PROTOCOL

PHR Project: 17/44/48

How can e-health interventions reduce the 'syndemic' of HIV/STIs and sexual risk, substance use and mental ill health among men who have sex with men? Systematic review and evidence synthesis

Versions

Version	Amendment	Rationale	Date	Submitted to NIHR	Submitted to PROSPERO
1 (proposal)	NA	NA	29/3/18	29/3/18	19/8/18
2	Added "For non-random evaluations, we will assess quality using the ROBINS-I tool."	We include random and non-random controlled outcome evaluations but previously only specify risk of bias tool for random designs.	3/10/18	4/10/18	3/10/18

This protocol guides the conduct of independent research funded by the National Institute for Health Research (NIHR) in England under its Public Health Research Board (17/44/48). The views expressed in this protocol are those of the authors and do not necessarily reflect those of the National Health Service (NHS), the NIHR or the Department of Health for England.

Background

This review will synthesise evidence on e-health interventions aiming to reduce the 'syndemic' of HIV/STIs and sexual risk, substance use (defined as use of alcohol and other drugs) and mental ill health among men who have sex with men (MSM).

Description of the problem

Despite major advances in treatments and pharmacological prevention, MSM continue to experience the highest incidence of STIs and HIV of any population group in the UK, and report high levels of sexual risk behaviour.[1, 2] The lifetime cost of treatment per HIV infection in the UK is almost £380,000.[3] Each case of other STIs is estimated to cost £1215 per infection.[4] MSM also report higher than average rates of alcohol [5-7]and legal and illegal drug use.[8-10] MSM also experience high rates of common mental illnesses.[11] MSM are twice as likely to be depressed or anxious compared to other men.[12] According to the 2013 Annual Report of the Chief Medical Officer, mental health problems cost the UK economy an estimated £70-£100 billion each year.[13]

Sexual risk, alcohol and drug use, and mental ill health are increasingly considered to constitute a 'syndemic' of simultaneous, mutually reinforcing epidemics. Drug use is both a symptom and cause of mental ill health and both drug use and mental illness increase sexual risk behaviours.[14] Nationally representative surveys suggest that almost half of MSM experience one or more of these outcomes.[15] There is consistent evidence that these outcomes inter-correlate strongly at the level of the individual and the sexual event.[16-22] For a significant proportion of MSM, drug use is an integral part of sex, known as 'chemsex'.[23] UK data indicate that MSM with depressive symptoms are more likely to report condomless sex with multiple partners and with serodiscordant partners, and MSM who report drug use and mental health problems are also more likely to report repeated use of post-exposure HIV prophylaxis[24] and are less likely to test for HIV.[21] Thus there is a clear rationale for public health strategies to address these outcomes together to achieve multiplicative effects.

Existing public health strategies have failed adequately to address these outcomes either separately or together.[25, 26] Common mental illnesses among MSM are under-diagnosed and under-treated partly because of low rates of GP registration.[27] One study reported that among MSM attending sexual health clinics in the UK, 42% of those with depressive symptoms were not diagnosed and 48% were not receiving treatment.[28] Spending on HIV prevention for MSM is falling[29] despite strong evidence, albeit primarily from non-UK studies, for effective interventions.[30] Drug treatment services tend to focus predominantly on heroin and crack cocaine rather than the 'club' drugs most commonly used by MSM. There is an urgent need for cost-effective new strategies to address these outcomes.

Description of the intervention

E-health interventions are those facilitated by electronic media and devices. Such interventions aim to promote healthy behaviours and mental health by: increasing/maintaining motivation; setting and reviewing goals; providing feedback on behaviour; and challenging thought patterns that obstruct change. Behaviour change interventions typically draw on social learning theory and the trans-theoretical model, while mental health interventions draw on mindfulness or cognitive behavioural approaches. There is good evidence from systematic reviews focused on general or mixed populations, that e-health interventions can reduce alcohol use[31] and address common mental illnesses.[32-38] There is also emerging evidence that drug use and sexual risk behaviour[39-42] may be reduced using e-health interventions. Given the inter-clustered nature of these problems among MSM, if e-health interventions were found to be effective in addressing these outcomes among MSM then this might suggest the value of developing an e-health intervention that addressed these outcomes simultaneously and holistically. Such an approach might

well have multiplicative not merely additive effects because of the interacting nature of these outcomes among MSM.

Rationale for the current study

However, we cannot assume that effects found for e-health interventions targeting general or mixed populations[31-39, 41-43] are applicable to MSM. Effect sizes may be greater for MSM because of MSM's greater use of social media, including to meet sexual partners and obtain drugs.[44] But effects may be limited by MSM's risk being influenced by factors that e-health interventions could not address such as such as early and ongoing experience of homophobia[45-47] and participation in social networks in which social norms support risk behaviour.[48] Therefore, there is a need to assess the potential effects of e-health interventions on these outcomes among MSM. A 2014 review by Schnall et al examined e-health interventions to reduce HIV and other sexual risks among MSM (but did not examine alcohol or drug use or mental health), reporting rather vaguely that such interventions have the potential to be effective.[40] This review had several important limitations such as a very narrow search (which missed some important studies described below under 'Size of available literature), unreliable quality assessment and lack of synthesis of effect estimates. These limitations explain why it was not able to provide a clear answer to the question of whether e-health interventions are effective in reducing sexual risk behaviour. A recent review by Daher et al synthesised evidence on a range of e-health interventions addressing different aspects of the prevention and treatment of HIV/STIs but not substance use or mental health.[49] This review had vague and broad inclusion criteria focused on ill-defined 'innovative' interventions and all populations not just MSM. Its very limited search strategy found only two studies pertinent to our own review and so can offer no clear indication of the impact of e-health interventions on sexual risk among MSM.[50, 51] Only one existing review has examined e-health interventions addressing mental ill health among gay and lesbian populations but has not synthesised empirical evidence on these and so provides no guide to their effectiveness.[52] Furthermore, none of the above reviews examined the theories of change underlying the included interventions or synthesise evidence on factors affecting delivery or receipt. Our proposal for a new systematic review aims to address these gaps in order to determine clearly what is the effectiveness of e-health interventions addressing these outcomes among MSM. It will: use rigorous methods; focus on interventions addressing HIV, STIs, sexual risk behaviour, alcohol and drug use, or mental health; and synthesise evidence on theories of change, process evaluations and outcome and economic evaluations. It will also aim to synthesise evidence on cost-effectiveness and use a network meta-analytic approach to compare the effectiveness of interventions that have not to date been the subject of empirical comparisons. This approach has not been used in any previous reviews of e-health interventions among MSM and could transform our understanding of which intervention approaches and combinations are most effective. The proposed review will thus provide the evidence required to determine the value of and potentially inform the development of an e-health intervention holistically addressing the syndemic of HIV and STIs, sexual risk behaviour, alcohol and drug use, and mental ill health among MSM.

Research aim and questions

To search systematically for, appraise the quality of, and synthesise evidence to address the following research questions:

RQ1. What approaches and theories of change do existing e-health interventions employ to prevent HIV, STIs, sexual risk behaviour, alcohol and drug use, or common mental illness symptoms among MSM?
RQ2. What factors relating to interventions, providers, participants or contexts promote or impede delivery or receipt of such interventions?

RQ3. What are the effects of such interventions on HIV and STIs, sexual risk behaviour, alcohol and drug use, and depression and anxiety, overall and by intervention and client sub-group?
RQ4. Are such interventions cost-effective in reducing these outcomes?
RQ5. Does the existing evidence overall suggest that these outcomes can coherently, feasibly and effectively be addressed by a single, joined-up e-health intervention targeting UK MSM and if so what might such an intervention look like?

