Digital interventions for relapse prevention in adolescence

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1. Excellence

1.1. State of the art, knowledge needs and project objectives

Globally, it is estimated that 4.6 % of all adolescents in the age group 15-19 years, experience an anxiety disorder and 2.8 % experience depression (1). Together with behavioural disorders, these disorders are the number one cause of illness and disability in this age group. Single episodes of depression and anxiety during teenage years can be immediately serious and potentially life-threatening (2). It is also a risk factor for developing more severe affective disorders, long-term psychosocial, educational, and vocational impairments, poorer physical health, increased risk of suicide and self-harm, and dependence of illicit drugs (3-6) Anxiety in the adolescent years, is associated with three-fold increase of depression in early-adulthood (7). Often, the two disorders co-occur or cross over to one another, suggesting that transdiagnostic factors are of importance.

Treatment for adolescent anxiety and depression are moderately effective (8, 9) and use of mental health services attenuate negative long-term outcome (6). Still, many are left with residual symptoms after treatment, (10) and a subsequent risk of relapse. Also, diagnostic instability is prevalent (e.g., newly arisen depression following remission from an anxiety disorder), markedly increasing the recurrence rates (11)). Moreover, since each new episode of MDD increases the risk of having further episodes (12), efforts needs to be undertaken in order to break this vicious cycle of repeated episodes during adolescence.

According to DSM-5, remission from depression is defined as having no significant symptoms of depression for at least two months. Relapse is then defined as reemergence of clinically significant symptoms of depression within 12 months after remission is being achieved, and if symptoms reemerge after that it is defined as recurrence (13). For anxiety disorders, these boundaries are less defined (14). In practice, relapse and recurrence are difficult to separate, and in ongoing trials on relapse prevention, they are often grouped together (15, 16).

While clinical practice guidelines for adolescent depression treatment indicates that research on effective approaches to hinder relapse and recurrence are lacking and needs to be prioritized (17), meta-analytic evidence suggests that studies on relapse prevention in adolescence is scarce and of suboptimal quality and none have targeted relapse to anxiety (18). On a positive note, however, all strategies that have been employed (e.g., psychological interventions, pharmacological interventions, or a combination thereof), have demonstrated efficacy in either reducing relapse rates, or increasing the time until relapse.

In both anxiety and depression, repetitive negative thinking (RNT), like worry and rumination, is common, and is found to be a transdiagnostic factor partly explaining their co-occurrence both cross-sectionally and prospectively (19). RNT also plays an important role in somatic complaints, and fully mediate the relationship between vulnerability factors for both mental and physical disorders, such as the relation between neuroticism and pain (20) and stress and somatic complaints (21). Interventions grounded in cognitive behavioral therapy can systematically reduce RNT, and thereby reduce relapse risk for depression and the tendency of anxiety to cross-over to depression. When negative thought content is recycled (i.e., rumination) or a tendency to anticipate negative scenarios are favored (i.e., worry), RNT introduces and sustains negative mood. Consequently, worry have been found to be a stronger predictor for depression relapse than residual depression (22) and rumination is known to predict relapse and recurrence of depression (23).

There is a pressing need for adopting new technology for serving the rising demand of mental health services (e.g., (24). By developing new methods that are scalable, we can reach more people in a

cost-efficient manner. Still, however, none has systematically investigated if interventions aimed at relapse prevention require therapist-involvement to be effective. While alliance is a central common factor for the effect of all psychological treatment, this factor is lacking in unguided treatment regiments. Yet, in a small young adult depression prevention trial in an at-risk population, the effect sizes for guided and unguided self-help programs were similar (25), suggesting that engagement is important when investigating outcomes of digital interventions (26). If the therapist is redundant when delivering these programs, barriers for entering relapse prevention programs are reduced considerably.

Among adolescents who has experienced depressive episodes and/or anxiety disorders, the current project will adopt a multiarmed randomized design for assessing the efficacy of targeting transdiagnostic processes for relapse prevention at different level of clinician involvement. The main aim is to reduce number of relapses to depression and time to relapse over the course of twelve months. The project will also investigate the mediating effect of the hypothesized mechanism (i.e., RNT) on the subsequent relapse risk.

