Strategies to Increase Cervical Screening Uptake at First Invitation (STRATEGIC)

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Protocol

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Chief Investigator:

Professor Henry C Kitchener

The University of Manchester

School of Cancer and Enabling Sciences

Research Floor (5th Floor)

St Mary's Hospital

Manchester

M13 9WL

0161 276 6772

Aberdeen Site Principal Investigator:

Professor Maggie Cruickshank

MacGillivray Academic Centre

Aberdeen Maternity Hospital

Aberdeen

AB25 2ZD

01224 553 230

Trial Statistician:

Professor Christopher Roberts

The University of Manchester

School of Community Based Medicine

1.318 University Place

Oxford Road

Manchester

M13 9PL

0161 275 5196

Trial Coordinator:

Carly Moseley

The University of Manchester

School of Cancer and Enabling Sciences

Research Floor (5th Floor)

St Mary's Hospital

Manchester

M13 9WL

0161 276 6772

Sponsoring Organisation:

The University of Manchester

Faculty of Medical and Human Sciences

Oxford Road

Manchester

M13 9PL

Contact email:

carly.moseley@manchester.ac.uk

STRATEGIC@cmft.nhs.uk

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1. Background Information

1.1 Existing research

A systematic review undertaken in preparation for this project concluded that there was a lack of published evidence regarding the effectiveness of interventions designed to increase cervical screening attendance amongst women aged under 35. It also identified a need to conduct further studies which aim to evaluate interventions designed to promote informed uptake in young women as none of the included studies were powered to detect a difference in this age group, and most data in the review represented only a sub-sample of the overall study cohort. The review included studies which had focused solely on promoting cervical screening, and excluded those which assessed uptake across a range of screening programmes (i.e. included programmes such as breast and bowel cancer screening). There was evidence from randomised controlled trials to suggest that reminder letters are effective at promoting attendance for cervical screening, but reminder letters are already a national standard for the NHSCSP. This conclusion was also reached by a Cochrane systematic review [1] examining interventions to increase cervical screening, although this did not focus on young women. Three studies were also found which evaluated the use of both telephone and physician reminders; however reliable conclusions on their effect on screening uptake could not be drawn. Other interventions evaluated in studies included in the review were invitation letters (again standard in the UK). No evidence was found evaluating the effectiveness of counselling, educational interventions, modifying sample taking procedures (i.e. altering the length of screening appointment or offering an alternative test e.g. HPV self sampling), or media campaigns.

Coverage (i.e. an adequate test recorded in the last 3.5 years) amongst women aged 25-29 in England for tests recorded in 2008/09 was 61.5%, compared with 77.8% of women aged 45-49. A recent paper has confirmed that a declining coverage amongst younger women is also being seen in other developing countries, however the reasons for this trend are not clear [2]. In Manchester PCT, with a diverse inner city population, coverage amongst women aged 25-49 was only 67.2%. Amongst women aged 25 who were called for cervical screening in this area in 2009 only 25% accepted their invitation, with subsequent reminder letters raising this figure to just 29%.

The reasons why women do not attend for screening are well documented [3-7] with a lack of evidence relating to effective solutions to help women overcome their perceived barriers to screening. In summary these include: a fear of cervical smears and speculum examination, a lack of understanding of the purpose of screening, underestimating the risk of developing cervical cancer, problems accessing convenient screening appointments, not having the time to attend for screening and not being able to afford the costs associated with attending a screening appointment. There is the additional problem of younger women being a transient population who are out of contact with health

services and consequently at risk of becoming lost to the system and not receiving an invitation to screening. The combination of these barriers and the lack of evidence regarding successful interventions indicate that there is not one single solution to the problem of the declining number of young women attending for screening. With this in mind, the interventions selected for evaluation have been designed to appeal to a range of young women based on the principle that 'one size does not fit all'.

1.2 Existing research in relation to proposed interventions

Cervicovaginal self testing for high risk HPV has been shown to be as sensitive as 'physician obtained specimens' in terms of detection of cervical intraepithelial neoplasia.[8] In a publication earlier this year from the Netherlands, self testing for high risk HPV was taken up by 25% of women who had failed to attend for screening. 10% were HPV+ve, and 90% followed up with their general practitioner regarding cytology. Of these women CIN2 or worse was found in 14% (1.5% of the entire self test group).[9] Internet booking has not, to our knowledge, been used for booking cervical screening appointments. Timed appointments for non-responders have previously been shown to be effective in an osteoporosis screening programme where a reminder letter was sent to women asking them to confirm their attendance at a specified appointment or risk having the appointment cancelled by the care provider.[10] Nurses are widely used to offer support and guidance to patients on a daily basis, we believe that having a nurse who is easily accessible to women who wish to discuss their concerns about cervical screening will help to allay their fears and 'navigate' them to overcome barriers to attending for screening appointments.

1.3 Addressing health inequality

We recognise that cervical screening coverage is much poorer amongst socially deprived and ethnic minority groups. Greater Manchester therefore represents an excellent setting with diversity across social and ethnic groups all of whom would have access to our community based study which will include the entire PCT catchment. Cervical screening is of course offered to all and our project is therefore aimed equally at women in the hope that our strategies will be of particular relevance to those women most in need of improvement over current arrangements.

1.4 Population to be studied

The population to be studied in this trial is young women aged 19 and a half or 24 and a half in Greater Manchester and Aberdeenshire, who will be receiving their first invitation for cervical screening. These women will be drawn from all general practices in the area and will be socio-demographically representative of women receiving their first invitation for cervical screening across the UK.

2. Trial Objectives and Purpose

2.1 Purpose of trial

The purpose of this trial is to determine whether a range of complex interventions designed to improve young women's receptivity to, and uptake of, cervical screening are successful when embedded within routine cervical screening programme practice