Research objectives

a) To conduct electronic and other searches by Feb 2019.
b) To screen found references and reports for inclusion in the review by May 2019.
c) To extract data from and assess the quality of included studies by September 2019.
d) To develop a typology of interventions and synthesise theories of change and process evaluations by January 2020.
e) To consult with policy/practice and community stakeholders on the typology and theory of change/process synthesis by February 2020.
f) To synthesise outcome evaluation and cost-effectiveness data by May 2020.
g) To draw on these syntheses to draft a report addressing our research questions by July 2020.
h) To consult with policy/practice and community stakeholders on the draft report (to inform amendments and dissemination) by September 2020.
i) To submit the final report to NIHR by October 2020.

Research design overview

Our proposal is for a multi-method systematic review of intervention types, theories of change, processes and outcomes, and cost-effectiveness of e-health interventions employed to prevent HIV and STIs, sexual risk behaviour, alcohol and drug use, or common mental illness symptoms among MSM. The review will follow criteria for the good conduct and reporting of systematic reviews (e.g. Centre for Reviews and Dissemination; Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The protocol will be registered with PROSPERO International Prospective Register of Systematic Review (http://www.crd.york.ac.uk/Prospero/).

Our review and synthesis of intervention descriptions and theories of change will enable us to categorise intervention types and describe theories of change (RQ1). Our review of process evaluations will develop hypotheses about what characteristics of interventions, providers, participants and contexts tend to facilitate or limit implementation and receipt (RQ2). Our review of outcome and economic evaluations will enable us to estimate the effectiveness (RQ3) and cost-effectiveness (RQ4) of the interventions. Synthesis across these elements will inform assessment of the value of developing an e-health intervention targeting UK MSM (RQ5).

Size of available literature

In an uploaded appendix, we provide the string used in a scoping search of PubMed (29/11/16). This searched only medical journals using a narrower set of terms (and no adjacency term) than will be used in the proposed review. Nonetheless, it identified 2,110 references. From these, we identified 28 outcome evaluations, 26 process evaluations and 5 theory of change study reports of e-health interventions for general or HIV-positive populations of MSM. Of these, 18 outcome evaluations of interventions aiming to prevent HIV, STIs or sexual risk behaviour were not identified in the existing review by Schnall et al[53-70] mostly because they had been published since this review. Schnall et al's review identified two outcome evaluations not found from our search.[71, 72] We also found one outcome evaluation and three process evaluations focused on alcohol and drug use[51, 73, 74] and six outcome evaluations, four process evaluations and one theory of change study report focused on mental health.[75-85] This suggests a substantial and

growing, unsynthesised but manageable literature to review. Given the large number of very recent papers and that our exploratory search was conducted in late 2016, there is likely to be a substantial body of evidence to synthesise when the review will commence in 2019.

Inclusion criteria for this review

Types of participant

The review will focus on gay, bisexual and other men (including trans men) who have sex with men including those who have been diagnosed as HIV-positive as well as those whose last HIV test was negative or who have never tested for HIV.

Types of intervention

The review will focus on interactive or non-interactive e-health interventions delivered via mobile phone apps, internet or other electronic media that aim to provide ongoing support to populations consisting entirely or principally of MSM to prevent HIV, STIs, sexual risk behaviour, alcohol and drug use, or common mental illnesses. These could include interventions that also aim to promote HIV treatment adherence or which address HIV testing or pre-exposure prophylaxis as long as these are part of ongoing not one-off support. It will exclude e-health interventions merely facilitating one-off as opposed to ongoing support regarding HIV self-testing, clinic attendance or STI partner notification. The e-health interventions are electronically delivered. The interventions may be distributed by commercial, statutory, academic or voluntary sector agencies. The review will be international in scope. The review will exclude interventions delivered by human providers via electronic media.

Types of control

The review will focus on treatment as usual, no treatment or other active treatment control groups.

Types of outcome

The review will focus on: HIV or STIs; sexual risk behaviour; alcohol consumption (e.g. self-reported alcohol consumption via questionnaires or diaries); legal or illegal drug use (e.g. self-reported drug use); and anxiety or depression (clinical or self-report measures). Studies will be included if they address any, some or all of these outcomes. Outcome measures may draw on dichotomous or continuous variables, and self-report or other raters. Behavioural outcomes may use measures of frequency (monthly, weekly or daily), the number of episodes of use or an index constructed from multiple measures. Alcohol measures may examine alcohol consumption or problem drinking. Drug outcomes may examine drugs in general or specific illicit drugs, including drug convictions.

Types of study

To address RQ1, we will include process and outcome evaluations providing intervention descriptions or theories of change, as well as theoretical reports. To address RQ2, we will include process evaluations. To address RQ3, we will include outcome evaluations. To address RQ4, we will include economic evaluations. To address RQ5 we will draw on all of the above. Included theoretical reports must describe intervention theories of change, logic models or mechanisms of effect. Included process evaluations can employ any quantitative and/or qualitative design but must report empirically how delivery or receipt varied by characteristics of intervention, provider, user or context using quantitative and/or qualitative data. These studies may report exclusively on process evaluations or report process alongside outcome data. Included outcome and economic evaluations must employ prospective experimental or quasi-experimental control groups.

Search methods for the identification of studies

Electronic searches

In appendix 1, we provide the search string that we have used in a preliminary search in PubMed. As explained above, this was a limited search but it will inform the development of a more sophisticated search strategy maximising sensitivity as recommended by the Cochrane Handbook for Systematic Reviews of Interventions.[86] Our search strategy will be informed by those used in previous systematic reviews focused on e-health intervention among MSM and general populations. Because studies are unlikely to be reliably indexed in databases with controlled vocabularies, we will use a large number of free text terms. We will take the following essential concepts of the inclusion criteria to develop the search string linked by "AND": men who have sex with men; and e-health. We will not use outcome terms in our searches as this is likely to miss studies reporting non-significant effects on our outcomes. Our searches will involve different free text and controlled vocabulary terms for each of these concepts using "OR". The combination of these concepts is considered specific enough to include all available studies regardless of study design. We will restrict the searches by date (1995 onwards since such media were unavailable prior to this) but not by language or publication type. We will search the following databases: ASSIA; BiblioMap (Database of health promotion research); Cochrane Central Register of Controlled Trials; The Campbell Library; CINAHL; CISDOC; Database of Abstracts of Reviews of Effects; Embase; Econlit; Health Management Information Consortium; IBSS (International Bibliography of the Social Sciences); Medline; OpenGrey (System for Information on Grey Literature in Europe); Proquest Dissertations and Theses; PsycInfo; Social Policy and Practice including Child Data & Social Care Online; Social Science Citation Index/Web of Knowledge; Sociological Abstracts; Dissertation Abstracts/Index to Theses; and Trials Register of Promoting Health Interventions.

Searching other resources

We will carefully search reference lists from all studies that meet our inclusion criteria. We will hand-search journals that published included studies which we found only via reference checking and which are not indexed on databases we have searched (initially for the last 5 years and if these elicit >1 new included studies, for a further 5 years). We will search for relevant government reports and non-governmental organization publications via a Google search. We will contact subject experts to identify relevant ongoing or completed research. We will search all available clinical trials registers (e.g. International Clinical Trials Registry Platform; clinicaltrials.gov) for relevant ongoing and unpublished trials.

