An interactive digital intervention to increase condom use in heterosexual men in sexual health clinics: a pilot trial (MenSS)

Statistical Analysis Plan (SAP)

Introduction

The following analysis plan covers the statistical analyses of the predetermined outcome measures (primary and secondary and other) from the MenSS pilot trial.

All analyses will be conducted in accordance with the University College London (UCL) Primary Care and Mental Health (PRIMENT) clinical trials unit (CTU) standard operating procedures (SOPs) in addition to conforming to the CONSORT statement.

Trial overview

Trial design

A phase 2 pilot multi-centre RCT of adult males who have sex with women, with a recent history of risky sexual behaviour comparing an interactive digital intervention (IDI) plus usual care with usual care alone on condom use.

Aim

To establish the feasibility and best design of a full scale trial of the IDI comparing usual clinical care plus the intervention to usual care alone.

Objectives

Optimise the parameters for a phase 3 randomised controlled trial (RCT) of usual care plus the IDI compared to usual care alone, using the primary outcome of self-reported condom use at the 3 month follow-up.

Optimise the data collection and analysis procedures for a health economic analysis for a future phase 3 RCT.

Setting

Participants will be recruited from three Genitourinary Medicine (GUM) clinics: The Homerton Hospital Department of Sexual Health; Barts Sexual Health Centre; and City of Coventry Integrated Sexual Health Services Department.

Inclusion criteria

Clinic attendee
Male
Age 16 years and over
Able to read English
Internet access with an active e-mail account
Report of recent sexual risk behaviour:
- Symptoms of acute STI or
- Seeking treatment for an STI or
- Two or more partners in the last year AND Non-condom use in the last 3 months

Exclusion criteria

HIV positive
Hepatitis B or C
Men who have sex with men (MSM):

Men who only have sex with men
Men who more often have sex with men
Men with no sexual experience

Intervention
Participants will work through a structured, individually tailored website whilst they are in clinic. Participants will receive access to the entire website; however, tailored information based on their individual responses regarding barriers to condom use will be presented most prominently on the homepage. They will be asked to set goals to change their behaviour. They will be sent text messages and/or e-mails to encourage them to visit the intervention website after leaving the clinic.

The intervention group will also receive usual clinical care.

Control
Usual clinical care.

Trial procedure
Clinic staff or researchers, flyers and posters will inform potential participants about the trial and direct them to the trial website available on an ipad in the clinic waiting room or side room. The software will take them through eligibility screening and consent. Eligible, consenting participants who provide contact details including at least an e-mail address and mobile number will be asked to create a password which will instigate a unique participant identifier (ID). Demographic and baseline questionnaire data will be collected electronically by the software. Participants will then be randomly allocated, by the software, to the intervention or control group. They will be informed of their allocation. The ID will give access to the intervention website for only those randomised as such. Automated e-mail reminders, including a link to the questionnaires, will be sent to all participants for the 3, 6 and 12 month follow-ups.

Sample size
Power calculations were performed based on data from the Sexunzipped online trial. The study is sufficiently powered to allow estimates of the effect of the intervention on episodes of condomless vaginal sex over the last 3 months. A sample size of 166 (83 intervention, 83 comparator, randomised 1:1 between experimental and control conditions) is adequate to find a reduction of 1.35 episodes of condomless sex with a conventional two sided alpha of .05 and 90% power. Even when accounting for potential loss to follow-up at 3 months (which is the primary outcome point), 122 participants (61 intervention, 61 comparator) is adequate to find a reduction of 1.35 episodes of condomless sex with a conventional two sided alpha of .05 and 80% power. In addition, this sample size is also sufficient to detect a 1.65 difference in safer sex intention, and a one-point difference in self-efficacy on Likert scales, with a conventional two sided alpha of .05 and 90% power.

Randomisation
The trial software will randomly allocate participants to the intervention or control groups in a ratio of 1:1 using a computer algorithm.

Blinding

Data collection is automated and trial personnel will be blind to allocation. Participants will be informed whether they have been allocated to the intervention immediately post automated randomisation.

Data entry
The majority of the study data will be entered directly by participants using the online questionnaires integral to the tailored software. Baseline data will be collected before randomisation and then participants will be prompted to complete follow-up questionnaires at 3, 6 and 12 months. Data will be saved and exported using ID numbers only.

Additional data will be collected by study personnel from clinical notes with regard to visits to the recruiting clinics, and diagnoses of STIs. Data for the period covering 6 months prior to the date of recruitment of the first patient up to 12 months from date of recruitment of the last patient will be collected for ALL patients.

Data collection
Baseline data collected with further follow-up data at 3, 6 and 12 months post initial clinic visit (point of randomisation).