1.2. Novelty and ambition

A main objective of this this multiarmed trial is to compare two digital versions of a transdiagnostic prevention program with varying level of therapist guidance, to assessment-only. The “Tankevirus”-(eng.: Thought viruses) program offers easily accessible, popularized knowledge and advice on how to develop psychological resilience. It is based on the principles of CBT and makes available different strategies for targeting heuristics and thinking traps leading to rumination and worry. By reducing thought viruses, risk of relapse can be reduced.

Digital interventions targeting mental health problems has grown profoundly more popular due to its availability, accessibility, scalability, and low cost associated with its use. Importantly, clinical trials investigating their effectiveness suggests that they offer value for money when compared with no intervention and non-therapeutic controls, but maybe not when controlled to interventions led by therapists (27). However, a direct comparison between digital interventions and therapist-led interventions in relation to relapse has not been conducted and no digital interventions for relapse prevention has been investigated in adolescent populations.

By investigating the efficacy of two types of digital interventions with different need for therapist involvement, and predictors for their effect, this trial will offer new insights and strategies for reducing relapse among adolescents, potentially paving the way for relapse prevention in the format of a readily accessible, personalized, digital solution for adolescents that can be easily implemented nationwide. By assessing the cost-effectiveness of the different versions of the interventions we can identify whether therapist involvement is necessary. While previous relapse prevention trials have shown efficacy (18), they have not been health economically evaluated. Digital intervention has an obvious economical advantage compared to individualized, therapist-guided interventions, however, the evidence regarding the cost-effectiveness of digital tools is scattered (28).

The trial will be conducted fully decentralized, implying that we will have a nationwide pool for recruiting participants, where access to internet is the only prerequisite. For people with reduced access to health providers due to long travels etc., this will build down barriers for taking part in research and will be particularly important for adolescents who may struggle with residual symptoms hindering their mobility. The broad recruitment will be beneficial for generalizing the findings.

1.3. Research questions and hypotheses, theoretical approach and methodology

RESEARCH QUESTION: Through a decentralized RCT investigating two digital interventions with differentiated levels of therapist-support, the goal is to expand knowledge about transdiagnostic relapse prevention strategies that can easily be scaled up and have the potential of cost-effectively reducing relapse rates for adolescents in an important phase of life. Alongside, collecting empirical

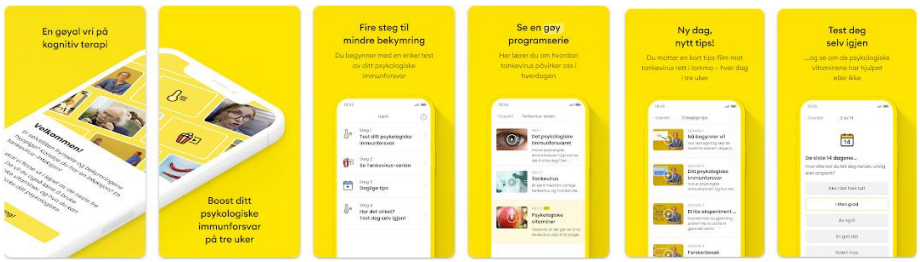
evidence for the association between repetitive negative thinking and relapse will increase knowledge regarding underlying mechanisms of relapse prevention strategies.

DESIGN: The trial is designed as a three-armed randomized single-blind open-label clinical trial (1:1:1) with stratification based on gender. It will not be possible to blind participants in the study due to the obvious differences between the interventions. We will investigate the effects of the "Tankevirus"-therapist-guided intervention and the "Tankevirus" smartphone app, respectively, and compare the effect of these transdiagnostic interventions to assessment only. All arms will be conducted in combination with care as usual. Assessments are done digitally, with no influence from the researcher. The primary endpoint of the trial will be analyzed blinded to treatment allocation. The trial will be preregistered with clinicaltrials.gov.

INTERVENTIONS: "Tankevirus" is an award-winning psychological intervention developed for adolescents aged 16 and above, including a book, a mastery course, and a smartphone app. It is based on the principles of CBT to help individuals identify and challenge negative thought patterns that can lead to anxiety and depression. "Tankevirus" has been extensively evaluated. From 2017-2021, 50.000 students took part in the overarching "Tankevirus" School program, and 9 out of 10 thought the interventions were useful and would recommend it to a fellow student. The "Tankevirus" smartphone app is freely available, and within 16 months, it was downloaded by 26.000 adolescents. Based on patient reported outcome measures, 7 out of 10 reported improvements in overall health and increased quality of life. The app includes several components to increase engagement with the intervention material, which is a necessary prerequisite for digital mental health interventions to be effective (26), and smartphone apps which have elements built in to promote engagement are associated with larger effect sizes (29). In this project we will include two different formats of the "Tankevirus"-interventions, in addition to a control condition:

- **"Tankevirus" therapist-guided group intervention**: The intervention will be delivered by therapists having extensive experience with this age group in the form of 3 weekly 75-minutes sessions to groups of approximately 30-35 particiapnts. An online GDPR-compliant webinar-platform including chat-options will be used (edumeet.org). Adolescents will remain anonymous to each other to decrease barriers to participation. The adolescents will book their preferred timeslot online. For the participants randomized to this intervention, a certain waiting period (~1week] must be expected. We will keep record of number of days waiting for each person and include this as covariate in the analysis.
- **"Tankevirus" smartphone app:** The app will be downloaded to their personal smartphone, and the app will give push-notifications once new modules are released – every day for 3 weeks. The app has several procedures built in for engagement purposes but will not involve contact with a therapist. Usage data will be recorded to verify compliance. The app is developed in accordance with the requirements of the Norwegian Health Authorities and complies with data protection laws.
- **Assessment-only:** All assessments will be conducted, but no intervention will be provided to this group. The assessment only condition is necessary for investigating natural trajectory and form the baseline level for assessing risk reduction in the interventional groups.

Figure 1. Screenshot from GooglePlay of the "Tankevirus" smartphone app.



All interventions and assessments for all trial arms will be fully digitalized through a research app, which is essentially a modification to the already developed "Tankevirus"-app, including all preassessments and follow-ups. Human interaction is limited to the therapist-led group, otherwise automized nudges and notifications will remined the adolescents to complete assessments. This will be beneficial when considering the scalability and implementation of the intervention, should it be successful, and for evaluating whether human interaction indeed is a driver of the effect between interventions.

HYPOTHESIS: The main hypothesis is that the outcome related to the therapist-guided group intervention will be more effective in reducing number of relapses and time to relapse during the follow-up period when compared to the app-based approach, and that the app-based approach will be more efficacious compared to an assessment-only condition/care-as-usual (the control group).

PARTICIPANTS: Participants will primarily be recruited through large scale marketing campaign in social media (i.e., TikTok, Snapchat, Instagram) and web pages of user organizations, informing about this trial and the opportunity to take part. This is the most efficient way of reaching eligible participants, as clinicians seldom refer to such a trial (Y. Stikkelbroek, PI of the StayFine-trial targeting adolescents in remission, *personal communication*, 21.07.24). Overall, 90 % of Norwegian adolescents are on social media (30). Currently, we have established contact with the social media coordinator in Mental Helse Ungdom. We will also post physical adds at places we expect adolescents to see them. Through other ongoing projects we have contact with ~150 general practitioners and we have established a collaboration with the low-threshold service UngArena.

The combination of elaborate marketing campaigns in social media and the research app will allow for a very efficient recruitment, eligibility check and data collection. Those being interested will register online after confirming inclusion criteria: 1) between the ages of 16-19, 2) have previously sought professional help for anxiety and/or depressive symptoms, 3) have been feeling fine or mostly fine for the last two months. Before further assessment and trial inclusion, the adolescent will sign informed consent digitally. After consent is obtained, they will be invited to download the research app. To ensure eligibility, preassessment with the digitalized self-report format of the clinical interview Composite International Diagnostic Interview 5th revision (CIDI 5.0 (31)) will be conducted to make sure that the adolescent have had a previous episode of depression and/or an anxiety fulfilling the DSM-5 criteria, and no current ongoing episode or ongoing anxiety disorder before trial entry and randomization are conducted.

Table 1. *Participant eligibility*

Inclusion criteria
• Currently in full or partial remission for a minimum of 2 months from a depressive disorder or an anxiety disorder. • Age between 16-19. • Native or fluent Norwegian or Scandinavian language skills. • Willingness to take part even when allocated to the non-preferred intervention.
Exclusion criteria
• Ongoing depressive disorder, ongoing anxiety disorder**.** • Recent (within ~1 year) completion of the "Tankevirus"-intervention. • No available smartphone.