Data collection and assessment

Data management and selection of studies

Results of comprehensive searching will be downloaded into EPPI- Reviewer 4.[87] An inclusion criteria worksheet with guidance notes will be prepared and piloted by two reviewers screening batches of the same 50 references. Where the two reviewers disagree, they will meet to discuss this and if possible reach a consensus. If the reviewers cannot reach consensus regarding inclusion of a specific article, judgement for selection will be referred to a third reviewer. If necessary, we will organise translation of papers published in languages in which we are not proficient. After this piloting process has achieved an agreement rate of at least 95%, each reference will henceforth be screened on the basis of title and abstract for potential inclusion by one reviewer Full reports will be obtained for those references judged as meeting our inclusion criteria or where there is insufficient information from the title and abstract to judge inclusion. A second round of screening with a comparable piloting process will then occur focused on full study reports to determine which studies are included in the review (see appendix 3: flow diagram). We will maintain a record of the selection process for all screened material.

Data extraction

Two reviewers will independently extract data from and assess the quality of theory, process, outcome and economic studies meeting our inclusion criteria based on existing tools.[88-90] Where the two reviewers disagree, they will meet to discuss this and if possible reach a consensus. If the reviewers cannot reach consensus regarding the particulars of data extraction for a specific study, judgement will be referred to a third reviewer. Included studies will be described using the EPPI-Centre classification system for health promotion and public health research[91] supplemented by additional codes developed for this review. For theory reports, we will extract data on the constructs and mechanisms described, the evidence presented in support of the theory and how it was developed. For all empirical studies, we will extract data on: basic study details (target population, study location, timing and duration, research questions or hypotheses); methods (design, sampling and sample size, data collection and analysis); and intervention description (timing and duration, programme development, theoretical framework/logic model, content and activities, providers, details of any intervention offered to the control group). For process evaluations, we will also extract data reporting empirically on how processes of delivery/ receipt varied with characteristics of interventions, providers, participants or contexts using an adapted version of an existing tool.[92] For outcome evaluations, we will also extract data on: allocation; sequence generation and concealment (RCTs); control of confounding (quasi-experimental studies); measures, follow-up and blinding; retention; and data on outcomes/ effects at follow-up(s) both overall and where available by sexuality and gender identity, socio-economic status (SES) and ethnicity. For economic evaluations, we will extract data on key issues such as the perspective (direct and indirect costs), evaluation framework, source of effectiveness estimates, critical assumptions, discount rates and cost-effectiveness in the form of either incremental cost-effectiveness ratios or net (health) benefits. We will also report on the key cost-effectiveness drivers. If included studies are reported in languages that cannot be translated by the review team, a review author will complete the data extraction form in conjunction with a translator.

Published reports may be incomplete in a wide range of ways. For example: they may not present information on all the outcomes that were measured (possibly resulting in outcome reporting bias); they may not provide sufficient information about the intervention for accurate characterisation; and they may not report the necessary statistical information for the calculation of effect sizes. In all cases where there is a danger of missing data affecting our analysis, we will contact authors of papers wherever possible to request additional information. If authors are not traceable or sought information is unavailable from the authors within two months of contacting them, we will record that the study information is missing on the data extraction form, and this will be captured in our risk of bias assessment of the study.

Assessments of quality and risk of bias

We will assess the quality of theories of change using a modified version of the criteria developed in our previous NIHR-funded systematic reviews of positive youth development and school health education interventions. The quality of theory will be assessed using a modified version of a tool used in our previous NIHR funded reviews, modified in the light of our more recent work on realist methods. This will focus on: a) the extent to which the theory describes the path from intervention to outcomes; b) the clarity with which theoretical constructs are defined; c) the clarity with which causal inter-relationships between constructs are defined; d) the extent to which the mechanisms underlying these inter-relationships are explained; and e) the extent to which the theory considers how mechanisms and outcomes might vary by context.

We will assess the quality of the qualitative and quantitative elements of process evaluations using standard Critical Appraisal Skills Program and EPPI-Centre tools.[93] These address the rigour of: sampling; data collection; data analysis; the extent to which the study findings are grounded in the data; whether the study privileges the perspectives of participants; the breadth of

findings; and depth of findings. These are then used to assign studies to two categories of 'weight of evidence'. First, reviewers will assign a weight (low, medium or high) to rate the reliability or trustworthiness of the findings (the extent to which the methods employed were rigorous/could minimise bias and error in the findings). Second, reviewers will assign an additional weight (low, medium, high) to rate the usefulness of the findings for shedding light on factors relating to the research questions. Guidance will be given to reviewers to help them reach an assessment on each criterion and the final weight of evidence. The two reviewers will then meet to compare their assessments, resolving any differences through discussion and, where necessary, by calling on a third reviewer.

For outcome evaluations, we will assess risk of bias within each included experimental study using the tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[88] For each study, two reviewers will independently judge the likelihood of bias in seven domains: sequence generation; allocation concealment; blinding (of participants, personnel, or outcome assessors); incomplete outcome data; selective outcome reporting; and other sources of bias (e.g. recruitment bias in cluster-randomised studies); and intensity/type of comparator. Each study will subsequently be identified as 'high risk', 'low risk' or 'unclear risk' within each domain. In cases of disagreement, the reviewers will meet to seek consensus but where they cannot, we will refer judgement to a third reviewer. For non-random evaluations, we will assess quality using the ROBINS-I tool.[94] We will assess reporting bias according to Sterne's guidance.[95] We will reduce the effect of reporting bias by focusing synthesis on studies rather than publications, avoiding duplicated data. Following the Cho statement on redundant publications,[96] we will attempt to detect duplicate studies and, if multiple articles report on the same study, we will extract data only once. We will prevent location bias by searching across multiple databases. We will prevent language bias by not excluding any article based on language.

We will assess the quality of the economic evaluations using an adapted version of the CHEERS reporting guidelines.[97] It requires the analyst to answer 24 questions regarding each study ranging from the type of economic evaluation (e.g. cost-utility analysis) to the time horizon and rationale for the choice of modelling approach. Although the questionnaire is detailed, we will expand a number of its questions to ensure that information that is particularly relevant to this review is extracted, such as identifying uptake rates and assumptions regarding the heterogeneity of risk.

Data analysis

RQ1 and 2: Thematic synthesis of intervention approaches/theories and process data

Intervention descriptions and theories of change (RQ1) will first be analysed to develop a taxonomy of interventions where possible describing these in terms of behaviour change techniques. This will include whether interventions are solely focused on the prevention of alcohol or drug use, HIV and other sexual risk or mental illness or whether they have other aims such as access or adherence to HIV testing or treatment. Then, using thematic synthesis method[98-100] we will undertake a number of syntheses. Syntheses of author narratives describing theories of change (RQ1) will be used to understand potential mechanisms of action for this category of intervention, some of which may apply across sexual health, substance use and mental health and some of which may be particular to each of these outcomes. Syntheses of findings from qualitative and quantitative elements of process evaluations (RQ2) will be used to understand: characteristics of interventions, participants and context acting as potential barriers and facilitators of implementation and receipt (RQ2) and which of these apply across or only within the domains of sexual health, substance use and mental health interventions.

