a trial, regardless of how small these risks are, is a significant move. One reason for concern is that there is no objective definition of an 'acceptable risk'. In a future health emergency, should an ethical committee raise the threshold of acceptable risk to individuals for the benefit of the community? It is not our goal here to answer such questions, and we are looking forward to future discussion on this matter. However, we have highlighted a pre-condition that could serve as a means of 'screening' cases in which a CRT could significantly bridge an epistemic gap: namely, a research design requiring the waiving of patients' consent rights must be highly likely to eliminate an epistemic gap.

Our Epistemic-Gap Condition serves two purposes. On the one hand, it reduces the number of cases in which a waiver of individual consent might even be considered. We maintain that with the prospect of a change in the law, some such screening is important. On the other hand, our criterion specifies which cases do qualify for a further evaluation of a possible waiver. This assessment may serve as a starting point for ethical decision-making. Even if Norwegian law had been changed in the direction proposed by the Norwegian Knowledge Program, the schools closure CRT would *not* have provided sufficient epistemic gain to qualify for an ethical evaluation, according to our criterion.

However, it is not hard to imagine that some future type of intervention might qualify. Possible examples are interventions based on new theoretical approaches, such as innovative technologies for air purification. Generally, in cases in which the understanding of the pathophysiological mechanisms is poor, the Epistemic-Gap Condition is easier to satisfy. Our criterion might even

persuade those who find it hard to countenance a change in Norwegian research ethics law that, with more rigorous justification, the possibility of the waiver of individual consent may sometimes be worthwhile.

Now is a good time to think about and prepare for future pandemics. Some time has passed since COVID-19 dominated our lives, yet our memories are still sufficiently fresh to truly appreciate the emergency. We would urge some healthy debate about attitudes to risk during pandemics (Abdin et al., 2023) in order to better prepare for the next pandemic.

Note

1. The Monographs programme of the International Agency for Research on Cancer (IARC), which conducts evaluations of carcinogenicity, provides an example of an agency whose methodology conforms closely to the principles of Evidential Pluralism (Williamson, 2019b). Evidential Pluralism should arguably also be applied to the evaluation of pharmaceutical interventions (Aronson et al., 2018; Maziarz & Stencel, 2022; Park et al., 2023). Currently, however, drug approval agencies only systematically scrutinise mechanistic evidence in certain contexts. One such context is the evaluation of biosimilar medicines, where mechanistic studies are routinely considered in place of clinical studies. Another is the US FDA Accelerated Approval Program: instead of demonstrating that a medicine directly induces a clinical outcome, the program evaluates whether there is some mechanism that leads to the clinical outcome via a surrogate endpoint, i.e. a mediating variable.

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Appendix 1

In this appendix, we discuss the Epistemic-Gap Condition in more detail.

Epistemic-Gap Condition: the study design must be highly likely to eliminate an epistemic gap.

What we call an *epistemic gap* occurs in a situation in which the total evidence available at present deems the effectiveness of the intervention (i) to be likely enough to consider waiving consent rights; but (ii) to be not so likely as to already warrant deploying the intervention.

The Epistemic-Gap Condition can be met by establishing the following claims:

(a) On the basis of current evidence, it is sufficiently likely that the intervention will be effective to consider imposing the intervention on those in the treatment group without their consent. This requires assessing the full range of available evidence – not just RCTs, for example.
(b) Current evidence does not already warrant the use of the intervention. (Otherwise, it would not be ethical to withhold the intervention from those in the control group without their consent.) Again, this judgement should be made on the basis of the full range of current evidence. It may also depend on the costs of intervening and of failing to intervene.
(c) The study addresses relevant questions, is appropriately designed and of high enough quality to eliminate the epistemic gap.

Claims (a) and (b) can be thought of as encapsulating a demand for a particular kind of equipoise. Our key point is that there is a strong ethical case for requiring this kind of equipoise when considering whether to override the right to consent, regardless of whether equipoise is required in other circumstances. Moreover, we maintain that claims (a) and (b) should be assessed on the basis of the full range of current evidence and that Evidential Pluralism provides a methodology for carrying out this assessment.