PRIMARY ENDPOINT: The primary endpoint will be time until relapse and number of relapses to depression during the 12-months follow-up post-randomization. To assess relapse, the app will give notifications for biweekly assessments with the ultra-brief PHQ-4 (32) assessing both anxiety and depressive symptoms. If the depression subscale indicates relapse (score≥3), the remaining questions from PHQ-A (33), that is the adolescent version of PHQ-9 (34), will pop-up. The items in PHQ-9 aligns with the diagnostic criteria for major depressives disorder as described in the Diagnostic and

Statistical Manual of Mental Disorders (35) and an algorithm can therefore indicate depressive relapse (36). This procedure of biweekly assessments will also provide a precise measure of time to relapse.

For exploratory purposes, we will also examine predictors of relapse and predictors for the efficacy of theses respective interventions for investigating whom that are most likely to benefit from these different options. In line with recent developments in clinical research, we will address outcome domains relevant from the adolescent perspective, like well-being and self-reported symptom load (37), described below.

SECONDARY OUTCOMEs (between trial entry, at 3 months, 6 months, and 12-months):

Repetitive negative thinking - RNT-10 (38) assess transdiagnostic repetitive negative thinking, such as worry and rumination. The questionnaire will be translated into Norwegian by means of a back-translation procedure.
Somatic complaints – SSS8 is an 8-item questionnaire about somatic complaints, freely available and translated into Norwegian (39).
Well-Being - EPOCH Measure of Adolescent Well-Being(40) is a 20-item validated questionnaire that is freely available and will be translated into Norwegian by means of a back-translation procedure.
Health related Quality of Life - EQ-5D-5L + EQ VAS (41, 42) is available in Norwegian and will be used for economic evaluation of the interventions.
Use of health care services – adapted version of the Client Service receipt inventory (CSRI) will assess use of health services, medication use, and school absence.

ASSESSMENTS: Assessments at baseline will serve as predictors of outcome, and include age, gender, parental educational level as proxy for socioeconomical status, in addition to the assessments listed as secondary outcomes. Adolescents are required to fill in questionnaires repeatedly at 3, 6 and 12-month follow up. To maintain fidelity to the trial and prevent fatigue, we have prioritized short, validated scales. All assessments will be conducted within a digital environment (i.e., the research app). In addition to the primary and secondary outcome, at 3-month follow-up, the 8-item Client Satisfaction Questionnaire adapted to Internet-based interventions (CSQ-I (43)) will be administrated to those taking part in one of the two interventional arms.

STATISTICAL POWER: For the primary endpoint investigating number of relapses within the follow-up period, we will conduct a fixed effects omnibus ANOVA. Presuming Cohen's f =.25, alpha = .0167 (.05/3; Bonferroni corrected) and power =.8 including three groups, we will require a total sample size of 207 (GPower 3.1). Presuming 15 % dropout, we will need 238 adolescents to take part in the study. For time to relapse, the power analysis was performed using Monte Carlo simulation. A large pool of simulated survival data was generated, reflecting a hazard ratio of 0.6 between two groups, a 15% annual dropout rate with competing risk, and a 1-year observation period. The simulation titrated the sample size, drawing 10.000 random samples at each step and fitting Cox proportional hazards models. Power was estimated as the proportion of samples yielding statistically significant results at the 0.05 level. The analysis concluded that approximately 165 individuals per group, meaning that a total of 495 adolescents would be required to achieve 80% power for detecting a hazard ratio of 0.6 under the specified conditions. This simulation method accounts for the complexities of survival data, including censoring and limited observation time, providing a robust sample size estimate for the study design. All randomized participants will be subjected to analysis in accordance with an intention to-treat approach. The multiarmed parallel group randomized trial will be reported according to the extensions recommended by CONSORT (44).

RISK: Recruitment is the main risk factors of this trial. A few trails are currently under way in adolescent populations (e.g., StayFine trial (16), RuMeChange (15)) and in the first, they were in contact with 3018 adolescent during a three-year period. Their strict inclusion criteria and elaborate pre-inclusion assessments hindered several from participating, but still they had 589 eligible

participants. Our pre-inclusion assessments and inclusion criteria will be less comprehensive, allowing for more participants to be included. Presuming that the three birth cohorts in Norway comprises 150.000 adolescents aged 16-19. Of these, 5 % will currently have an anxiety disorder and 2% will have a depressive disorder as per diagnosis in specialized health care (45), amounting to approximately 10.500 potential participants. We would then need to recruit 4.7 % of this population (495/10.500) to complete this study. When considering that we require the adolescents who are in remission only, that they may have fulfilled the criteria at earlier ages, and that only a minority of adolescents are diagnosed and/or treated in specialized health care even when having profound symptom load (46), these numbers are conservative.

