Title: Enabling Access to Sexual Healthcare in Youth at high risk of STI: the EASY project
Project number: 10150511910058

Dear members of the ZonMw Committee Infectious Disease Control,

We would like to sincerely thank reviewers 1529961, 1529971, and 1538788 for their detailed feedback, which allowed us to clarify and further improve our EASY project proposal. Overall, the reviewers considered our proposal to innovatively address a relevant and important public and sexual health issue with adequate focus on end-user participation throughout the project. In addition, all reviewers believed that the project would make an important contribution to understanding and addressing sexual healthcare service (SHCS) needs of youth at high risk of STI. As reviewer 1529971 stated: *'I think the proposal in its entirely is innovative and the knowledge gained will make an important contribution to our understanding of the SHCS needs of youth, their attitudes around sex, STIs and the need for testing, and ultimately will lead to improved control of STIs and reduction in STI burden'.* We would like to thank reviewers 1529961 and 1529971 for assessing the overall quality of our proposal as 'Good' and reviewer 1538788 for assessing the overall quality as 'Very good'.

Below, we address the points raised by the reviewers. We would like to start by apologizing for our unfortunate error to submit our proposal without the 'project team' section, which was inadvertently replaced by a copy of the 'knowledge transfer' section. We realize this may have caused some confusion regarding the execution of the EASY project and the further implementation of its results, in particular because our project members play an important role in these regards. In this letter, we therefore emphasize our project members' roles, when relevant. We conclude by describing the effects of the ongoing COVID-19 pandemic on the relevance and logistics of our proposal.

Strategy and feasibility
Overall, reviewers 1529971 and 1538788 rated our strategy as 'Very good' and 'Excellent', describing our proposed strategy as 'highly appropriate' to achieve the desired outcomes. Nevertheless, several specific points were raised.

Recruitment strategies
Reviewer 1529961 noted that the recruitment strategy described in WP2 may be unethical, as door-to-door visits may expose youth's sexual activities/interests to their families, and individuals aged 16-18 years old are targeted. We wish to clarify that door-to-door visits merely serve to motivate youth to participate in the study. Data collection does not take place during these visits. In addition, though not specified in the proposal as such, door-to-door visits only focus on individuals aged 18 or above. A study protocol describing this recruitment strategy was previously approved by the Medical Ethical Research Committee (METC) of the University Medical Center Utrecht, as it was part of Knowledge Center for Sexual and Reproductive Health Rutgers' previous 'Seks onder je 25e' (SO25) studies. Therefore, we are confident that we do not violate ethical guidelines through this approach.

Reviewer 1529971 commented that though the strategy for recruiting (un)reached and at-risk youth are clearly described, the strategy for recruiting SHCS-providers have been described in less detail. We assume this concerns WP1, where we aim to collaborate with general practitioners (GP) and providers of home-based STI self-sampling kits. Our project team member dr. (10)(2e) (10)(2e) will play an important role in this regard, as he is chairman of SeksHAG (expert network of GPs with a special interest in sexual health) and is involved in soapoli-online.nl (provider of home-based STI self-sampling kits) as medical supervisor. Both parties have readily expressed their willingness and interest to participate in the EASY project and our next step is to work on collaboration agreements. Therefore, we are confident that we will be able to successfully recruit the necessary SHCS-providers.

Reviewers 1529971 and 1538788 expressed concerns regarding the dependency of work package 2's (WP2's) data collection on integration with Rutgers' SO25 study. Though we will indeed not operate fully autonomously if we join Rutgers' SO25 data collection, we believe that this collaboration will provide us with otherwise unattainable opportunities to collect sexual health data from a large-scale, nationally representative sample of youth aged 16-25 years old. In addition, the SO25 questionnaire will be established through consultation between different stakeholders with an interest in sexual health of youth in the Netherlands, including for example municipal public health services ("GGD") and the National Institute for Public Health and the Environment ("RIVM"). The principal

investigator of SO25 (10)(2e) (10)(2e) 0)(2 (10)(2e)), who is also part of our project team, has readily indicated that we can join these consultations to represent the EASY project. As such, we will have an active role in Rutgers' SO25 data collection, which makes us confident that we will be sufficiently able to incorporate our aims into the SO25 questionnaire and, more generally, have increased the feasibility of conducting the proposed research. In the worst-case scenario that we will not be able to obtain the data needed for the EASY project, we reserved budget to organize our data collection independently through a research panel (such as through Flycatcher).