2.2 Objectives

Phase 1

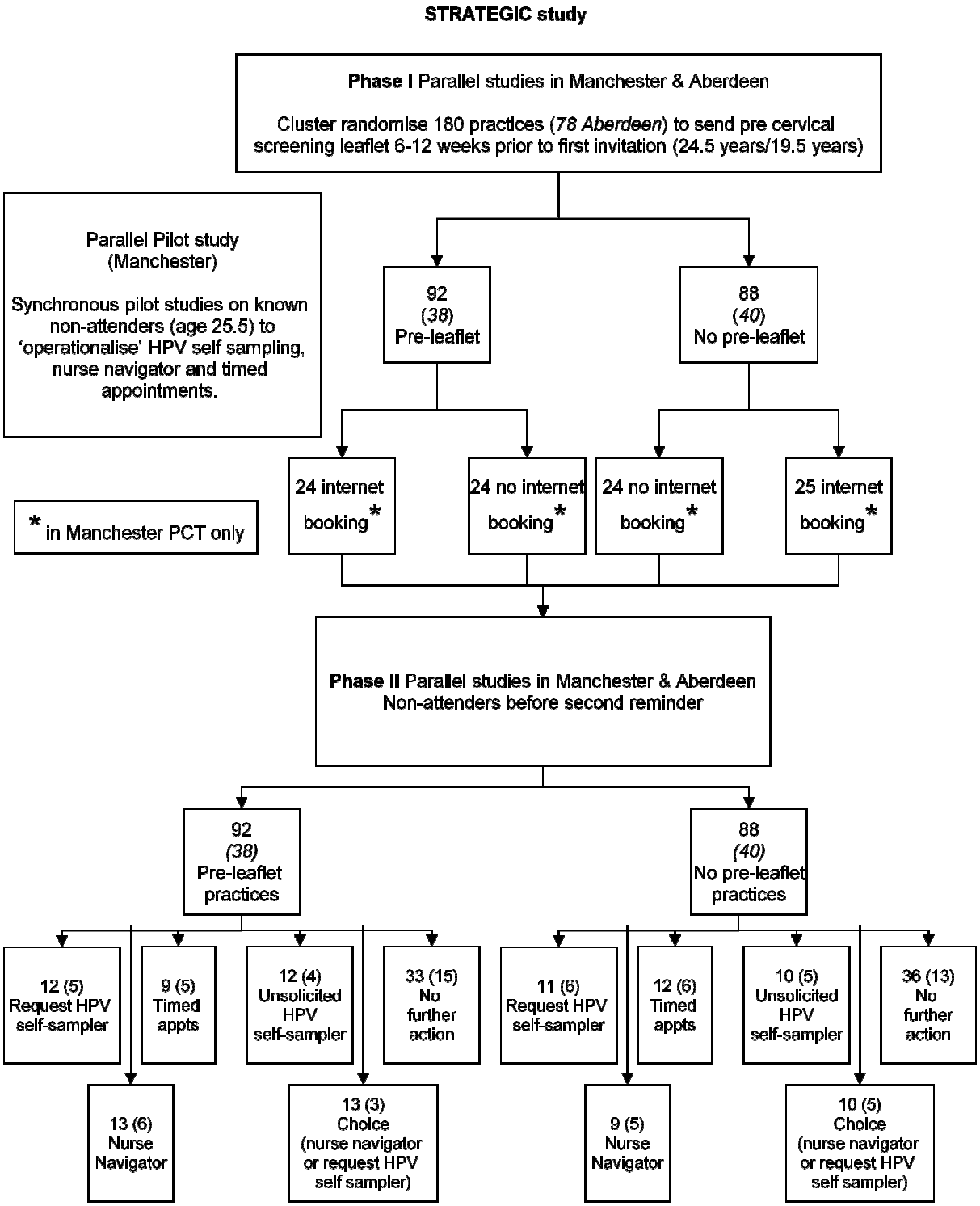
1. To determine the value of a pre-first invitation leaflet which has been designed to increase receptivity of young women to cervical screening. The development of this leaflet has been completed prior to this study, and is based on focus group work with young women which targeted issues which influence them (North West 2, Reference 10/H1005/47).
2. To determine the feasibility, acceptability, effectiveness and cost effectiveness of offering internet booking as an alternative to phoning the GP as a means of making an appointment at first invitation.

Phase 2

3. To determine amongst those women who fail to attend after a first reminder, the feasibility, acceptability, effectiveness and cost-effectiveness of several novel strategies: a) self sampling for HPV status as a determinant of the need for cervical cytology, b) a specialist nurse 'navigator' to help a woman overcome her barriers to screening, c) timed appointments for cervical screening to encourage women to attend d) a choice of HPV self sampling or the nurse navigator.
4. To determine amongst women in Scotland, who have recently been offered HPV vaccination as part of the national catch-up campaign:
    a) the first invitation uptake following the pre-invitation leaflet (phase 1)
    b) the uptake amongst those who have failed to attend following a first reminder letter, as a result of the novel strategies mentioned in objective no. 3.
5. To estimate the costs and cost-effectiveness of each of the strategies for improving cervical screening uptake.
6. As well as estimating the effects of individual interventions we will estimate the effectiveness and cost effectiveness of packages of interventions.

3. Trial design

3.1 Flow diagram



3.2 Research methods

The research methods have all been validated and are used routinely. The feasibility of some interventions will be evaluated in pilot studies (see below). Our research proposals address equity of access, through the project including a PCT with one of the worst rates of cervical screening uptake in England despite cervical screening being universally available. Our study will involve women in general practices across the entire Manchester, Salford and Trafford PCT and Aberdeenshire catchment. This includes practices with a range of social deprivation and screening coverage amongst the study age group. The screening invitation is automatically sent to every woman registered with a general practice so screening is available to all.

3.3 Planned Interventions

3.3.1 Pre-call cervical screening information leaflet (pre-leaflet)

Women in England aged 24 and a half years will be sent a bespoke information leaflet around six weeks prior to their first invitation. The content of this leaflet has been informed by focus groups and consultation exercises with women aged around 24 in Manchester and 19 in Aberdeen. The rationale will be to convert them from 'pre-contemplators' to 'contemplators' (based on the Transtheoretical model) by the time the standard NHSCSP invitation is received. This will deal with key themes and issues that emerged from the focus group and consultation work which has already been completed. Leaflets produced for use with the Aberdeen cohort will be sent to young women aged 19 years who are deciding whether to accept their invitation for cervical screening. They will have recently been offered HPV vaccination and the leaflet should be equally applicable to vaccinated women in England when they begin to receive their invitations 5 years from now.

In Manchester and Aberdeen the pre-leaflet will be sent to eligible women (i.e. those aged 24 and a half or 19 and a half) in randomised practices. This will be facilitated by the local screening agencies who maintain the population based register for the cervical screening programme and routinely have access to women's details.

The outcome of this intervention will be the proportions of women screened in the intervention and control practices measured primarily at 2-3 months, prior to the first reminder and secondarily at 12 month. These data will be provided by the local screening agencies who routinely monitor the screening uptake in the practices within the boundaries of the Primary Care Trusts for which they are responsible. The screening agency will create an anonymised record for each woman involved in the trial using a unique identifier.