Attrition is another risk factor. The evidence in relation to decentralized trials and retention among adolescents is still scarce, and recommendations currently rely on the use of well-evidenced strategies (e.g., incentives, reducing barriers and burden, and investing in building positive relationships with participants) when engaging adolescents in longitudinal health studies (47). Hence, the adolescents will be issued a universal gift card worth 1200 NOK when they have completed their participation. Each assessment will be initiated by a prompt about how much it's pays to promote its completion. The therapists in the therapist-led interventional arm have extensive experience delivering these interventions to youths and are good at building positive relations. Due to the digitalized format, push notification will be used to promote engagement.

ETHICS: There is an inherent risk of relapse among these adolescents, and it will therefore be important to detect if their state deteriorates during the trial and offer them advice on how they can proceed to receive the adequate level of care. The contact information to the project group will always be available in the app. At all follow-ups, if a certain symptom load is detected, a pop-up message will appear, including our contact information and information about treatment providers. If CIDI 5.0 pre-assessment reveals an ongoing disorder, the adolescent will be advised on whom to contact for receiving adequate level of care and will not be included in this trial.

Currently, there is no systematic relapse prevention strategies offered to this group within the health services. If the adolescent does receive care at any level within the health services, enrolment in this trial will not interrupt ongoing care regiments, nor will enrolment put any restrictions on initiating new care regiments, but we will ask them not to download other mental health apps during their participation. Ongoing care will be registered and will be controlled for when analysing the outcome.

GENDER: We will register the gender of the participants and conduct separate analysis to better understand the gender imbalance of experiencing depression. A low number of binary participants may hinder separate analysis for this group.

USER KNOWLEDGE: Adolescents 16-19 years of age have been involved in all stages of the development of the "Tankevirus"-interventions, from idea to product. Their voices have extensively influenced its current content, like its duration, scope, means of communication (i.e., short videos), examples, humour, illustrations, music, and ensuring that it meets their prior knowledge. The app received the highest-ranking score by DigiUng, the panel of youths advising The Norwegian Directorate of Health. For this project, we have initiated collaboration with the Competence Center for Lived Experience and Service Deployment (KBT), who specializes in bringing forward service user voices. By involving persons with lived experiences in our research group, we will ensure that this project cater their needs. Their voices have been heard in the development of this project, f. ex. regarding outcome measures, the participant burden, and their compensation, and will also be important when building recruitment campaigns, in designing and writing information material, and ensure that the workload associated with participation is manageable. They will also be important when interpreting and disseminating the results. In the planning phase, the project will also be discussed with the national youth user panel of FACT (Flexible Assertive Community Treatment).

2. Impact

2.1. Potential impact of the proposed research

Should this trial be successful, we will have a scalable solution for breaking the unfortunate cycle of reoccurrence of depression among adolescents, which will have long-term beneficial impact. Based on prediction analysis, the two different alternatives of relapse prevention in this trial, including either clinician supported intervention or self-help intervention, allow for staging of care according to individual needs and cost-benefit calculations.

Anxiety and depression often go hand in hand with physical complaints. The "Tankevirus"-program targets transdiagnostic factors underlying physical complaints and pain and might therefore be beneficial in a broader health related context and reduce the overall burden associated with recurrent depression in adolescence on the health care system.

This trial will in addition to depression relapse, also investigate the diagnostic instability represented by the cross over from anxiety to depression. In this undescribed field of research, this represents a major leap when quantifying the potential benefit of introducing programs in an intermittent phase of the disorders and hinder its transgression into episodes of depression. Hence, this high-quality large-scale trial with long-term follow-up will provide evidence for the efficacy of depression relapse interventions among adolescents. The head-to-head comparison of interventions will disentangle the level of clinician-involvement required, and the inclusion of a cost-effectiveness analysis will bring leverage for its implementation.

2.2. Measures for communication and exploitation

Open access publications in high-rank international journals will inform the scientific community. By reaching out to clinicians and policy makers with this newly derived knowledge about treatment efficacy and predictors of treatment success, we can implement this newly derived knowledge into clinical guidelines making appropriate recommendations. Also, reaching policy makers are central for securing funding to support the continued delivery of "Tankevirus"-courses and app.