Sample, data collection, and analyses

Reviewer 1529971 noted that our focus on heterosexual, gay, and bisexual youth is far from representative for the entire LGBTQIA+ spectrum. This is certainly true. As such, we may conduct more than the originally indicated 50 interviews in WP1, if needed to reach data saturation and maximum variation. If we reach a sufficiently large sample size in WP2, we may also conduct subgroup analyses for different sexual orientations.

Reviewer 1529961 questioned how our thematic analysis in WP1 will be conducted and how we ensure trustworthiness of our analyses. In short, as we are mainly investigating underlying motivations and perceptions, we take an inductive approach to our thematic analysis, focusing on latent content. The trustworthiness of our analyses is enhanced through conducting intermediate analyses after each 3-5 interviews to check for data saturation and to revise the interview guide if necessary. In addition, analyses are performed by (at least) 2 independent researchers and discussed frequently with the research team, which minimizes researcher bias.

Reviewer 1529961 noted that our indicated sample size for WP2 (N=383) would be insufficient to conduct subgroup analyses. The sample size indicated in the proposal is necessary to conduct 'confidence interval based estimation of relevance' (CIBER) analysis in one specific group (i.e. youth at risk of STI), with a 95% confidence interval half-width of 0.10 and a correlation of 0.05 (Moinester & Gottfried, 2014, DOI: 10.20982/tqmp.10.2.p124). Rutgers' previous SO25 data collection (2017) yielded 11,366 sexually active participants, out of which 23% of men and 28% of women were at-risk of STI because they did not use a condom with their most recent sexual partner (including e.g. one-night stands). As such, we are confident that through Rutgers' SO25 data collection, we will reach a sufficiently large sample size to conduct subgroup analyses for main demographic variables, such as assigned gender at birth and age. For more stratified variables (e.g. sexual orientation), it may be necessary to group categories in order to be able to conduct subgroup analyses. If we resort to recruitment through an online panel (as described previously), we will instruct the panel to recruit a prespecified number of participants, sufficient to conduct wanted subgroup analyses. This will depend on findings of our qualitative research in WP1 (i.e. which characteristics are most important?).

Reviewer 1529961 stated that it would have been a strength to include state of the art risk factors for sexual risk behavior, such as binge drinking, recreational drug use, and mental issues. Though not explicitly mentioned in the proposal, we do intend to include the most recent and relevant insights on risk factors for sexual risk behavior in our data collection and analyses in all WPs. This is also one of the main goals of the literature search performed in WP1.

Intervention objectives and evaluation

Reviewer 1529961 commented that it is unclear how the intervention will be evaluated and that a quasi-experimental approach may be appropriate to this purpose. As described in our proposal, we do indeed evaluate the SHCS-linkage tool through a quasi-experimental approach, namely through follow-up measurements at different time points (i.e. a one-group pretest – posttest design). The purpose of our evaluation is to investigate if the intervention works in the sense that previously unreached youth at risk of STI (intend to) use it to engage with SHCS and if we reach our intended target population. In addition, as the SHCS-linkage tool is highly innovative, there is much emphasis on preparatory research (WP1 & 2) and there will be an extensive period of development and piloting. Based on earlier experiences, we assessed that a more laborious and extensive research design (e.g. using randomization and a control group) would be overly ambitious within the scope of this project. As such, we believe that the one group pretest – posttest design is both appropriate and realistic.

