Protocol

Screening women for abdominal aortic aneurysm

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Scientific abstract

A one-off ultrasound screening of men at age 65 for abdominal aortic aneurysm (AAA) and subsequent recall of individuals with identified AAA has been shown to reduce AAA-related mortality and to be cost-effective for the NHS. Whether this extends to women is unknown, so at present the national AAA screening programme in the UK is restricted to men. However, 34% of deaths from AAA are now in women, and this proportion is likely to increase in the future. In this project, we will evaluate the effectiveness and cost-effectiveness of AAA screening in women.

This will involve:
(a) Adapting a previously validated long-term cost-effectiveness model of AAA screening in men as a more flexible individual simulation model;
(b) Obtaining relevant input parameters for women from the literature and/or other data sources;
(c) Running the model for women, to estimate AAA-related mortality, all-cause mortality, life-expectancy, costs, and cost-effectiveness in terms of cost per life-year gained, and per quality adjusted life-year (QALY) gained, over both short-term and lifetime horizons.

It is recognised that some input parameters will be very uncertain or even unknown for women (in which case parameters for men may initially have to be used). A key component of the research will therefore be to evaluate the uncertainty in conclusions by both probabilistic and deterministic sensitivity analyses. Where unknown parameters are likely to have a major influence on conclusions, the expected value of information (EVI) related to them will be assessed.

Aortic diameters are typically smaller in women than men, life-expectancy is greater, and AAA rupture rates are about four times higher for a given AAA diameter. So in addition it is proposed to evaluate some possible departures from the design of the AAA screening programme in men. These include the definition of an AAA (for example an aortic diameter of at least 2.5 cm in women as opposed to the conventional definition of at least 3.0 cm), age at screening (for example age 70 years for women rather 65 years for men), and the AAA diameter threshold for consideration for surgery (for example 5.0 cm for women rather than the conventional 5.5 cm). Within these options we will also consider the choice of surveillance intervals for AAAs in women below the surgical threshold. Another issue to be addressed is whether there are subgroups of women (for example current and ex-smokers, or sisters of men with an AAA) at whom such screening should be targeted.

Although this project has a UK focus, its results will have implications for the development of AAA screening programmes internationally, as is evident for example from the recent recommendations on AAA screening from the US Preventive Services Task Force.

Lay summary

Abdominal aortic aneurysms (AAAs) are bulges in the main vessel carrying blood from the heart to the lower body. They occur predominantly in older people, more frequently in men than women and in those who have ever smoked than never-smokers. AAAs increase in size over time, and can eventually rupture. The mortality rate following rupture is about 80%. So what can be done to prevent this from happening? An AAA is

easy to detect by a simple ultrasound scan, taking less than 5 minutes to perform. If an AAA is detected, its size can be monitored over time by repeat scans. If it has grown to a large size (5.5 cm in diameter or more), surgery is usually recommended. Either open surgery or a key-hole technique (endovascular surgery) can be used to repair the aneurysm.

Such ultrasound screening of men for AAA at age 65 has been shown to reduce mortality and to be cost-effective for the NHS. Whether this extends to women is unknown, so at present the national AAA screening programme in the UK is restricted to men. In this project, we will evaluate whether screening women for AAA could save lives and provide value for money to the NHS.

The research team includes specialists in vascular surgery, AAA epidemiology, medical statistics and health economics, from the Universities of Cambridge, Leicester, Brunel and Imperial College. The team will identify published studies and unpublished data that provide information about AAAs in women, and adapt a long-term model of AAA screening, previously developed for use in men, to evaluate AAA screening in women. One main challenge will be to identify relevant and reliable information that applies to women alone. Another will be to investigate what possible changes there should be to the way AAA screening, surveillance and intervention are undertaken for women, as compared to the existing national screening programme in men – for example in terms of the age at screening and the AAA diameter threshold for consideration of surgery.