Synthesis will follow a meta-ethnographic approach. Second order constructs (author narratives) will be distinguished from first order constructs (directly quoted qualitative data). In the case of findings from qualitative elements of process evaluations, we will synthesise both author

narratives and interpretations of findings (i.e. 2nd order concepts) together with any direct qualitative data reported (i.e. 1st order concepts). In the case of findings from quantitative elements of process evaluations, we will synthesise author 2nd order narratives and interpretations (and as part of quality assessment we will have checked that these appear consistent with the quantitative data presented). The synthesis will draw these together through a thematic analysis which will develop third order constructs by drawing connections between these data. These two syntheses will not be restricted to studies judged to be of high quality. Instead conclusions drawing on poorer quality reports will be given less interpretive weight. First, the reviewers will prepare detailed tables to describe: the quality of each theoretical and process evaluation report; details of the intervention examined; study site/population; and full theory/process evaluation findings. Second, for each of the two syntheses addressing RQ1 and RQ2, the two reviewers will undertake pilot analysis of two studies. The reviewers will read and re-read the theory/findings contained within the tables relating to the two high-quality studies, applying line-by-line codes to capture the content of the data. They will draft memos explaining these codes. Coding will begin with in-vivo codes which closely reflect the words used in theory/findings sections. The reviewers will then group and organise codes, applying axial codes reflecting higher-order themes. The two reviewers will meet to compare and contrast their coding of these first two high-quality studies for each synthesis, developing an overall set of codes. Third, the two reviewers will go on to code the remaining studies for each synthesis drawing on the agreed set of codes but developing new in-vivo and axial codes as these arise from the analytical process, and again writing memos to explain these codes. At the end of this process, the two reviewers will meet to compare their sets of codes and memos. They will identify commonalities, differences of emphasis and contradictions with the aim of developing each overall analysis which draws on the strengths of the two sets of codes and which resolves any contradictions or inconsistencies, drawing on a third reviewer if necessary to achieve this. Analysis will produce tables demonstrating how first, second and third order constructs relate to one another, enhancing transparency about these emergent themes. Through this process will be developed overall syntheses addressing RQ1 (theory of change) and RQ2 (factors affecting implementation).

RQ3: Synthesis of outcome data

We will first produce a narrative account of the effectiveness of these types of interventions. This narrative synthesis will be ordered by outcome then within this by intervention type and follow-up time. Outcomes will be categorised into HIV, STIs, sexual risk behaviour, alcohol use, drug use, anxiety and depression. Categorisation by intervention type will be into 'clinically meaningful units', or subgroups of interventions that are useful and meaningful from a clinical and practice perspective, and will be informed by our prior taxonomy of intervention descriptions and synthesis of theories.[101] We will describe study results in the 'characteristics of included studies' table, or enter the data into additional tables. We will produce forest plots for each of our review outcomes, with separate plots for different outcomes and follow-up times, and pairwise comparisons between intervention types (e.g. intervention versus no treatment control, or versus another treatment type). Plots will include point estimates and standard errors for each study, such as risk ratios for dichotomous outcomes or standardised mean differences for continuous outcomes.

We will calculate pooled effect sizes within each pairwise comparison (e.g. intervention type versus control), accounting for the extent of heterogeneity among the studies (as determined both by a Cochran's *Q* test and inspection of I^2).[102] The results of statistical tests will be evaluated in accordance with the Cochrane handbook.[88] If an indication of substantial heterogeneity is determined (e.g. study-level I-squared value greater than 50%) that cannot be explained through meta-regressions, then we will not produce a pooled estimate and will present only the narrative summary. If we consider that we have high levels of unexplained statistical heterogeneity (e.g. study-level $I^2 > 50\%$) in any of our study groupings, we will investigate this further using subgroup and sensitivity analyses.[103] As is appropriate for complex interventions, we will use the random-

effects model in meta-analyses but we will also conduct a sensitivity check by using the fixed-effect model to reveal differences in results.

If we do produce pooled estimates, we will consider using a robust variance estimation (RVE) meta-analysis model to synthesise effect sizes.[104] This is because outcome evaluations are likely to include multiple measures of conceptually related outcomes and RVE meta-analysis improves on previous strategies for dealing with multiple relevant effect sizes per study, such as meta-analysing within studies or choosing one effect size, by including all relevant effect sizes but adjusting for inter-dependencies within studies.[105] Unlike multivariate meta-analysis, it does not require the variance-covariance matrix of included effect sizes to be known. We will estimate separate models for each outcome: HIV, STIs, defined sexual risk behaviours, alcohol use, drug use, anxiety and depression. We will regard follow-up times of less than three months, three months to one year and more than one year post-intervention as different outcomes. We will run these models for interventions overall and where sufficient studies are found we will run separate models for different pairwise comparisons of intervention types and comparators. This categorisation will be informed by the taxonomy derived from our prior synthesis of intervention descriptions and theories of change. Where meta-analyses are performed, we will include pooled effect sizes in forest plots, with the individual study point estimates weighted by a function of their precision.

In addition, we will seek to consider all outcome evaluation evidence jointly in a network meta-analysis (NMA). NMA integrates all pairwise comparisons for a specific outcome in the same model, to allow for the comparison of intervention types that may not have been directly compared head-to-head in empirical studies, and to combine direct, empirical head-to-head evidence with indirect estimates. We will consider estimating an NMA model for each outcome. As part of this, we will note if pairwise comparisons form a connected network for a given outcome, and if the trials included in a network are similar enough across pairwise comparisons in terms of populations, outcome measures and other potential trial-level effect modifiers (e.g. risk of bias) to justify proceeding on the assumption of transitivity. Having established that networks include conceptually similar trials, we will convert effect size estimates in each network to odds ratios and estimate an NMA using summary trial-level data with a lognormal likelihood and random effects. Inconsistency will be checked using an omnibus Wald test from a design-by-treatment interaction model, and then followed up using a side-splitting test if necessary to identify specific sources of inconsistency. Where inconsistency exists, we will explore this using network meta-regression. Finally, we will rank interventions using the surface under the cumulative ranking curve (SUCRA). All analyses will be undertaken using the package network for frequentist NMA in Stata. However, if necessary (e.g. to use a stabilising prior distribution for between-studies variance in sparse networks), we will consider undertaking NMAs in WinBUGS with vague prior distributions for relative treatment effect parameters.

While most included outcome evaluations are likely to allocate individuals rather than clusters, we will check for correct analysis where appropriate by cluster and report values of: intra-cluster correlation coefficients (ICC), cluster size, data for all participants or effect estimates and standard errors. Where proper account has not been taken of data clustering, we will correct for this by inflating the standard error by the square root of the design effect.[48] Where ICCs are not reported, we will contact authors to request this information or impute one, based on values reported in other studies. Where imputation is necessary, we will undertake sensitivity analyses to assess the impact of a range of possible values. In other instances of missing data (such as missing follow-up periods), it may not be possible to include a study in a particular analysis.

We will use the GRADE approach as described in the Cochrane Handbook for Systematic Reviews of Interventions to present the quality of evidence and 'Summary of findings' tables. The downgrading of the quality of a body of evidence for a specific outcome will be based on five factors: limitations of study; indirectness of evidence; inconsistency of results; precision of results; and publication bias. The GRADE approach specifies four levels of quality (high, moderate, low and very low). If sufficient studies are found, we will draw funnel plots to assess the presence of possible

publication bias (trial effect versus standard error). While funnel plot asymmetry may indicate publication bias, this can be misleading with a small number of studies. We will discuss possible explanations for any asymmetry in the review in light of our number of included studies.

We will undertake a sensitivity analysis to explore whether the findings of the review are robust in light of the decisions made during the review process. We will also assess the impact of risk of bias in the included studies via restricting analyses to studies deemed to be at low risk of selection bias, performance bias and attrition bias. Where data allow, we will undertake additional exploratory meta-analyses to determine intervention effects on theorised intermediate outcomes (such as goal setting or self-efficacy) to examine the plausibility that these might mediate or otherwise precede behavioural effects, as well as to explore whether intervention effects on some of our outcomes (e.g. drug use) appear to mediate effects on other outcomes (e.g. risk of HIV infection). Such analyses will be informed by the synthesis of theories of change and process evaluation findings to avoid data-dredging. Where possible we will examine intervention effects by participant sub-groups in terms of participant sexuality and gender identity, SES and ethnicity to explore potential impacts on health inequalities. This will draw on existing methods involving an 'equity lens': examining evidence that equity-related characteristics (individual sexuality or gender identity, SES or ethnicity or geographical factors) moderate intervention effects, in terms of evidence for significant effect modification. This will where data allow include examination of moderation within studies (drawing on meta-analyses of subgroup effects) and between studies (meta-regression drawing on studies with different participant or site characteristics).