3.3.2 Internet booking

Women in surgeries randomised to receive the internet booking intervention will receive a letter providing them with information on how to make an internet booking and a list of participating clinics. This information will be sent with their first invitation letter and with the first reminder letter from the screening agency, which is sent to women without a test recorded three months after their test due date. An online appointment scheduling system will be used (http://www.supersaas.com/), to which women will be directed from a webpage held on a University of Manchester server. A separate appointment schedule will be created for each clinic in the Palatine Contraception and Sexual Health Service, which will only show available appointments to users who are not logged in to the system. Women accessing the service will be asked to input only their name and a contact number, and will not be able to see appointments that have been booked by other users. An administrator account will be held for the system by the research team, who will forward on details of booked appointment to an administrator at the Palatine clinics using the NHS.net email system. Family Planning staff will be asked to indicate whether a woman who had booked online had attended and consented to screening. Women will be informed of who will be able to access the data held on the booking system when they access the system to book an appointment.

The number of women using the system and attending for cytology will be recorded. Local screening agencies will be asked to supply screening uptake data for all women in the trial on an individual level in both the control and intervention practices in order to ascertain the proportion of cytology that was obtained as a result of internet booking. The outcome of this intervention will be measured at 5 months post call, prior to the second reminder.

3.3.3 Human Papillomavirus (HPV) self sampling

Women in surgeries randomised to receive the HPV self sampling intervention will receive a letter describing the study in a second reminder letter from the screening agency, which will be sent to women without a test recorded six months after their test due date. The letter will explain the purpose of HPV self sampling, how the test is taken and the implications of the test results. Women will be given details of how to contact the trial office and request a self sampling kit by phone, text message or email.

A self sampling kit will be sent to women which comprises the following:

1. A self sampling kit.(either Delphi lavage or The Rovers® Evalyn-Brush)
2. Return sample packaging compliant with transport regulation UN3373 for Category B Biological Substances.

3. An information sheet explaining the purposes of the test, how the results will be conveyed to the woman and her General Practitioner, the implications of the results and instructions on both taking the vaginal sample and returning it to the Virology laboratory.
4. A consent form for processing the sample, reporting the results to the woman (giving her the option of not having correspondence to her home address) her GP and local screening agency and also seeking permission for the research team to check the Exeter screening database for subsequent cytology samples in the event of a positive result.

Women will return the sample to the Manchester Virology Laboratory using a postage paid UN3373 compliant overpack envelope. The sample will be processed and the result sent to the trial staff who will notify the woman, her GP and the screening agency of the result (unless the woman explicitly expresses a wish for her GP not to not be informed). Women who test HPV positive will be advised to attend for cytology screening and will be sent a results letter advising them of how to arrange a screening test with either their GP or local family planning service. GPs will also be advised of any management recommendations made to the woman. Any woman receiving a positive HPV result will also be given the contact details of the study nurse should they wish to discuss their result. Recording of HPV results on the NIHS Exeter database has not been possible to operationalise in the study time frame. Therefore, recall of HPV positive women for cytology will be the responsibility of the research team. In the event that women testing positive have not subsequently attended for cytology 12 months after the self-sampling intervention the research team will send a reminder to the woman. Women testing HPV negative will be reassured and will revert to routine recall.

The number of women both requesting and returning the HPV self sampling kits will be monitored directly by the trial office. Specific consent will be sought from the women to check for the presence of a cytology sample on the national screening database in the event of a HPV positive result, allowing the researchers to monitor compliance with management recommendations. Local screening agencies will be asked to supply anonymised screening uptake data for all women in the trial in both the control and intervention practices at an individual level in order to ascertain the proportion of cytology that was obtained as a result of women testing HPV positive by self sampling. The outcome of this intervention will be measured primarily at 12 months and secondarily at 30 months post call.

3.3.4 Nurse navigator (NN)

Women in surgeries randomised to receive the NN intervention will receive a letter describing the study together with a second reminder letter from the screening agency, which will be sent to women without a test recorded six months after their test due date. The letter will provide contact details and explain how the NN may be able to offer help and advice, and to allay any anxieties they might have regarding attending for a cervical screening test. Women will be encouraged to contact the NN via phone to speak to her directly during daytime hours, or to contact the trial office via phone, email or text messaging to request that the nurse navigator calls them at a convenient time. The NN will discuss the woman's perceived barrier(s) to accepting her invitation for cervical screening and assist the woman in booking an appointment if necessary. If the nurse deems internet booking or HPV self sampling to be appropriate to the woman's needs she would facilitate access to these interventions. Written consent for follow up will be sought by the nurse at the time of the woman making contact with her. Consent forms and an information sheet will be sent to the woman, with her permission, so she is able to provide written consent to her details being stored in the trial's database and used to check for the presence of a cytology sample on the national screening database, allowing the researchers to monitor compliance with screening after contact with the nurse navigator. Women would also be asked if they would like to receive a follow up call from the nurse navigator to discuss whether they had arranged/attended for screening.

The number of women contacting the NN will be monitored directly by the trial office. Local screening agencies will be asked to supply anonymised screening uptake data for all women in the trial on an individual level in both the control and intervention practices in order to ascertain the proportion of cytology that was obtained as a result of women contacting the nurse navigator. The outcome of this intervention will be measured primarily at 12 months and secondarily at 30 months post call.

Nurse Navigator (NN) Training

The following NN training programme is envisaged:

1) cervical cancer and HPV knowledge
2) logistics of HPV self sampling and cytology test procedure
3) implications of results of HPV, advice if –ve/ +ve
4) principles of motivational interviewing
5) structured interviewing skills
6) assessment of women's readiness for screening
7) approaches for women who are ambivalent towards attending for cervical screening (contemplation), or are ready to act (action)

Description of the role of the NN

The optimal means of contacting the nurse navigator, hours of access, interaction with practice nurses, are all issues which will be addressed during the piloting of the nurse navigator role along with other interventions during the first years of the project.

NN's would conduct a semi structured interview over the phone to identify barriers to screening and talk through suitable options for overcoming these:

- supportive contact with the woman by telephone
- improve women's understanding of the importance of cervical cancer screening
- offer HPV self testing if appropriate. The NN could also offer to review the HPV self testing instructions with the woman again over the phone once the woman has received the pack
- encourage the woman to become active (attend screening). For women who following discussion of barriers intend to attend screening, the NN could discuss the test procedure and provide information for the woman to arrange a screening appointment (internet appointment booking system).
- follow-up on test scheduling (reminder call: NN call the woman one day prior to their screening appointment.
- follow-up on results
- to provide reassurance
- address language needs e.g. link worker at GP

NN keep records of interactions with patients, including frequently asked questions.