The outputs from this research will have an immediate impact, either on national policy or on what additional studies are required. If it is clear that AAA screening in women is likely to both effective and cost-effective, this will be a major impetus to launch a national screening programme for women. The research will also provide information on how such a screening programme should be designed. If the conclusion about AAA screening in women is unclear, because some of the necessary information in women is either lacking or very uncertain, this research will point to what future studies are required in order to provide a more definitive answer.

BACKGROUND AND RATIONALE

What is the problem being addressed?

The prevalence of AAA in women aged 65 or 70 may be around 0.5% (Derubertis et al, 2007; Svensjö et al, 2013; Li et al, 2013). Moreover it is known that women have an AAA rupture rate about four-fold that in men for a given AAA diameter (Sweeting et al, 2012), although their AAA growth rates are similar (RESCAN, 2013). Women may also have worse outcomes after AAA surgery than men (Egorova et al, 2011; Lo et al, 2013), for example because of their typically shorter aneurysm necks (IMPROVE, submitted). A higher proportion of women are turned down for both elective and emergency surgery (Karthikesalingam et al, 2011). Some of these differences between women and men would likely favour the outcome of systematic AAA screening in women, whereas others would not. So the effectiveness and cost-effectiveness of AAA screening in older women needs formal assessment.

There are a number of reasons why the design of an optimal AAA screening programme for women might differ from that currently adopted for men. The prevalence of AAA increases with age, and women have a greater life-expectancy than men. So screening

women at age 70 might be more beneficial than at age 65. Women typically have smaller aortic diameters than men (Rogers et al, 2013), as a result of body size, and the aortic diameter defining an aneurysm could be lowered from the conventional 3.0 cm. Because of their higher AAA rupture rates, a diameter threshold for considering elective surgery lower than the usual 5.5 cm may be better in women. Again these suggestions need formal evaluation.

Why is the research important in terms of improving the health of the public and/or to patients and the NHS?

The UK national AAA screening programme for men aged 65 (NAAASP, 2014) was launched on the basis of the results of four randomised trials of AAA ultrasound screening that almost exclusively recruited men (Cosford, 2007). These trials showed that AAA-related mortality could be halved by offering AAA screening along with appropriate clinical follow-up that included elective surgery when an AAA reached a threshold size. Long-term modelling based on the largest of these trials, the Multicentre Aneurysm Screening Study (MASS Group, 2002), showed that AAA screening in men aged 65 was extremely cost-effective with an estimated cost of £3000 per quality adjusted life-year (QALY) gained (Kim et al, 2007).

This cost-effectiveness estimate has come under scrutiny recently, because initial data from the NAAASP showed an AAA prevalence in men aged 65 of 1.5% rather than 4.9% observed in the MASS trial. When the long-term model was revised to reflect this lower prevalence, as well as the attendance rates observed in NAAASP and updated cost estimates, this increased the cost per QALY. Nevertheless the NAAASP was still estimated to be highly cost-effective, at £7400 per QALY gained (Glover et al, 2014). Indeed, provided the AAA prevalence was above 0.35%, it was estimated that screening would be cost-effective at a willingness-to-pay of £20,000 per QALY. The prevalence of AAA in women aged 65 or 70 is around 0.5%, so it is now clear that the cost-effectiveness of AAA screening in women needs to be formally assessed.

We make three additional observations here. First, the substantial decrease in deaths from AAA observed in UK men during this century has not been matched in women. One third of all deaths due to AAA now occur in women. Second, aortic diameter is a prognostic indicator for cardiovascular risk and referral of those women with aneurysms for a simple cardiovascular health check (as for men in the national screening programme) may have benefits beyond the simple detection of an aneurysm. Third, the development of a more sophisticated and flexible model for estimating the long-term cost-effectiveness of AAA screening will allow the evaluation of possible modifications to the AAA screening programme design currently being used nationally for men, which could lead to improvements in its clinical or cost-effectiveness.

Why is this research needed now?

The UK currently screens men aged 65 for AAA, but not women. Until recently, the prevalence of AAA in women has been substantially lower than that for men. However, women now account for 34% of all deaths due to ruptured AAA (ONS, 2014). AAA ruptures are fatal in about 80% of cases, and women with a small AAA have been found to have a four-fold higher risk of rupture than men. Moreover, in younger age groups the prevalence of smoking is higher in women than men, so that in the future AAAs are likely to become even more frequent in women.