RQ4: Synthesis of resource use and cost data

Measures of costs and indirect resource use and cost-effectiveness will be summarised using tables. If measures of resource use are judged sufficiently homogeneous across studies, these will be synthesised using statistical meta-analysis.[90] Measures of costs, indirect resource use and cost-effectiveness will be adjusted for currency and inflation to the current UK context. These data will be used to inform a narrative synthesis of economic analyses and applicability to the UK context (RQ4). We do not intend to perform de novo economic modelling since the identified interventions and their outcomes are likely to be extremely diverse.

RQ5: Interpreting overall findings

The discussion section of our report will draw together what we have learnt overall from the syntheses of theories of change, facilitators and barriers to implementation, and outcomes of e-health interventions addressing sexual health, substance use and mental health among MSM (RQ5). This will focus on implications for intervention research. We will assess whether interventions addressing the various outcomes, or some subsets of these, appear to have similar or at least compatible theories of change (for example, similar mediating factors or mechanisms) which could pragmatically be combined to develop an overall intervention with a coherent theory of change addressing the syndemic or some sub-elements of the syndemic. We will then assess whether different or similar factors appear to facilitate or impede implementation or receipt of interventions addressing the various outcomes in order to further develop our sense of whether these outcomes might be feasibly addressed by a single intervention or might be better addressed by separate interventions addressing some but not all outcomes. Finally, we will draw on the findings from our outcome syntheses to judge whether there is really scope for a single intervention addressing sexual health, substance use and mental health to have synergistic effects. We would judge that this is likely where there is evidence that e-health interventions addressing the various outcomes all tend to be effective and particularly where there is evidence that interventions addressing different outcomes appear to impact effectively on similar mediators. Where this is found not to be the case, for example, because of evidence for lack of or even harmful effect on some outcomes, or a lack of evidence for some outcomes, our recommendations will reflect this. For example, we might recommend that future intervention research needs to focus on some single-outcome interventions

where there is currently insufficient evidence, or that research should focus on e-health interventions that do not address outcomes where there is evidence of no or harmful effects.

Patient and public involvement

We have consulted with LGBT community and health organisations in developing this proposal. Terrence Higgins Trust and London Friend (uploaded letters of support) run online support groups and counselling service for men concerned about drug use. London Friend provides face to face drug and alcohol support for gay men. These organisations are interested in exploring the potential of e-health interventions which do not require human personnel to deliver if these are demonstrably more cost-effective than face-to-face provision. This has informed our focus on economic evidence. These organisations also expressed interest in interventions addressing multiple, interrelated health concerns in a joined-up fashion. We have also consulted with Stonewall which campaigns for LGBT health. This organisation was interested in our proposal's focus on gay men's holistic health and what factors might affect implementation or impact, for example whether e-health is accessible and effective for minority ethnic, lower SES or trans MSM. This has informed our inclusion of such factors in our planned moderator analyses.

In the course of the project, we will institute a PPI stakeholder group which will meet twice during the review. First, the group will review the typology of interventions and synthesis of evidence on theories of change and factors affecting delivery and receipt. The group will consider and advise us whether the interventions presented could feasibly inform the development of an overall intervention addressing the syndemic of HIV/STIs, sexual risk, alcohol and drug use, and mental ill health among UK MSM. Second, the group will review the syntheses and draft report to inform dissemination and knowledge transfer. At this stage, the group will consider and advise us whether the evidence of effectiveness and cost-effectiveness overall and by subgroups suggested that it would be worth investing in the development of an e-health intervention to address multiple outcomes among UK MSM. We anticipate that were the review to inform a further proposal for intervention development or optimisation these organisations would continue to collaborate, with some being involved in co-production and piloting.

Socio-economic position and inequalities

We will use an 'equity lens' [106]to examine effects by participant sexual/gender identity, SES and ethnicity to determine effectiveness in reducing health inequalities (RQ3).

Knowledge exchange and translation

Our aim is to provide research outputs which provide rigorous evidence on the approaches, theories of change, processes, effectiveness and cost-effectiveness of e-health interventions in preventing HIV/STIs and sexual risk as well as substance use and mental ill health among MSM, and to inform the development of a future intervention that will address the syndemic of these outcomes among MSM. We will produce three reports: a full technical report for NIHR; a briefing report for policy and practice audiences; and a concise report for the affected communities of MSM. All three reports will be published online on the Sigma Research website which is widely accessed by the HIV and sexual health community and by the gay community. The research will be launched at an event organised through Sigma Research, which has unsurpassed community and policy networks. In addition, we will disseminate the research via open-access international scientific journals, and via academic and policy conferences. We will undertake seminars at LSHTM to which we will invite representatives of the UK and devolved national government departments of health as well as sexual health commissioners and service providers to present the research to discuss policy

implications and next steps. We will also use existing stakeholder and academic networks to support dissemination as well as existing web and social media platforms managed by Sigma Research.

It is impossible in advance of the systematic review itself to say how our results will be translated into policies and interventions. We hope that our synthesis of outcome evaluations will provide an informed view of whether e-health interventions are likely to be effective in preventing each of the outcomes examined in this systematic review, and reducing health inequalities in these outcomes. We anticipate that our synthesis of process evaluations will shed light on which approaches have the most potential for public health improvement in different settings including across the UK. Depending on our findings, our review is likely to inform the development of a research proposal either to the MRC's Public Health Intervention Development stream or the NIHR Public Health Research Board. The former will occur if there is evidence that this is a promising approach but there is no obvious existing candidate intervention to implement or evaluate in the UK so that new intervention development is called for. The latter will occur if there is clear evidence that a current intervention is a good candidate for effectiveness but further research is required to assess its effectiveness in a UK context. Our aim would thus be either to develop or to optimise and then evaluate an e-health intervention that simultaneously and holistically addresses HIV/STIs and sexual risk, substance use and mental health among MSM. Our review will determine the precise array of outcomes to be targeted as well as the theories of change and intervention approaches to be used. We anticipate that any such proposal would be developed in collaboration with appropriate community and health organisations such as Stonewall, London Friend or the Terrence Higgins Trust.

Research governance and ethics

The principal investigator will be responsible for the conduct and delivery of the work. The sponsor of the research is Professor Richard Smith, Dean of the Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine. The co-applicants will form an investigator committee which will meet monthly throughout the project, overseeing its conduct. These meetings will be minuted to keep a record of tasks, deadlines and responsibilities. The research involves no human participants and draws solely on evidence already in the public realm, so RAS approval is not required. Review and approval by the London School of Hygiene and Tropical Medicine research ethics committee will be sought. The team will follow relevant guidelines and best practice including the Social Research Association's (SRA) ethical guidelines[107] and refer also to guidance recommended by the National Coordinating Centre for Public Engagement. [108]

Expertise

Professor Chris Bonell (LSHTM) will direct the review overseeing all stages and components. He will be directly involved with other investigators in screening, data extraction, quality assessment and synthesis of theory and qualitative evidence. He will also oversee searching and synthesis of statistical evidence. He is experienced in leading systematic reviews including three previous reviews funded by the NIHR Public Health Research programme and two previous reviews of interventions for MSM. He is also experienced in primary research on the health needs of and public health interventions for MSM. Dr G.J. Melendez-Torres (Cardiff University) is an experienced systematic reviewer with ongoing involvement in several evidence synthesis projects, and expertise in MSM drug use and sexual behaviour. He will lead quantitative analyses, data extracting, quality assessing and synthesising quantitative evidence. Rebecca Meiksin (LSHTM) is a research fellow with previous experience of evidence synthesis and sexual health research. Peter Weatherburn and Charlie Witzel work in LSHTM's Sigma Research group which has been researching the health of gay, bisexual and other men who have sex with men for over 25 years. They will advise on the conduct and write-up of the research, and in particular lead PPI and contribute to drawing together the findings from each synthesis to determine the value of developing or optimising an e-health study among UK MSM. Dr Alec Miners (LSHTM) is a health economist with particular expertise in sexually transmitted

infections and blood borne viruses who will examine the evidence and advice on appropriate methods of quality appraisal and synthesis for the cost-effectiveness evidence.