Demographic (baseline) data
Age (in years)
Employment status (choice of 1 of 6 categories or "other" with free text)
Ethnicity (choice of 1 of 15 categories plus "other" with free text or "prefer not to say")

Baseline data (over last 3 months)
Number of female partners:
- Regular
- Occasional
- One off
- Sex worker
- Other (plus free text)

Number of male partners:
- Regular
- Occasional
- One off
- Sex worker
- Other (plus free text)

Number of women had condomless sex (vaginal or anal) with
Number of times had condomless sex (vaginal or anal) with a woman
Number of men had condomless anal sex
Number of times had condomless sex because drunk or high
Any STIs (tick all that apply of 10 options, plus "can't remember name", "other" with free text and "none")
Antibiotic treatment for STI (Yes/No)
Female partner pregnant (Yes/No/Don't Know)
- Outcome (4 categories plus "Don't Know")

Motivation to use condoms (4 options plus 'does not apply for me' with free text)
Intention to use condoms (4 options plus 'does not apply for me' with free text)
Impact of condom use on sexual pleasure (each likert rating scale: strongly disagree, disagree, undecided, agree, strongly agree):
- Feel unnatural
- Interrupt mood
- Don't feel good

Reduce quality of climax/orgasm
Uncomfortable
Don't fit right
Feel closer to partner without
Worry less if use
Partners worry less if use

Sexual health Quality of Life (each likert rating scale with 4 categories):
Sexual performance
Sexual relationship
Sexual anxiety

General health **today** (EQ5D – each likert rating scale with 3 categories):
Mobility
Looking after myself
Usual activities
Pain or discomfort
Feeling worried, sad or unhappy

General Health (EQ5D):
Mark thermometer (0-100)

Three, six, nine and twelve month data (each over previous 3 months)
(Red text indicates data NOT collected at baseline)

Number of female partners:
Regular
Occasional
One off
Sex worker
Other (plus free text)

Number of male partners:
Regular
Occasional
One off
Sex worker
Other (plus free text)

Number of women had condomless sex (vaginal or anal) with
Number of times had condomless sex (vaginal or anal) with a woman
Number of men had condomless anal sex

Number of times problems experienced (0, 1, 2, 3 or more):
Condoms not available
Using condoms stored in wallet more than 1 month
Using condoms not lubricated
Applying condom after sex begun
Removed condom before sex finished
Not changing condom between different forms of sex
Erection lost when putting on condom
Erection lost during sex
Condom broke
Condom slipped off during sex
Condom slipped off during withdrawal
Ejaculate dripped on partner's genitals
Condom put on wrong way then turned around
Not changing condom between different partners

Number of times had condomless sex because drunk or high

Types of contraception used (tick all that apply of 9 options, plus "don't know", "none", "none – trying for baby", "don't know name" and "other" with free text)

Any STIs (tick all that apply of 10 options, plus "can't remember name", "other" with free text and "none")
Antibiotic treatment for STI (Yes/No)
Female partner pregnant (Yes/No/Don't Know)
    Outcome (4 categories plus "Don't Know")
Number of times used each sexual health service:
    Condom pick-up
    Self-test kit
    Urine test/swabs (GP)
    Urine test/swabs (clinic)
    Blood test (GP)
    Blood test (clinic)
    STI treatment (GP)
    STI treatment (clinic)
    Sexual health advice (GP)
    Sexual health advice (clinic)
    Outreach
    Counselling or therapy
    Other (specify)
Self-efficacy (each likert rating scale: strongly disagree, disagree, undecided, agree, strongly agree):
    Get hold of condoms
    Use condom correctly
    Put condom on without erection loss
    Remove and dispose of condom
    Choose correct condom
    Discuss condom use with partner
    Suggest condom use with new partner
    Suggest condom use with new partner without them feeling diseased
    Remember to use even if drunk/high
    Stop to put condom on in heat of the moment
Knowledge (True/false/unsure):
    Getting STIs is just luck
    Would know you have STI without test
    Can tell who has an STI
    Can have HIV and not know
    Can Catch STIs from oral sex
    Safe from catching STIs if in a relationship
    Less likely to catch an STI from someone you know
    Some STIs can't be treated
    With condom on only withdraw after penis soft
    Baby oil or Vaseline is a good lubricant
    Standard sized condoms are suitable for all
Motivation to use condoms (4 options plus 'does not apply for me' with free text)
Intention to use condoms (4 options plus 'does not apply for me' with free text)
Evaluation of condom use (choice of 1 of 4 categories)
Impact of condom use on sexual pleasure (each likert rating scale: strongly disagree, disagree, undecided, agree, strongly agree):
    Feel unnatural
    Interrupt mood
    Don't feel good
    Reduce quality of climax/orgasm
    Uncomfortable
    Don't fit right