To standardise the way that the NN's respond to women, a manual will be written containing the Standard Operating Procedure (including frequently asked questions) and patient educational materials.

3.3.5 Timed appointments

GPs will be asked to send women an invite letter detailing a time and date for them to attend for a cytology appointment. In this invite letter women will be given the option to rearrange for a more convenient time if needed. Local screening agencies will be asked to supply anonymised screening uptake data for all women in the trial on an individual level in both the control and intervention practices in order to ascertain the proportion of cytology that was obtained as a result of timed appointments. The outcome of this intervention will be measured primarily at 12 months and secondarily at 30 months post call.

3.4 Piloting of Planned Interventions

Each of the proposed interventions in phase 2 would be piloted in Manchester during the timeframe of phase 1. Women aged 25.5 to 27.5 years i.e. those women who have failed to attend for their first cervical screening despite reminders, will be targeted. We will use the methods proposed in phase 2 to contact women and to offer the interventions in the ways described. The purpose of these pilots is to evaluate the feasibility of the intervention e.g. arranging pre-booked appointments, the practicalities e.g. the arrangements for self testing, the accessibility of our proposals to these women, and most importantly the uptake of screening as a result. We aim to target 720 women and offer 120 each of the intervention options; i.e. i) nurse navigator, ii) offer of ordering a self-sampling, iii) unsolicited mailing of two different self sampling kits, iv) timed appointments, a choice of i) and ii), with 120 being offered no intervention. Interventions will be taken forward to phase 2 if the null hypothesis of a two-sample test of proportions comparing the uptake rate in the pilot interventions and the control is rejected at a one-tailed 25% significance level. In addition, the piloting phase will include a discrete choice experiment (DCE) on non-responding women identified by the screening agency who are not directly involved in the pilot study (see section 6). The piloting would involve 2-3 months of offering the interventions, 3-4 months of follow up including qualitative interviews and 2 months for analysis.

3.5 Proposed outcome measures

The primary outcome measure for all interventions is attendance for cervical screening which will be obtained from the Exeter Information System. This will be measured at 3 months post-call (prior to the first reminder letter), 12 months post-call and 30 months post-call (prior to the next recall). The primary endpoint for the pre-leaflet and online booking will be uptake at 3 months post-call. The primary outcome for the self-sample, the nurse navigator and timed appointment intervention will be uptake at 12 months post-call.

The main outcomes of the study are estimates of:

1. The uptake of cervical screening:
    a) In response to the pre-leaflet (phase 1).
    b) In response to the offer of each of the interventions (phase 2).
2. The uptake of internet booking (phase 1).
3. The differences between outcomes in Aberdeen between vaccinated and unvaccinated women.
4. The differences between Aberdeen and Manchester.
5. Cost-effectiveness of the interventions, individually and as packages of interventions.

3.6 Proposed sample size and design

Two interventions are intended to increase the response to the initial screening invitation; a pre-leaflet and online booking. These will be tested in a two factor factorial cluster randomised trial. Outcome will be attendance for a cervical screening test at 3 months, 12 months and 30 months after their 25th birthday. Adoption of a factorial design in which any one intervention is balanced for other interventions means the effect of any one intervention can be assessed independently of others provided there is no interaction on the scale of measurement.

Without a factorial design, to detect an interaction of the same magnitude, for example that the treatments are no better in combination as separately, would require an approximately fourfold increase in sample size. In phase I of this study the pre-leaflet and on-line booking are being tested in a factorial design, but only for the Manchester sample. There is unlikely to be a substantive interaction between these interventions, and so it would be difficult to justify the additional sample size required for this to be investigated. It will nevertheless be possible to check the robustness of the evaluation of the pre-leaflet intervention by comparison of effect in Manchester with that found in Salford & Trafford. In phase 2 of this study a factorial design was not chosen as we believe there is a possibility of interaction between the interventions being compared when used in combination.

Two interventions to improve response following non-attendance after 6 months will be tested, separately and in combination, with outcome being attendance at 12 months and 30 months post first call.

3.7 Randomisation methods

The screening uptake rate in the target age group, the uptake rate after a reminder and the screening uptake rate overall in the year prior to the study are likely to be strong predictors of the trial outcome measures. Data for the year prior to the trial will be extracted from the Exeter system to estimate these rates for each practice. These rates will then be used to balance the characteristics of treatment groups. To do this, the procedure described by Butler and Raab [11] will be adapted for the complex factorial design of this trial. Where practices have formed or merged the baseline uptake rates required for the minimization will be imputed using characteristics of the practice such as size and location or data from the constituent practices. A sample of allocations that give good balance between the 4 intervention factors will be identified using stochastic methods. An allocation will then be randomly selected from the sample of good allocations. This procedure will be stratified by PCT and carried out with the names and location of the practices concealed.

3.8 User Involvement

We have approached Jo's Cervical Cancer Trust (www.jostrust.org.uk) who take an active interest in cervical screening and are happy to support our proposed project. This project outline and a lay description of the project have been reviewed by young women who are members of the charity. Although the women who are members of Jo's Cervical Cancer Trust have all been affected by Cervical Cancer or Cervical Intraepithelial Neoplasia they are also women who may or may not have previously attended for cervical screening. Feedback from some of Jo's Cervical Cancer Trust's panel of women both endorsed the importance of research and our proposed strategies, including the new leaflet aimed at improving engagement with screening.

A project consultation questionnaire was also completed by 26 women, including a proportion of ethnic minorities, aged 20-25 at an inner city GP surgery in Manchester. Overall, the women were very supportive of the research. The majority of women surveyed agreed that each of the interventions would be an improvement. Views were sought from each woman regarding the proposed interventions, and the results support the interventions we are proposing. A large majority supported the idea of the pre-leaflet prior to the routine invitation. All had internet access, with half expressing a preference to book online and most of those believing it would be easier than phoning the GP. A large majority would be prepared to attend a family planning clinic for a cytology sample but half expressed a preference for their GP. Pre-booked appointments (PBA) evoked a positive response in a large majority and most of these women said that they would rearrange if the PBA was not convenient. Around 40% said they would prefer a self test for HPV and if positive would attend for a cytology sample. Finally, all of the women felt that nurse support would be beneficial, with phone contact being the most popular means of communication. This consultation with potential users makes us feel confident that different options suit different women and all of our options were viewed positively by at least a sizeable proportion of those consulted.