References

1. Beyrer, C., et al., *Global epidemiology of HIV infection in men who have sex with men.* Lancet, 2012. **380**(9839): p. 367-77.
2. Aghaizu, A., *HIV in the United Kingdom: 2013* 2013, PHE: London.
3. Nakagawa, F., et al., *Projected Lifetime Healthcare Costs Associated with HIV Infection.* PLoS One, 2015. **10**(4): p. e0125018.
4. Brook, F.P.A.a., *Unprotected Nation: The Financial and Economic Impacts of Restricted Contraception Services*, 2013, FPA/Brook: London.
5. Guasp, A., *The gay and bisexual men's health survey*. 2012, London: Stonewall.
6. Buffin, J., *Part of the picture: lesbian, gay and bisexual people's alocohol and drug use in England (2009-2011)*. 2012, Manchester: The National LGB Drug & Alcohol Database.
7. Lee, J.G.L., G.K. Griffen, and C.L. Melvin, *Tobacco use among sexual minorities in the USA 1987-May 2007: a systematic review.* Tobacco Control, 2009. **18**: p. 275-282.
8. Vosburgh, H.W., et al., *A review of the literature on event-level substance use and sexual risk behavior among men who have sex with men.* AIDS Behav, 2012. **16**(6): p. 1394-410.
9. Hickson, F.C.I., et al., *Illicit drugs use among men who have sex with men in England and Wales.* Addiction Research and Theory, 2010. **18**(1): p. 14-22.
10. Schmidt, A.J., et al., *Illicit drug use among gay and bisexual men in 44 cities: Findings from the European MSM Internet Survey (EMIS).* Int J Drug Policy, 2016. **38**: p. 4-12.
11. King, M., et al., *A systematic review of mental disorder, suicide, and deliberate self harm in lesbian, gay and bisexual people.* BMC Psychiatry, 2008. **8**: p. 70.
12. McFall, S.L., *Understanding Society*. 2012, Colchester: Institute for Social and Economic Research, University of Essex.
13. Davies, S.C., *Chief Medical Officer's summary*, in *Annual Report of the Chief Medical Officer 2013: Public Mental Health Prioriites: Investing in the Evidence*, A. Metha, Editor. 2013, Department of Health: London.
14. Stall, R., F. M., and J. Catania, *Interacting epidemics and gay men's health: a theory of syndemic production among urban gay men*, in *Unequal Opportunity: Health Disparities Affecting Gay and Bisexual Men in the United States*, R.J. Wolitski, R. Stall, and G. Valdiserri Roberson Editors. 2008, Oxford University Press: New York. p. 251---274.
15. Mercer, C.H. *The health and well-being of men who have sex with men (MSM) in Britain: Evidence from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3).* BMC Public Health, 2016. DOI: doi: 10.1186/s12889-016-3149-z [E-pub].
16. Regier, *Comorbidity of mental disorders with alcohol and other drug abuse. Results from the epidemiologic catchment area (ECA study).* Journal of the American Medical Association, 1990. **264**(19): p. 2511-2518.
17. Colfax, G., et al., *Drug use and sexual risk behavior among gay and bisexual men who attend circuit parties: a venue-based comparison.* JAIDS, 2001. **28**(4): p. 373-379.
18. Mansergh, G., et al., *Alcohol and drug use in the context of anal sex and other factors associated with sexually transmitted infections: results from a multi-city study of high-risk men who have sex with men in the USA.* Sex Transm Infect, 2008. **84**(6): p. 509-11.
19. Mustanski, B., et al., *Psychosocial health problems increase risk for HIV among urban young men who have sex with men: preliminary evidence of a syndemic in need of attention.* Ann Behav Med, 2007. **34**(1): p. 37-45.
20. Daskalopoulou, M., et al., *Recreational drug use, polydrug use, and sexual behaviour in HIV-diagnosed men who have sex with men in the UK: results from the cross-sectional ASTRA study.* Lancet HIV, 2014. **1**(1): p. e22-31.

21. Dearing, N. and S. Flew. *MSM: the cost of having a good time? a survey about sex, drugs and losing control*. Sexually Transmitted Infections 2015; Available from: http://dx.doi.org/10.1136/sextrans-2015-052126.255.
22. Heiligenberg, M., *Recreational drug use during sex and sexually transmitted infections among clients of a city sexually transmitted infections clinic in Amsterdam, the Netherlands.* Sexually Transmitted Diseases, 2015. **39**(7): p. 518-527.
23. Bourne, A., et al., *Illicit drug use in sexual settings ('chemsex') and HIV/STI transmission risk behaviour among gay men in South London: findings from a qualitative study.* Sex Transm Infect, 2015. **91**(8): p. 564-8.
24. Martin, M., *The impact of adherence to preexposure prophylaxis on the risk of HIV infection among people who inject drugs.* AIDS, 2015. **29**(7): p. 819-24.
25. England, P.H., *Promoting the health and wellbeing of gay, bisexual and other men who have sex with men: initial findings*. 2014, London: PHE.
26. HIV, I.A.G.o.S.H.a., *Building on progress. Enhancing the response to HIV in England*. 2009, London: Department of Health.
27. Practitioners, R.C.o.G., *Guidelines for the Care of Lesbian, Gay and Bisexual Patients in Primary Care*, 2014, Royal College of General Practitioners: London.
28. Miltz, A., *Depression and sexual behaviour among men who have sex with men in the UK.* Sexually Transmitted Infections, 2015.
29. Pebody, R. *UK government halves the budget of HIV prevention programme for England*. 2014 22 November 2016]; Available from: http://www.aidsmap.com/UK-government-halves-the-budget-of-HIV-prevention-programmefor-England/page/2930244/. .
30. Johnson, W.D., et al., *Behavioral interventions to reduce risk for sexual transmission of HIV among men who have sex with men.* Cochrane Database Syst Rev, 2008(3): p. CD001230.
31. Riper, H., et al., *Effectiveness of guided and unguided low-intensity internet interventions for adult alcohol misuse: a meta-analysis.* PLoS One, 2014. **9**(6): p. e99912.
32. Andersson, G. and P. Cuijpers, *Internet-based and other computerized psychological treatments for adult depression: a meta-analysis.* Cogn Behav Ther, 2009. **38**(4): p. 196-205.
33. Andrews, G., et al., *Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis.* PLoS One, 2010. **5**(10): p. e13196.
34. Arnberg, F.K., et al., *Internet-delivered psychological treatments for mood and anxiety disorders: a systematic review of their efficacy, safety, and cost-effectiveness.* PLoS One, 2014. **9**(5): p. e98118.
35. Pasarelu, C.R., et al., *Internet-delivered transdiagnostic and tailored cognitive behavioral therapy for anxiety and depression: a systematic review and meta-analysis of randomized controlled trials.* Cogn Behav Ther, 2017. **46**(1): p. 1-28.
36. Spijkerman, M.P., W.T. Pots, and E.T. Bohlmeijer, *Effectiveness of online mindfulness-based interventions in improving mental health: A review and meta-analysis of randomised controlled trials.* Clin Psychol Rev, 2016. **45**: p. 102-14.
37. Christensen, H., P. Batterham, and A. Calear, *Online interventions for anxiety disorders.* Curr Opin Psychiatry, 2014. **27**(1): p. 7-13.
38. Kaltenthaler, E., et al., *Computerised cognitive-behavioural therapy for depression: systematic review.* Br J Psychiatry, 2008. **193**(3): p. 181-4.
39. Gabarron, E. and R. Wynn, *Use of social media for sexual health promotion: a scoping review.* Glob Health Action, 2016. **9**(1): p. 32193.
40. Schnall, R., et al., *eHealth interventions for HIV prevention in high-risk men who have sex with men: a systematic review.* J Med Internet Res, 2014. **16**(5): p. e134.
41. L'Engle, K.L., et al., *Mobile Phone Interventions for Adolescent Sexual and Reproductive Health: A Systematic Review.* Pediatrics, 2016. **138**(3).
42. Noar, S.M., H.G. Black, and L.B. Pierce, *Efficacy of computer technology-based HIV prevention interventions: a meta-analysis.* AIDS, 2009. **23**(1): p. 107-15.