Feel closer to partner without
Worry less if use
Partners worry less if use

Communication, discussed following with partner(s) (Yes/No):
How to prevent pregnancy
How to use condoms
How to prevent STIs/HIV
Your sex history
Their sex history

Identity (each likert rating scale: strongly disagree, disagree, undecided, agree, strongly agree):
Feel like a responsible person so use condoms
Feel like a spontaneous person so don't use condoms
Using condoms is the woman's responsibility
Condoms make me feel less of a man
Use condoms due to health concerns
Use condoms due to concerns about partner's health
Getting a girl pregnant proves I'm a real man

Sexual health Quality of Life (each likert rating scale with 4 categories):
Sexual performance
Sexual relationship
Sexual anxiety

General health **today** (EQ5D – each likert rating scale with 3 categories):
Mobility
Looking after myself
Usual activities
Pain or discomfort
Feeling worried, sad or unhappy

General Health (EQ5D):
Mark thermometer (0-100)

Has being part of the study had any good or bad effects on your life (explain)? (free text)

Additional data

Website usage data (number of times site visited, number of times pages visited, number of pages visited).
Intervention development costs.
Recruitment and retention rates.

Primary outcome

Number of episodes of condomless vaginal or anal sex with a woman (without a condom) over the previous 3 months at the three months follow-up.

Secondary outcome

STI diagnoses **from clinic notes:** total number of new STI diagnoses in the last twelve months.

Other outcomes (each collected baseline at 3, 6 and 12 months except where indicated)

STI diagnoses **from self-report:** total number of STIs* in previous 3 months at each follow-up (3, 6 and 12 months).
*(exclude possible recurring conditions: i.e. include only Chlamydia, gonorrhoea, pubic lice, trichomoniasis, NSU)

Problems with condom use (score calculated from 14 questions each with frequency category: 0, 1, 2, 3 or more times). **Not collected at baseline.**

Number of times condomless sex because drunk or high.

Condom use self-efficacy (score calculated from 10 questions each with Likert scale: 1 of 5 options). **Not collected at baseline.**

Knowledge (score calculated from 11 questions each with yes/no/unsure response). **Not collected at baseline.**

Motivation to use condoms (single question: 1 of 4 options).

Intention to use condoms (single question: 1 of 4 options).

Evaluation of condom use (single question: 1 of 4 options). **Not collected at baseline.**

Impact of condom use on pleasure (score calculated from 9 questions each with likert scale: 1 of 5 options).

Communication (score calculated from 5 questions each with yes/no response). **Not collected at baseline.**

Identity (score calculated from 7 questions each with likert scale: 1 of 5 options). **Not collected at baseline.**

Analysis population
Individuals who have both baseline (where appropriate) and follow-up data available will be included in the analyses.

Data analysis
All analyses will be undertaken on an intention to treat (ITT) basis using available data.

Missing data
Missing data is likely to be not missing at random. However, under the assumption that there is no interaction between treatment group and "missingness" a complete case analysis will provide unbiased estimates.

CONSORT diagram
A consort diagram will be produced summarising:
Numbers of individuals initially interested in participating in the trial;
Numbers meeting the eligibility criteria;
Numbers consenting to be randomised;
Numbers randomised to each group;
Numbers completing follow-up questionnaires at each time point (by group).

Descriptive analysis
Descriptive data for all variables will be presented by group and overall for each follow-up: baseline, 3, 6 and 12 months.

Continuous data that are approximately normally distributed will be summarised in terms of the mean, standard deviation and number of observations. Skewed data will be presented in terms of the median, lower quartile, upper quartile and number of observations. Categorical data will be summarised in terms of frequency counts and percentages. No statistical inference will be used (i.e. there will be no significance testing or use of confidence intervals).

Analysis of primary outcome
Comparison between the intervention and control group of the number of episodes of condomless vaginal or anal sex with a woman (without a condom) over the previous 3 months at the three months follow-up will be undertaken using Poisson regression.

The baseline value for this outcome will be used as an explanatory variable. The ratio of the number of events over the three month period, between the intervention and control group with an associated 95% CI and p-value will be estimated from this model.

The model will be assessed for the presence of over dispersion (extra Poisson variability). If there is evidence of over dispersion a random intercepts term will be included to model the over dispersion.

Sensitivity analyses
Additional analyses, as per the model described above, will be undertaken in order to assess the robustness of the results. This will include:

(i) The assumption that individuals with missing outcome data in the intervention group had a poorer outcome than individuals with missing data in the control group

(ii) The assumption that individuals with missing outcome data in the control group had a poorer outcome than individuals with missing data in the intervention group

Analysis of secondary outcome
Comparison between the intervention and control group for the secondary outcome will be based on generalised linear models with appropriate link function and error structure. Baseline data for the outcome has will be included as an explanatory variable in the model.