It is anticipated that members of Jo's Cervical Cancer trust and young women, including ethnic minorities, recruited locally will form a panel of user representatives who will advise the trial management group throughout the duration of the project. Their remit is likely to involve reviewing the patient information leaflets and letters used as part of the trial and retrospectively reviewing the advice given by the nurse navigator to ensure that this is not overly 'medicalised'. We would obtain translated versions as required for ethnic minorities. The logistics of running the panel will be decided by the women involved; Jo's Cervical Cancer Trust provides both face to face and internet based support , women may wish to offer advice to the investigators via email, however if they felt it was appropriate to have biannual or annual meetings the volunteers would be reimbursed for any travelling expenses they incurred. The panel would also be asked to elect a user representative to serve as a member of the Trial Steering Committee.

Women volunteering to serve as a member of the user representative panel will be provided with training by the trial team to provide them with the knowledge required to offer advice to the trial management group and review both the patient information and the nurse navigator's responses. It is likely that this will involve training on the purpose of cervical screening, the conduct of randomised controlled trials and an introduction to qualitative and quantitative research skills.

4. Selection and withdrawal of subjects

4.1 Planned inclusion criteria

Women aged 24 years and 6 months who are due to receive an invitation for cervical screening will be eligible to receive the pre-leaflet. Women living in Manchester PCT will be eligible for the internet booking intervention but not those from Salford, Trafford or Aberdeen. Women aged 25 years and 6 months in NW England (and 20 years and 6 months in Aberdeen) who do not have a test recorded on the Exeter system will be eligible for the nurse navigator, HPV self sampling and timed appointments interventions.

4.2 Planned exclusion criteria

Women who are not aged 25 and receiving their first invitation for screening will not be eligible for inclusion in the study. Of those women aged 25 and receiving their first invitation the following groups will be excluded:

- Women who are pregnant and have advised their GP (and consequently the screening agency) that they wish to defer their call until 3 months post delivery.
- Women who do not have a cervix and have been ceased on the screening system.
- Women who have informed their GP (and consequently the screening agency) that they have made an informed decision not to participate in this screening round.

4.3 Withdrawing participants

Should any participant that had consented to their personal details and screening attendance being recorded express a wish to withdraw at any stage of the trial, any information collected from them until that point would be retained in the trial database but no further follow up data would be collected. Retaining data will be important in the HPV self sampling cohort in order to maintain a record of the results of HPV testing. Participants will not be contacted further after they have withdrawn from the trial. Should any participant lose the ability to consent whilst the trial is ongoing, any screening attendance which has already been recorded will remain within the dataset, however further follow up data will not be collected.

5. Statistics

5.1 Sample size

5.1.1 Phase 1

Please note the following phase 1 power calculations are subsequent to the latest practice number information, for a priori calculations see earlier versions of the study protocol.

The pre-leaflet will be tested across Manchester, Salford and Trafford PCTs, which have respectively 100, 55 and 46 general practices (the total of general practices had altered by July 2013, the current totals are 97, 47 and 36 , [12] with an average practice size of 4,900 patients conservatively suggesting that approximately 40 women per GP practice would become eligible for the screening programme over a 12 month period. Data from Manchester PCT suggest that the initial response to the first invitation is fewer than 30%.

The power of a cluster randomised trial designed depends on the Intra-Cluster Correlation (ICC), the number of clusters, the cluster sizes and variation in cluster size. Jensen et al suggest an ICC for a similar outcome of 0.026.[13]

Pre-leaflet intervention: With 92 practices randomised to pre-leaflet (leaflet sent to around 4000 women) and 88 control practices, the trial will have a power of 89% to detect a 5% improvement of attendance assuming an ICC of 0.026 and an average cluster size of 40.

On-line booking intervention: The online booking intervention will be tested in Manchester PCT only. With 49 practices randomised to on-line booking and 48 to control, the trial will have a power of 93% to detect a 7.5% improvement in attendance by 3 months assuming an ICC of 0.026 and an average cluster size of 40. Given that the on-line booking intervention is introduced on a different occasion to the pre-leaflet we feel that any interaction between the two interventions is unlikely so that a factorial design is justified.

Phase 2 of this study is designed to improve uptake amongst women who have not attended at 6 months. Given that entry into phase 2 depends on the outcome of phase 1, any effect of the intervention in phase 2 will bias estimates of the long term effects of the interventions in phase 1. For example the interventions in phase 2 could, at least in theory, remove any effect of the phase 1 interventions. Whilst this could be addressed through statistical analysis we plan to have a larger control group for the phase 2 interventions. Of the 180 practices 111 will receive an intervention in phase 2 of the study whilst 69 will receive no further intervention.

The effect of online booking may be cumulative over the follow-up period as access to online booking would continue to be available. 63 Greater Manchester practices will receive no intervention. These will have a power of 94% to detect a 10% increase due to access to online booking.

A modified pre-leaflet will be tested in women who have been offered HPV vaccination as part of the catch-up component of the Scottish vaccination programme (Aberdeen Cohort). The primary outcome would be the absolute increase in screening uptake by 3, 12 and 30 months compared to control. Due to the potential adverse effect of vaccination on attendance a larger intervention effect is to be expected. With an ICC of 2.6%, 38 intervention and 39 control practices (leaflet sent to 1520 women) the trial will have a power >95% to detect a 10% increase in attendance.

Figure 1 Phase 1

		Pre-leaflet	Pre-leaflet Control	Total
Manchester	Online Booking	24	25	49
	Online Booking Control	24	24	48
Salford		26	21	47
Trafford		18	18	36
Total (NW)		92	88	180
Aberdeen		38	40	78

5.1.2 Phase 2

The standard first reminder may increase response by 5%. At 6 months (second reminder) we estimate that at least 50% will not have attended, that is a mean of 20 women per practice. In part 2 of the study the following 5 interventions will be test (i) self-test offered (ii) self-test sent,(iii) nurse navigator, (iv) choice between nurse navigator & self-test offered (v) timed appointments. Statistical analysis will compare each intervention as compared to control.

We might assume that a further 5% attend without further intervention by the time of next recall, and that a follow-up intervention increases uptake by an additional 5%. Amongst the 50% of women that we estimate will not have attended by 6 months this corresponds to a difference between 10% to 20%. A study with 30 practices in each of the five intervention arms (self-sample, nurse navigator, timed appointments, nurse navigator or self-sample) and 100 control practices would have a power of greater than 80% to detect this difference provided the ICC does not exceed 0.07. This calculation includes a

bonferroni correction of the significance level to allow for 5 comparisons with the control and an allowance for additional variation in cluster sizes due to the effect of stage/part 1 intervention. Self test kits will be sent by the trial centre. About 600 self test kits will be sent out. So that the acceptability of the two kit can be compared, women will be randomised to receive either kit types using randomisation stratified by site with a random block size of 4,6 or 8. In each study site the screening centre will assign kits in order according to a pre-prepared list.