43. Tait, R.J., R. Spijkerman, and H. Riper, *Internet and computer based interventions for cannabis use: a meta-analysis.* Drug Alcohol Depend, 2013. **133**(2): p. 295-304.
44. Melendez-Torres, G.J., E. Nye, and C. Bonell, *Internet sex-seeking is inconsistently linked with sexual risk in men who have sex with men: systematic review of within-subjects comparisons.* Sex Health, 2015. **12**(3): p. 183-7.
45. Sullivan, P.S., et al., *Successes and challenges of HIV prevention in men who have sex with men.* Lancet, 2012. **380**(9839): p. 388-99.
46. Johnson, M.O., et al., *Internalized heterosexism among HIV-positive, gay-identified men: implications for HIV prevention and care.* J Consult Clin Psychol, 2008. **76**(5): p. 829-39.
47. Ryan, C., et al., *Family rejection as a predictor of negative health outcomes in white and Latino lesbian, gay, and bisexual young adults.* Pediatrics, 2009. **123**(1): p. 346-52.
48. Hamilton, C.J. and J.R. Mahalik, *Minority stress, masculinity, and social norms predicting men's health risk behaviors.* Journal of Counseling Psychology, 2009. **56**: p. 1.
49. Daher, J., et al., *Do digital innovations for HIV and sexually transmitted infections work? Results from a systematic review (1996-2017).* BMJ Open, 2017. **7**: p. e017604.
50. Solorio, R., et al., *Tu Amigo Pepe: evaluation of a multi-media marketing campaign that targets young Latino immigrant MSM with HIV testing messages.* AIDS and Behavior, 2016;. **20**: p. 1973-88.
51. Lelutiu-Weinberger, C., *Feasibility, acceptability, and preliminary efficacy of a live-chat social media intervention to reduce HIV risk among young men who have sex with men. .* AIDS and Behavior, 2015. **19**: p. 1214-27.
52. Rozbroj, T., et al., *Assessing the applicability of e-therapies for depression, anxiety, and other mood disorders among lesbians and gay men: analysis of 24 web- and mobile phone-based self-help interventions.* J Med Internet Res, 2014. **16**(7): p. e166.
53. Young, S.D., *Social media technologies for HIV prevention study retention among minority men who have sex with men (MSM).* AIDS Behav, 2014. **18**(9): p. 1625-9.
54. Hirshfield, S., *Developing a Video-Based eHealth Intervention for HIV-Positive Gay, Bisexual, and Other Men Who Have Sex with Men: Study Protocol for a Randomized Controlled Trial.* JMIR Res Protoc, 2016. **5**(2): p. e125.
55. Ybarra, *Ethical Considerations in Recruiting Online and Implementing a Text Messaging-Based HIV prevention Program With Gay, Bisexual, and Queer Adolescent Males.* J Adolesc Health, 2016. **59**(1): p. 44-99.
56. Miranda, J., *An Internet-Based Intervention (Condom-Him) to Increase Condom Use Among HIV-Positive Men Who Have Sex With Men: Protocol for a Randomized Controlled Trial.* JMIR Res Protoc, 2013. **2**(2): p. e39.
57. Bowen, A.M., K. Horvath, and M.L. Williams, *A randomized control trial of Internet-delivered HIV prevention targeting rural MSM.* Health Educ Res, 2007. **22**(1): p. 120-7.
58. Mustanski, B., *Effects of messaging about multiple biomedical and behavioral HIV prevention methods on intentions to use among US MSM: results of an experimental messaging study.* AIDS Behav, 2014. **18**(9): p. 1651-60.
59. Schonnesson, L.N., A.M. Bowen, and M.L. Williams, *Project SMART: Preliminary Results From a Test of the Efficacy of a Swedish Internet-Based HIV Risk-Reduction Intervention for Men Who Have Sex With Men.* Arch Sex Behav, 2016. **45**(6): p. 1501-11.
60. Mitchell, J., J.Y. Lee, and R. Stephenson, *How Best to Obtain Valid, Verifiable Data Online From Male Couples? Lessons Learned From an eHealth HIV Prevention Intervention for HIVNegative Male Couples.* JMIR Public Health Surveill, 2016. **2**(2): p. e152.
61. Liu, C., *Comparing the effectiveness of a crowdsourced video and a social marketing video in promoting condom use among Chinese men who have sex with men: a study protocol.* BMJ Open, 2016. **6**(10): p. e010755.
62. Wilkerson, J.M., *The role of critical self-reflection of assumptions in an online HIV intervention for men who have sex with men.* AIDS Educ Prev, 2011. **23**(1): p. 13-24.