The therapist-led part of "Tankevirus" would require building up competency in this specific method. Courses are already in place and supported by the Norwegian directorate of health. The digital online format of the intervention implies that each person being licenced, could deliver courses nationwide, supporting the scalability of the intervention. Infrastructure for referring remitted adolescents into these courses would need to be developed.

Should this trial be successful, it will allow the "Tankevirus"-program to be applied to a new target group. Since the app already is available and recommended as selfcare strategy for depression and anxiety within HelseNorge.no, the official website for information about and access to health services for Norwegian residents, our collaboration with user organizations will be essential in our efforts at reaching the adolescent who has the largest predicted effect from the app-version of "Tankevirus". Presentations at national clinical conferences will be essential for transmitting knowledge to clinicians.

3. Implementation

3.1. Project manager and project group

The project is led by the Clinical Neuroscience Research Group (CNRG) at the Dept. of Psychology, University of Oslo (UiO), who has extensive experience conducting hybrid trials in relation to digitally deployed relapse prevention strategies for depression (48) and fully digitalized trials for depression treatment (49) among adults and have also conducted studies among adolescent populations (50). The PI will oversee the day-to-day administration of the project, as well as training research assistants. The PI will write papers in close collaboration with the other members of the research group. Brorson will ensure that the interventions are delivered as intended by the team in Bergen

municipality, who has extensive experience with disseminating digital interventions to adolescents. Hansson will be responsible for the diagnostic procedures and for upholding clinical perspectives in the planning and execution of the project. Rand will conduct the cost-benefit analysis. Landrø will ensure the quality of the trial and provide guidance on conducting decentralized trials. The persons with lived experience will ensure the quality of the participant information and make recommendation on how to recruit and retain participants, in addition to interpreting and disseminating the results. The project group cover expertise on all necessary areas, including clinical, theoretical, and methodological skills in clinical psychology, psychiatry, statistics, and project management, as well as lived experience and knowledge about the mental health care system.

Table 2: Overview of project collaborators

	Expertise	**Project role**
CNRG, Dept. of Psychology, UiO: ***Ragnhild Bø***, Researcher, psychologist ***Nils Inge Landrø***, Professor, specialist in clinical neuropsychology	- Psychological assessments - Depression and comorbidity - Decentralized trials	Study design, Data collection, Recruiting/supervising students in data collection, Analyzing data, Writing papers, Dissemination
Brorson & Sande ***Hanne Brorson****, Psychologist*	- Interventions	Plan and supervise intervention, revise papers, dissemination.
Ahus, Maths in Health ***Kim Rand*****,** *Psychologist and Ph.D. in research on health services*	- Health economy	Conduct cost-benefit analyses. Deliver app-intervention
Bergen municipality ***Friskliv and public health coordinators***	- Interventions	Deliver therapist-guided intervention
Competence center for lived experience and service development (KBT) ***Juni Raak Høiseth*****,** professional advisor with lived experience ***Hannah Børdahl,*** user representative	- User experience and involvement	Designing, recruitment, information to participants, dissemination

3.2. **Project organization and management**

Project period: June 2025-June 2028.

Table 3*: Gantt chart*

		Year 1				**Year 2**				**Year 3**			
Activity	Responsible	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Preparation													
Designing	RB, HB, KR, NIL, KBT												
Data protection	RB, KR												
Ethical approval	RB												
Preregistration	RB, NIL												
Piloting	RB, HB												
Recruiting patients	JRH, RB												
Data collection													
Interventions	BM, HB												
Follow-up	RB												
Statistical analysis													
Primary endpoint	RB, KR												
Exploratory analysis	RB												
Dissemination													
Publish inter.	NIL, RB, HB, KR												
Communication	RB, HB, JRH												

Through Nettskjema and Tjenester for sensitive data (TSD), the University of Oslo will provide research infrastructure for collecting informed consents digitally with MinID or BankID. This is the only identifiable information we will collect. The “Tankevirus” smartphone intervention is already developed and will be incorporated in a research platform allowing for all data to be collected in a streamlined, and anonymized manner. This app is currently being developed by Maths in Health and the anonymity of the platform will be assessed by SIKT for adherence to privacy regulations (GDPR).

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