Figure 2 Phase 2

	Pre Leaflet	Online Booking	Self Test Sent	Self Test Offered	Nurse Nav	Nurse Nav + Offered	Timed appointment	Control	Total
Manchester	Yes	Yes	3	4	3	4	2	8	24
	Yes	No	3	3	4	3	2	9	24
	No	Yes	4	3	3	3	3	9	25
	No	No	2	3	2	3	4	10	24
Salford &	Yes	-	6	5	6	6	5	16	44
Trafford	No	-	4	5	4	4	5	17	39
Aberdeen	Yes	-	4	5	6	3	5	15	38
	No	-	5	6	5	5	6	13	40
Total			31	34	33	31	32	97	258

5.1.3 Pilot study

The interventions in phase 2 are expected to increase attendance amongst those who have not attended for 10% to 20% (see above). In proof of concept studies a larger significance level and increased power is appropriate so that potential beneficial treatments are not rejected.[15] With 120 subjects in each arm, the study will have a power of 90% to reject the null hypothesis of no increase in uptake with a one-sided significance level of 25%.

5.2 Statistical analysis

A detailed statistical analysis plan will be prepared and agreed with the Trial Steering Committee (TSC) at the end of the pilot study. Due to the nature of the primary outcome we envisage complete data being available on all subjects in the trial regarding attendance, via the Exeter system.

Descriptive analysis will tabulate the rate of attendance and rate differences by intervention group. Formal inferential statistical analysis of cluster randomised trials needs to take account of the clustering of patients within practices.[16] This will be accomplished by fitting a logistic multilevel

model,[17] with covariates for treatment group, the uptake rate for each practices in the year prior to the study, and site (Manchester/Salford and Trafford/Aberdeen) with a random effect included for practice. Where new practices have formed or practices have merged, the baseline uptake rate will be imputed. Preliminary analyses will also include a site with treatment interaction to investigate possible differential effects of an intervention between Aberdeen and NW, important for understanding the implications of vaccination. A sub-group analysis of just the Aberdeen cohort will examine the effect of pre-study vaccination status on uptake and any interaction with the interventions. In stage 1 of the study the effect of a pre-leaflet and on-line booking on uptake are being tested within a factorial design in Manchester PCT. Whilst we do not envisage an interaction between the two analyses a sub-analysis in the Manchester cohort will test for an interaction between the interventions.

For the nurse-navigator intervention statistical analysis will be based on intention-to-treat (ITT). In addition the proportion contacting the nurse navigator and the proportions subsequently attending will be estimated. Similarly for on-line booking ITT will be used. Analysis will also estimate the proportion of women who use the on-line booking system and the proportion of those who subsequently attend.

Due to differences in the participants and context there may be differences in the intervention and the treatment effect between sites (England and Scotland). For example, the pre-leaflet intervention will differ between the Manchester/Salford/Trafford and Aberdeen sites due to the vaccination and younger age of the Aberdeen cohort. Data analysis for the pre-leaflet will therefore be carried out separately for each cohort. For other interventions (HPV self sampling, nurse navigator and timed appointments) that are being tested across sites, differences in the intervention will be not so great. For these a treatment-site interaction will be used to investigate site difference. The number of practices allocated to different interventions across the sites should ensure a demographic spread which will reduce the risk of confounding.

6. Economic Analysis and Organisational Impact Assessment

An economic analysis will be conducted alongside this project. The analysis has been designed as a "streamlined" study along similar lines to the statistical analysis, and will make extensive use of routine screening data. The economic analysis will have three components:

1) The costs of each intervention will be calculated. For the leaflet, this will include development costs and printing and distribution costs. For internet booking the costs will include programming and IT changes required to implement the system. For the specialist nurse navigator, the calculated costs will include all letters, telephone calls and publicity

material, and average time involved in providing advice and facilitating access, which will be obtained from a simple log maintained by navigators over sample periods.

2) Other health care costs related to the interventions will be calculated. These will include attendances at screening clinics, consultations, and screening-related tests and diagnostic procedures. These will also be captured using routine information sources as described above.
3) Cost-effectiveness will be calculated. This will take two forms: One, the incremental cost per percentage point increase in screening attendance within the study time-horizon will be estimated for each of the strategies being examined compared to standard practice. Second, lifetime cost-effectiveness and cost-utility will be estimated. Construction of a new lifetime model is not proposed, as several validated models already exist and have been used to produce published estimates of the cost-effectiveness of the current screening programme. Instead, we propose to combine the cost and attendance results of the study with these published estimates of the lifetime costs and effects of participating in cervical cancer screening programmes, to obtain lifetime cost-effectiveness and cost-utility estimates. Results will be presented within a probabilistic framework, using cost-effectiveness acceptability curves and net-benefit statistics.

This approach will provide reliable estimates of cost and cost-effectiveness while adhering to the general approach of the project, which maximises use of routine data sources and minimises the need for direct contact with women participating in the study. The health economist would also be involved in the design and analysis of a discrete choice experiment (DCE). In 2013/2014, a sample of approximately 2000 non-responders to screening will be identified by the screening agency. These women will be invited to state their preferences for different attributes of the possible interventions, in order to assist the selection and detailed design of interventions for the main trial phase. Non-responding women in Aberdeen will be included to measure the effect of HPV vaccination in women's preferences. It is not envisaged that the results of the DCE would be used directly in the final economic evaluation, although it will be possible to compare stated preferences with revealed preferences manifested in uptake rates, and may also be possible to give estimates of values placed on attributes other than clinical effectiveness, such as convenience, control and confidentiality.

6.1 Qualitative interviews (pilot phase)

6.1.1 Aims

1. To investigate the acceptability of three novel interventions designed to improve young women's receptivity to, and uptake of, cervical screening programmes.
2. To identify the attributes and their levels for the discrete choice experiment (DCE) exploring young women's preferences for cervical screening programmes.

6.1.2 Methods

This is a telephone interview based qualitative study with young women.