63. Milam, J., et al., *Randomized Controlled Trial of an Internet Application to Reduce HIV Transmission Behavior Among HIV Infected Men Who have Sex with Men.* AIDS Behav, 2016. **20**(6): p. 1173-1181.
64. Fernandez, M.I., et al., *A Randomized Controlled Trial of POWER: An Internet-Based HIV Prevention Intervention for Black Bisexual Men.* AIDS Behav, 2016. **20**(9): p. 1951-60.
65. L'Engle, K.L., et al., *Scaled-Up Mobile Phone Intervention for HIV Care and Treatment: Protocol for a Facility Randomized Controlled Trial.* JMIR Res Protoc, 2015. **4**(1): p. e11.
66. Millard, T., et al., *Online self-management for gay men living with HIV: a pilot study.* Sex Health, 2015. **12**(4): p. 308-14.
67. Kurth, A.E., et al., *Linguistic and Cultural Adaptation of a Computer-Based Counseling Program (CARE+ Spanish) to Support HIV Treatment Adherence and Risk Reduction for People Living With HIV/AIDS: A Randomized Controlled Trial.* J Med Internet Res, 2016. **18**(7): p. e195.
68. Horvath, K.J., et al., *Feasibility, acceptability and preliminary efficacy of an online peer-to-peer social support ART adherence intervention.* AIDS Behav, 2013. **17**(6): p. 2031-44.
69. Du Bois, S.N., S.E. Johnson, and B. Mutanski, *Examining racial and ethnic minority differences among YMSM during recruitment for an online HIV prevention intervention study.* AIDS Behav, 2012. **16**(6): p. 1430-5.
70. Bull, S.S., et al., *Improving recruitment and retention for an online randomized controlled trial: experience from the Youthnet study.* AIDS Care, 2008. **20**(8): p. 887-93.
71. Bourne, C., et al., *Short message service reminder intervention doubles sexually transmitted infection/HIV re-testing rates among men who have sex with men.* Sex Transm Infect, 2011. **87**(3): p. 229-31.
72. Reback, C.J., et al., *Text messaging reduces HIV risk behaviors among methamphetamine-using men who have sex with men.* AIDS Behav, 2012. **16**(7): p. 1993-2002.
73. Schwinn, T.M., et al., *Preventing drug use among sexual-minority youths: findings from a tailored, web-based intervention.* J Adolesc Health, 2015. **56**(5): p. 571-3.
74. Yang, C., et al., *Feasibility and Acceptability of Smartphone-Based Ecological Momentary Assessment of Alcohol Use Among African American Men Who Have Sex With Men in Baltimore.* JMIR Mhealth Uhealth, 2015. **3**(2): p. e67.
75. Krishnan, A., et al., *Communication technology use and mHealth acceptance among HIV-infected men who have sex with men in Peru: implications for HIV prevention and treatment.* AIDS Care, 2015. **27**(3): p. 273-82.
76. Lin, Y.J. and T. Israel, *A computer-based intervention to reduce internalized heterosexism in men.* J Couns Psychol, 2012. **59**(3): p. 458-64.
77. Millard, T., et al., *The Positive Outlook Study: A Randomised Controlled Trial Evaluating Online Self-Management for HIV Positive Gay Men.* AIDS Behav, 2016. **20**(9): p. 1907-18.
78. Fleming, J.B. and M.N. Burns, *Online Evaluative Conditioning Did Not Alter Internalized Homonegativity or Self-Esteem in Gay Men.* J Clin Psychol, 2016. **73**(9): p. 1013-1026.
79. Abbott, J.A., et al., *Out & Online; effectiveness of a tailored online multi-symptom mental health and wellbeing program for same-sex attracted young adults: study protocol for a randomised controlled trial.* Trials, 2014. **15**: p. 504.
80. Millard, T., et al., *Informing the development of an online self-management program for men living with HIV: a needs assessment.* BMC Public Health, 2014. **14**: p. 1209.
81. Hightow-Weidman, L.B., et al., *HealthMpowerment.org: Building Community Through a Mobile-Optimized, Online Health Promotion Intervention.* Health Educ Behav, 2015. **42**(4): p. 493-9.
82. Adam, B.D., et al., *hivstigma.com, an innovative web-supported stigma reduction intervention for gay and bisexual men.* Health Educ Res, 2011. **26**(5): p. 795-807.

83. Rozbroj, T., et al., *Improving self-help e-therapy for depression and anxiety among sexual minorities: an analysis of focus groups with lesbians and gay men.* J Med Internet Res, 2015. **17**(3): p. e66.
84. Swendeman, D., et al., *Smartphone self-monitoring to support self-management among people living with HIV: perceived benefits and theory of change from a mixed-methods randomized pilot study.* J Acquir Immune Defic Syndr, 2015. **69 Suppl 1**: p. S80-91.
85. Burns, M.N., E. Montague, and D.C. Mohr, *Initial design of culturally informed behavioral intervention technologies: developing an mHealth intervention for young sexual minority men with generalized anxiety disorder and major depression.* J Med Internet Res, 2013. **15**(12): p. e271.
86. Shemilt, I., et al., *A national evaluation of school breakfast clubs: evidence from a cluster randomized controlled trial and an observational analysis.* Child: Care, Health and Development, 2004. **30**(5): p. 413-427.
87. Thomas, J., J. Brunton, and S. Graziosi, *EPPI-Reviewer 4.0: software for research synthesis. EPPI-Centre software.*, 2010, Social Science Research Unit, Institute of Education: London.
88. Higgins, J.P.T. and S. Green, *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. 2011, Oxford: The Cochrane Collaboration.
89. Shepherd, J., et al., *The effectiveness and cost-effectiveness of behavioural interventions for the prevention of sexually transmitted infections in young people aged 13 to 19: a systematic review and economic evaluation.* Health Technol Assess Monographs 2010 **14**(7): p. 1-206
90. Shemilt, I., et al., *Incorporating economics evidence*, in *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1* J.P.T. Higgins and S. Green, Editors. 2008, The Cochrane Collaboration.
91. Peersman, G., S. Oliver, and A. Oakley, *EPPI-Center review guidelines: data collection for the EPIC database*, 1997, EPPI-Centre Social Science Research Unit: London.
92. Egan, M., et al., *Reviewing evidence on complex social interventions: development and testing of a new tool for appraising implementation.* Journal of Epidemiology & Community Health, 2009. **63**: p. 4-11.
93. Shepherd, J., et al., *Young People and Healthy Eating: A systematic review of barriers and facilitators*. 2001, London: EPPI-Centre, Social Science Research Unit.
94. Sterne, J.A.C., et al., *ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions.* British Medical Journal, 2016. **355**: p. i4919.
95. Sterne, J., M. Egger, and D. Moher, *Addressing reporting biases*, in *Cochrane Handbook for Systematic Reviews of Interventions*, J.P.T. Higgins and S. Green, Editors. 2008, Wiley: Chichester. p. 297-334.
96. Cho, B.K., et al., *Joint statement on redundant (duplicate) publication by the Editors of the undersigned cardiothoracic journals.* Ann Thorac Surg, 2000. **69**: p. 663.
97. Husereau, D., et al., *Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement*

British Medical Journal, 2013. **346**: p. f1049
98. Arai, L., et al., *It might work in Oklahoma but will it work in Oakhampton? Context and implementation in the effectiveness literature on domestic smoke detectors.* Inj Prev, 2005. **11**: p. 148-51.
99. Noyes, J., J. Popay, and P. Garner, *What can qualitative research contribute to a Cochrane systematic review of DOT for promoting adherence to tuberculosis treatment?* , in *Qualitative Research and Systematic Reviews workshop*2005: Continuing Professional Development Centre, University of Oxford.
100. Thomas, J. and A. Harden, *Methods for the thematic synthesis of qualitative research in systematic reviews.* BMC Medical Research Methodology, 2008. **8**: p. 45.

101. Melendez-Torres, G.J., C. Bonell, and J. Thomas, *Emergent approaches to the meta-analysis of multiple heterogeneous complex interventions.* BMC Medical Research Methodology, 2015. **15**: p. 47.
102. Kalaian, H.A. and S.W. Raudenbush, *A multivariate mixed linear model for meta-analysis.* Psychological Methods, 1996. **1**: p. 227-235.
103. Thompson, S. and S. Sharp, *Explaining heterogeneity in meta-analysis: a comparison of methods.* Statistics in Medicine, 1999. **18**(2): p. 693-708.
104. Borenstein, M., et al., *Introduction to Meta-Analysis*. 2009, Chichester: John Wiley & Sons Ltd.
105. Cheung, M.W.-L., *Modeling dependent effect sizes with three-level meta-analyses: a structural equation modeling approach*, 2014, American Psychological Association.
106. Kavanagh, J., et al., *School-based cognitive behavioural interventions: a systematic review of effects and inequalities.* Health Sociology Review 2009. **18**: p. 61-78.
107. Social Research Association, *Ethical Guidelines*. 2003, London: Social Research Association.
108. Centre for Social Justice and Community Action and National Co-ordinating Centre for Public Engagement, *Community-based participatory research: a guide to ethical principles and practice, national coordinating centre for public engagement*. 2012, Bristol: National Coordinating Centre for Public Engagement.