Reviewer 1529961 suggested that Bleijenberg et al.'s (2018) addition to the Medical Research Council (MRC) framework would be an appropriate alternative to the Intervention Mapping (IM) approach used in our proposal. We are not against using the MRC framework as such, but IM is considered to be a much more comprehensive

framework (O'Cathain et al. 2019, DOI: 10.1186/s40814-019-0425-6#Tab6). Moreover, within our project team we have extensive in-house experience with the application of IM. For example, prof. dr. (10)(2e), dr. (10)(2e), and prof. dr. (10)(2e) have been involved, or were principal investigator, in successful research projects that used IM (e.g. Désiron et al., 2016, DOI: 10.1007/s10926-015-9620-3; Theunissen et al., 2013, DOI: 10.1186/1471-2458-13-996). Also, prof. dr. (10)(2e) is one of the lead authors on the fifth edition of the book on this framework (to appear in 2021). As such, this is a notable strength of our project team that we capitalize on in the EASY project.

Reviewer 1529961 questioned the behavioral change objectives and related outcomes of the proposal. The reviewer stated that the behavioral aim could be improved, since intention to test for STI is not really a behavior change, and intention often differs from behavior in practice. Subsequently, the reviewer questioned why the sample size for the SHCS-linkage tool evaluation was based on intention rather than actual behavior change. The reviewer also proposed that the main outcome measure of the SHCS-linkage tool should be STI-testing, rather than previous STI-testing. Based on these comments, we believe that there has been a misunderstanding regarding the EASY project's behavior change objectives and outcomes. We would like to clarify that our main behavioral objective of the SHCS-linkage tool is to achieve behavioral change, with intention to engage with SHCS being a secondary objective. For example, for the evaluation of the SHCS-linkage tool's effectiveness, we report both on engagement with SHCS (behavior) and intention to engage with SHCS. Nevertheless, *previous* engagement with SHCS (e.g. previous STI-testing) remains an important outcome in the EASY project, as it is used to evaluate whether we reach our intended target population (i.e. previously unreached youth) by distributing our eHealth tool using 'web-based respondent-driven sampling' (webRDS). In addition, previous engagement with SHCS (including STI-testing) is used as an outcome in WP2 in order to identify factors that influence SHCS-seeking behavior. As for our sample size calculation in WP3, we indeed determined our sample size by change in intention, as this would require the largest sample size (N=664, as mentioned in the project proposal). To detect engagement with SHCS in 5% (conservative estimate) of previously unreached youth at risk of STI during follow-up, we may conduct a one-sided test for comparing paired proportions with an alpha level of 0.05, a power of 0.8, assumed design effect of 2.0, and expected dropout during follow-up of 40%. This would require a sample size of N=550. As such, using a sample size based on actual behavior change, we would be unable to evaluate the SHCS-linkage tool's effects on intention. Therefore, we opt to recruit even a larger sample (N=664), as this makes the study adequately powered for all proposed outcomes.

Ethical approval and trial registration

Reviewer 1529961 commented that ethical approval is required for all planned studies, rather than only the evaluation study, and that the planned intervention trial needs to be officially registered. We apologize for not having described these topics clearly in the proposal. We intend to seek ethical approval for all planned studies as soon as possible if the current proposal is accepted for funding. Similarly, we will register the planned intervention at the Netherlands Trial Register as soon as the current proposal is accepted for funding.

Implementation in practice

Reviewer 1529971 commented that little is mentioned in regard to engagement with policy makers, piloting results in clinical practice, or next steps towards implementation in general. Unfortunately, in our project proposal, the section in which we further detailed this topic was lost in the submission process. The main applicant for this project is the RIVM, the National Coordination Centre for Communicable Disease Control ("LCI"), who develop sexual healthcare guidelines for public health services in the Netherlands. These guidelines are managed by LCI's Sexual Health Editorial Board, of which project member drs. (10)(2e) (10)(2e) is chairwoman. Similarly, the SeksHAG (of whom project member dr. (10)(2e) (10)(2e) is chairman) develops and organizes trainings, supports research, and develops guidelines to improve sexual health care provided by GPs.

In addition, Soa Aids Nederland and Rutgers, who are also involved in the EASY project, are well-experienced with the development and implementation of sexual health (care) projects and interventions targeting youth. They will actively support the implementation of our SHCS-linkage tool through different online channels (e.g. through project members' websites) and its dissemination to other relevant stakeholders and a larger audience of youth in the Netherlands. As such, we have the relevant and necessary in-house connections and expertise to apply our project results for implementation in practice.