6.1.3 Participants and recruitment

A sub sample of 21 to 33 women who are taking part in the pilot study in Manchester (in phase 1) will be recruited to this qualitative component. In order to capture a diverse range of views, purposive sampling will ensure we include a mix of women who are offered the three novel interventions (nurse navigator, self-sampling, timed appointments). We will also attempt to interview a mix of white British and non-white British women, and interview women who have taken up the offer of the intervention and those who have declined. The final number of interviews will be determined when saturation is achieved. Our previous experience suggests this sample size will allow inclusion of participants with a breadth of experiences while retaining a depth to each interview. All the women who are invited to take part in the pilot study will also receive a participant information sheet and consent form for this qualitative component of the study (see Appendix 2). The details of the women who agree to take part in the pilot study *and* to be interviewed (name, allocated arm in pilot study, phone number and best times to telephone) will be forwarded from the lead researcher in Manchester to the qualitative researcher in York. This will be done using a nominated fax, with a telephone call to pre-warn of transmission. Alternatively, the women can send a reply slip with a FREEPOST envelope directly to the University of York.

The screening agency, in conjunction with the researchers in Manchester, will be able to identify women who do not respond to the invitation to participate in the pilot study. A different participant information sheet (see Appendix 3), consent form with attached reply slip and a FREEPOST envelope will be sent to these women from the screening agency, avoiding the need to pass patient identifiable data onto the research team. Women will be asked to return the reply slip and consent form directly to the qualitative researcher in York who will then be able to arrange an interview.

Women will then be telephoned by a researcher from York to conduct the interview. Before the interview starts the researcher will revisit the purpose and format of the interview with the participant, discuss any questions she may have, and reconfirm that she is happy to be interviewed, and for the interview to be recorded.

6.1.4 Data Collection

The telephone interviews will be semi-structured, with the use of a topic guide to ensure that the same general issues are discussed in each interview. However, there will be scope for participants to raise issues that are important to them and we will adopt an iterative approach where data collection and data analysis occur simultaneously. This will allow us to develop the topic guide to explore emerging

issues and to probe, and eventually confirm, the importance of different attributes of cervical screening programmes for the DCE. Whilst there are two sets of questions to meet the two aims of the interviews (see Appendix 4) these are not mutually exclusive. Women's views on a novel intervention may usefully inform the identification of the attributes for the DCE.

Both sets of initial questions are informed by existing literature on women's views of cervical screening programmes [18-21] and good practice for identifying attributes and levels for a discrete choice experiment [22].

Where consent is given, interviews will be digitally recorded. Where consent is not provided by the participant, the researcher will take detailed notes.

6.1.5 Data Analysis

The audio-recordings will be transcribed verbatim with all personal data anonymised to ensure confidentiality. The data will be analysed using the constant comparison method through thematic coding of the data [23]. Coding will take place using a combination of a prior themes and emergent themes. Negative cases will actively be sought throughout the analysis and emerging ideas and themes modified in response [24]. ATLAS-ti software will aid data handling.

6.2 Discrete choice experiment (DCE)

6.2.1 Aims

To investigate the value non-responding women place on cervical screening and the three novel interventions designed to improve young women's uptake at first invitation.

6.2.2 Methods

This is a postal/online survey questionnaire DCE. The DCE questionnaire will comprise a section on women's general views about the value of the current cervical screening programme and a second section containing a number of choice scenarios which incorporate the attributes and levels developed from the qualitative data collected for the three novel interventions. The questionnaire will also include questions on basic demographic information such as age, education and employment status. Women will also be asked about any difficulties encountered when completing the DCE questionnaire.

6.2.3 Participants and recruitment

A sample of 2000 Manchester non-responders to cervical screening invitation separate to those invited into pilot interventions or into phase I will be recruited for the DCE. This figure is informed by work conducted by the ISPOR Conjoint Analysis Experimental Design Task Force in which simulation studies were used to explore the impact of alternative sample sizes on the precision of

parameter estimates. [Reed et al (2012) Constructing Experimental Designs for Discrete-Choice Experiments: Report of Value in Health. In press]. The screening agency, in conjunction with the researchers in Manchester, will identify non-responding women who are eligible to participate in the DCE study. Women will be sent a participant information sheet the paper-based version of the DCE and a FREEPOST envelope by the screening agency. As women will have the choice of whether to complete the paper-based version or to complete the DCE online (see section 6.24) the weblink for the online version will be provided in the patient information sheet. The paper-based DCE will be returned to York in the freepost envelope.

6.2.4 Data collection

Participants will be given the option of completing a paper-based DCE survey or an online version. The online version will be hosted by the University of Oxford and monitored by the trial team in Oxford. The web version will comply with the required information governance standards of the University of Manchester.

6.2.5 Data Analysis

A sample of 2000 non-responding women will be included in the DCE survey. A sample size of 2000 will provide a precision of 0.25-0.75 in the standard errors of the model coefficients, and will allow the evaluation of setting sub-group (e.g. the impact of HPV vaccination on preferences). Several categorical dependent models will be evaluated, including multinomial logit / probit and conditional logit models, to obtain women's valuations and preferences.

6.3 Timeline

February/early March: secure ethics approval (substantial amendment)
Mid July to end September (10 weeks): Interviews and simultaneous data analysis
Mid September 2013 to mid October 2013: Design and pilot DCE questionnaire
Mid November 2013 to mid December 2013: secure ethics approval (substantial amendment)
Mid January 2014 to mid March 2014 (depending on response rate): Run DCE
March 2014 June 2014: DCE analysis

7. Direct access to source data/documents

The investigators will permit trial related monitoring, audits and regulatory inspections, providing direct access to source documents as and when required.

8. Ethics

8.1 Ethical arrangements

For phase 1 of the study we would seek to avoid the need for individual signed consent which would be impracticable for a study of this kind. Women would receive the pre-leaflet in addition to routine mailings from the Cervical Screening Programme, and would not be contacted directly by the researchers. No identifiable data will be passed from the screening agencies to the research team, and women will still receive the routine NHSCSP information which allows them to make an informed choice about attending for screening. Women receiving the pre-leaflet as part of the study will receive additional information which is designed to be more relevant to women attending for their first cervical screen. The outcome measure for this phase would be the rates of screening in practices randomised to their women receiving the information sheet compared to those who receive only the standard mailings, and therefore no patient details are required by the research team. Seeking individual consent to send the information sheet would require women to send their personal details to the research team when they are not necessarily being sought. Such a process of signing consent forms may also have the unintentional effect of deterring women from attending cervical screening. In order to monitor the number of women using the online booking service, clinic staff would be asked to provide the date of birth, GP and whether the woman attended the booked appointment for each booking made on the online system. The date of birth will be used to calculate how many months post invitation each woman was, whilst their GP practice details will allow the researchers to determine what proportion of women at each practice accepted the offer of online booking. Women will be informed that this information will be passed onto the research team at the time of booking the appointment. No identifiable data will be held on the trial database without explicit consent. Women will be offered the chance to make an online booking in the screening invitation letter they receive from the call/recall agency, and again the research team will not be given any personal identifiable data by the screening agency.