Analysis of other outcomes
Descriptive data for all variables will be presented by group and overall for each follow-up: baseline, 3, 6 and 12 months (where collected).

No formal statistical comparisons will be undertaken.

Economic Analyses

Aim of analysis

There are two key aims of the analysis:

1) Assess the feasibility of collecting QoL and health care resource use to do a cost-effectiveness analysis of a digital sexual health intervention; and
2) Assess the suitability of using the SQoL and EQ-5D and associated utility scores to calculate quality adjusted life years (QALYs) for an incremental cost-utility ratio.

Calculating utility scores

Individual level utility scores will be calculated from individual responses to the EQ-5D and the SQoL at baseline, 3, 6 and 12 months. The EQ-5D utility scores will be calculated using the algorithm published by Dolan and the SQoL using the re-scaled utility algorithm where death equals zero published by Ratcliffe et al (2009).

Agreement of QoL measures

Descriptive statistics including mean, standard deviation, data completeness and box plots to assess ceiling and floor effects will be reported for the utility scores for the EQ-5D and SQoL. Pairwise agreement between the two different QoL instruments will be assessed using the Bland and Altman approach. The Pearson's correlation coefficient for the correlation between the EQ-5D and SQoL will be reported in addition to the correlation the two questionnaires and: the primary outcome, other measures of instances of condomless sex, total number of times problems are experienced with condoms, self-efficacy, impact of condom use on sexual pleasure and communication. We will use appropriate regression models to see if there is any significant relationship with STI diagnosis and antibiotic treatment. 95% confidence intervals will be constructed from bootstrapping.

Suitability of Sexual health care resource use questionnaire

Descriptive statistics for the different types of sexual health resource use at each follow up point will be reported, along with data completeness. Sexual Health resource use collected via individual questionnaire will be compared with resource use collected from patient records.

Cost of the intervention

We will calculate the total cost of developing and maintaining the MenSS website. There is no clear way to incorporate these costs into an economic evaluation given (a) the intervention has now been developed and hence could be considered a "sunk cost" as no further costs are required to develop it; (b) it is free to patients and providers at the point of access; (c) it is unclear how many people will go on to use the site hence the cost per patient is hard to calculate; and (d) it may be hard to disentangle costs associated with the trial (e.g. developing questionnaires and databases to store trial related data) with the costs of developing the intervention and day to day maintenance if it were to be made widely available. An estimation of the cost of the website being implemented in practice is also potentially relevant. As a result we will report the different costs associated with developing the website, and the number of individuals that accessed the website to give some estimation of cost per individual. This will be subject to extensive sensitivity testing of the different assumptions though as part of the analysis.

Cost of 12 month health and social care service use

Sexual health service use for the intervention and control group will be calculated from patient completed questionnaires at baseline, 3, 6 and 12 months. These will be costed for each patient using unit costs from the most recent Unit Costs of Health and Social

Care published by the Personal Social Services Research Unit, Department of Health reference costs, sexual health commissioning guidance and other published sources. Mean cost per patient for intervention and control groups will be reported by type of service use for each follow up point and the total 12 months. Total 12 month costs and CIs will be calculated from bootstrapping and adjusted by baseline service use from patient records.

QALYs

We will calculate the mean quality adjusted life year (QALY) of the MenSS website compared to control over 12 months. QALYs will be calculated using the EQ-5D and the formula developed by Dolan and colleagues. We will calculate the mean area under the curve for each group from baseline to 12 months, controlling for any baseline differences using regression analysis.

We will also calculate the mean QALYs of the MenSS website compared to control over 12 months calculating QALYs from utility scores obtained from the SQoL.

Confidence Intervals and Missing data

Confidence intervals will be constructed using bootstrapping. Missing data will be handled in line with the rest of the statistical analysis plan (complete case).

Incremental cost-effectiveness ratio (ICER)

The mean costs and QALYs calculated above will be used to calculate the mean incremental cost per QALY gained of MenSS compared to control.

The incremental cost per infection avoided and per change in primary outcome will also be reported.

Cost-effectiveness plane (CEP) and cost-effectiveness acceptability curve (CEAC)

The results of the non-parametric bootstrap will be presented on a CEP. A CEAC will also be constructed using the bootstrap data from a range of values of willingness to pay for a QALY gained. The probability that the website is cost-effective compared to control at a willingness to pay for a QALY gained of £30,000 will be reported.

Sensitivity Analyses

If any key assumptions become apparent during the analysis these will also be tested for as part of the sensitivity analyses – in particular in relation to the cost of the intervention and the impact it has on the results and cost estimations from different methods of collecting resource use.