The EASY project and COVID-19

Relevance of the EASY project in the context of COVID-19

The ongoing COVID-19 pandemic, and the far-reaching measures taken to retain control over the outbreak, affect almost all aspects of daily life in many countries worldwide. Sexual (risk) behavior of youth and the delivery of SHCS are no exceptions in this regard. As social distancing and lock-down measures have reduced physical interactions between individuals, it is likely that sexual risk behaviors, such as having multiple partners or one-night stands, have decreased. On the other hand, there are indications that access to contraceptives (including condoms) has decreased, which increases chances of unprotected sex and (unwanted) pregnancies (Tang, Gaoshan & Ahonsi, 2020, DOI: 10.1186/s12978-020-0900-9). In addition, some studies describe how access to SHCS, including STI-testing, have declined, in particular among youth and different minorities, such as men who have sex with men and immigrants (Hall et al. 2020, DOI: 10.1016/S0140-6736(20)30801-1; Sanchez et al. 2020, DOI: 10.1007/s10461-020-02894-2). These findings suggest that the COVID-19 outbreak may negatively influence sexual health and access to SHCS, in particular among those who are readily at increased risk of poor sexual health and STI. This is a major issue that urgently requires further exploration, as it may further exacerbate existing health disparities.

As of June 2020, little research exists on the above outlined issues so far, in particular in the Netherlands. We believe the EASY project offers an exceptionally well-suited platform to investigate sexual risk behavior and (disparities in) access to SHCS in youth in the Netherlands in the context of COVID-19. To this purpose, few adjustments to the EASY project are needed, as these topics are readily of primary interest. Furthermore, our project partners Rutgers and Soa Aids Nederland are currently conducting research regarding the impact of the ongoing COVID-19 outbreak on sexual health of youth (preliminary results expected on the 6th of July). This provides mutually beneficial opportunities to build on newly generated, highly relevant knowledge. As such, depending also on the outcomes of the current investigations, we will be able – and intend to explore several highly relevant topics, such as: the influence of the COVID-19 pandemic on sexual risk behavior of youth, characteristics of youth who are (more frequently) engaged in risky sexual behaviors during the COVID-19 pandemic, the influence of the COVID-19 pandemic on access to SHCS in youth, and characteristics of youth who were (un)able to engage with SHCS during the COVID-19 pandemic.

Influence of COVID-19 on EASY project execution

The impact of the COVID-19 pandemic on the execution of the EASY project is dependent of the measures in place to retain control over the outbreak. As these may vary over time, we will adopt flexible approaches to ensure continuous execution of planned activities in line with the outlined project planning.

Interviews: In line with social distancing and lock-down measures, interviews may be organized through digital platforms (e.g. SURF, which is secure and GDPR compliant, and available through the University of Maastricht, or GoToMeeting, available at the RIVM), or with sufficient distance between the interviewer and the interviewee if interviews are conducted in-person. In the latter case, adequate attention will be paid to minimize any infection risk, e.g. through hygienic measures and organizing a location with sufficient air circulation. If in-person interviews are possible, participants may always opt for a digital interview instead.

Participant recruitment: Recruitment of interviewees who are unreached by SHCS may largely take place as described in the current proposal, e.g. through advertising at schools, sports clubs, etc. However, we may reach a limited audience with this strategy, if such institutions continue to operate at reduced capacity. Therefore, we will increase our focus on recruitment through online channels (e.g. Facebook, Instagram, Snapchat). Recruitment of interviewees who were previously reached by SHCS was planned to take place online through home-based self-sampling providers and in-person at GP practices. Based on our previous research (Joosten et al. 2020, manuscript in preparation), we know that recruiting and directly interviewing participants on location lowers the threshold to participate. Therefore, we do intend to continue in-person recruitment as planned. Nevertheless, if this is not possible, we will change our strategy to e.g. (online) banner/flyer advertising at GP practices. Recruitment of seeds (WP3) may continue as planned. If necessary, the focus will be increased on online as opposed to offline recruitment.

Project team meetings: Consultations with project members will mainly take place online.