In phase 2, the only interventions whereby the woman would be required to donate time or undertake any action for no benefit is the discrete choice experiment, for which we would obtain informed consent. We would not seek personal details, such as a mobile phone number, without informed consent. Women in surgeries randomised to receive the offer of the nurse navigator or HPV self-sampling would be asked, via a reminder letter from the screening agency, to contact the research team to request the intervention. Women would then be able to be sent individual consent forms to give their consent for the research team to store their details for the purposes of checking the Exeter screening database to see whether they attend for screening as a result of the intervention. For the timed appointments, participating general practices would be asked to provide the same information as the clinics participating in online booking so the research team can identify how many women from each practice attended as a result of the intervention.

At no point will the research team be contacting the women directly, as the details of the women eligible for participation will be known only to the screening agencies. If women do not wish to accept the offer of the intervention they are free to do so and will not be sent any further trial related communications from the screening agency. As proportions of women attending for screening in each practice can be obtained from routine statistics, the research team do not require any personal details on the individuals unless they are required to enable the woman to participate in the intervention i.e. if they wish the nurse navigator to contact them, or they wish to be sent a HPV self-sampling test. As part of the pilot we would wish to send a small number of women (around 120) a HPV self-sampling test unsolicited to see what response rate is obtained. This would be facilitated by the screening agencies and women receiving the kit would be under no obligation to return it. The results of this exercise would be used to determine the most acceptable method of offering the intervention to women during phase 2 of the study.

8.2 Trial governance

The TSC met on 19:01:2012 and signed off the protocol; and will then convene at necessary time points during the trial to review progress, agree the taking forward of piloted interventions into phase 2, and advise the Trial Management Group when difficulties arise. The DMC would review the statistical plan, approve it and receive data at intervals specified by them. Independent members for the TSC include Professor Usha Menon (Professor of Gynaecological Oncology, UCL), Mr Patrick Walker (Consultant Gynaecologist, Royal Free), Robert Music (Director of Jo's Cervical Cancer Trust) and Dr Wendi Qian (Statistician, MRC).

9. Data handling and record keeping

9.1 Data management

The data management requirement for this project will largely involve processing and interpreting routine screening data. Screening agencies will be asked to supply anonymised data on an individual level for all women in the trial who have been screened each month in the control and intervention practices, along with the initial date of the women's invitations. A record will be maintained for each practice showing the number of women screened each month and the number of months post call each woman was when she attended for screening. This record will detail the date of the pre-notification list (PNL) for cervical screening, date of invitation, date of reminder letter, test due date, GP, date of the intervention, date of screening test, test result, venue sample obtained in (GP or family planning clinic), date woman changed GP and new GP details (where applicable).

The trial team will create a record for each woman who consents to having her data stored and cytology samples traced on the Exeter system as part of the phase 2 interventions. This record will detail the date of call, the woman's personal details and GP, the date of the intervention, the result of

the intervention i.e. a positive or negative HPV result or agreed to attend for screening after speaking to the nurse, and the date (and number of months post call) any subsequent cytology was taken. The trial team will collect data (as described in 6.1) in order to calculate the costs of delivering the interventions. Data will be stored securely on a University of Manchester or Central Manchester University Hospitals NHS Foundation Trust network drive and the PC will be password protected, in line with university data protection policy. Patient-identifiable information will be stored in a separate secure network location and linked to non-patient identifiable data by a unique identifier wherever possible. Access to patient-identifiable data will be strictly restricted to the trial team. A copy of the data will be burned onto a CD each month and stored in a fire proof safe within the department, and a second CD at another site.

10. Financial and Insurance Matters

The project is sponsored by the University of Manchester and funded by the NHS NIHR Health Technology Assessment Programme (Ref 09/164/01).

11. Publication Policy

The final results of the trial will be published as a monograph in the HTA journal series and will also be published in high impact, peer-reviewed journals.

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Appendix 1 Co-applicants and collaborators

Coapplicants:

- Henry Kitchener would be the Principal Investigator. He has considerable experience in leading clinical trials to a successful conclusion and a lot of expertise in the field of cervical screening. He led the ARTISTIC and MAVARIC trials, both funded by the NIHR HTA, to a successful completion and publication within time and on budget. He is adept at managing a multidisciplinary group of researchers and ensuring compliance with research governance.
- Margaret Cruickshank, Senior Lecturer in Obstetrics and Gynaecology, has considerable research experience and leadership role in cervical screening. She was chief investigator of the MRC TOMBOLA trial of low grade cytology.
- Chris Roberts, Reader in Biostatistics, would be the trial statistician. He is experienced in large clinical trials and has expertise in design and analysis of cervical screening trials including ARTISTIC.
- Loretta Brabin, Reader in Women's Health, is an experienced investigator in the field of reproductive health. She has published extensively in the field of HPV vaccination particularly in relation to uptake. She is leading focus group work and development of the pre first invitation leaflet.
- Alastair Gray would lead the health economic component of the research and its analysis. He has also had a lot of experience in the field of cervical screening, including large randomised controlled trials.
- David Torgerson is Director of the York Trials Unit – an accredited trials unit with a large portfolio of past and current trials. He has expertise not only in Health Economics but also in cluster randomised trials and has published widely on trial methodology.
- Joy Adamson is Deputy Director of the York Trials Unit. She has expertise in trials, epidemiology and mixed methods health services research covering a wide range of topics. She would be responsible for the day-to-day supervision of the York based researcher and trial secretary.
- Aneez Esmail is a Professor of General Practice and has research experience of working with ethnic minorities. He is our primary care advisor and will collaborate with us in piloting our interventions in the Robert Darbishire Practice, which has a lot of young people and ethnic minorities.
- Alex Sargent is a clinical scientist who runs the routine HPV testing service in the Manchester Virology laboratory. She was involved in the ARTISTIC trial.
- Dr Emma Crosbie is a NIHR Clinical Lecturer in Gynaecological Oncology at the University of Manchester. She will be providing clinical support to the Principal Investigator.

Collaborators:

- Mina Desai is a consultant cytopathologist, who directs the Manchester Cytology Centre. She also has experience of working with ethnic minorities, with regard to self testing.
- Julian Hannah, Consultant in Public Health, chairs the Salford and Trafford cervical screening steering group and has an in depth knowledge of the process of cervical screening from an organisational point of view.