So research is now needed to assess the cost-effectiveness of screening women for AAA. Only one published study has attempted to address this question (Wanhainen et al, 2006); this was based on a prevalence of AAA in women of 1.1% and suggested that screening may be cost effective at US$6000 per life-year gained. However, more data are now available to inform such modelling, and a more sophisticated and realistic model can be used that would produce more reliable and convincing conclusions. We will also be able to use the recent literature review undertaken by the US Preventive Services Task Force (USPSTF, 2014); one of their conclusions was that high-quality modelling studies need to be done to determine whether AAA screening is beneficial in women. We may also be able to derive useful information from the recent NIHR HTA project to personalize recommendations for elective AAA surgery according to age, sex and other risk factors (McCollum et al, HTA report under revision; Grant et al, 2013).

If we show that screening women is convincingly cost-effective, this has immediate policy relevance, both in the UK and internationally. If the conclusion is in doubt due to lack of relevant information in women, this will provide impetus to undertake new relevant studies to help resolve the uncertainties.

Aims and objectives

The overall aim is to estimate the clinical and cost-effectiveness of systematic population-based AAA screening for women. Offering ultrasound screening for AAA to women will be compared to a policy of no systematic screening. Outcomes will be in terms of AAA-related mortality, all-cause mortality, life-expectancy, elective AAA operations, emergency AAA operations, costs, and cost-effectiveness. Cost-effectiveness will be expressed as cost per life year gained and, using age-adjusted quality of life norms, cost per quality adjusted life-year (QALY) gained.

The specific objectives are:
1. To set up and run a PPI group of women to inform the project and help disseminate its outputs.
2. To adapt a previously validated multi-state model of AAA screening in men as a more flexible individual simulation model.
3. To obtain information from the published literature, where possible, on input parameters for this model relevant to women rather than men.
4. To seek other information or data sources on input parameters for women which are not available in the published literature.
5. To run the adapted model for women to estimate both short-term and lifetime cost-effectiveness.
6. To assess the impact of parameter uncertainty on the conclusions using probabilistic and deterministic sensitivity analyses.
7. For influential parameters, which are unknown or very uncertain for women, to estimate the expected value of obtaining information (EVI) on them to reduce the uncertainty of the conclusions.
8. To assess modifications of the AAA screening programme used for men that may be more appropriate and cost-effective for women.
9. To compare population-based AAA screening of women with targeted screening of at-risk groups, in terms of overall life-years gained and costs.

RESEARCH PLAN

The main challenge to this research is that information specifically for women on AAA prevalence, growth, rupture, quality of life, and elective and emergency surgical mortality may be limited. Most previous AAA research has either been conducted in men alone (such as the MASS trial), or the results predominantly reflect those in men as they formed the great majority of subjects studied. For example, in randomised trials of endovascular versus open repair, more than 75% of the patients recruited are men, for both elective repair (EVAR, 2012) and emergency repair (IMPROVE, 2014). In contrast, information on AAA growth rates and rupture rates, available separately in women and men, has recently been collated and published (Thompson et al, 2013). Thus a major component of the work will be to extract estimates applicable to women from the published literature or other sources.

The work can be based on adapting a previously developed long-term cost-effectiveness model of AAA screening for men (Kim et al, 2007). However, since the design of an optimal AAA screening programme for women may require some quite substantial modifications compared to that adopted for men, it will be necessary first to translate the existing model into the more flexible format of an individual simulation model. This will enable relevant potential modifications (regarding age at screening, surgical threshold and surveillance intervals), as well as EVI, to be more easily and efficiently assessed.

We will reflect the procedures used in NAAASP in terms of the measurement of aortic diameters. In this regard, we will consider aortic diameters measured at screening or surveillance as inner-to-inner (ITI) by ultrasound, and measurements taken in hospitals during consideration for surgery taken by CT scan.

Here we address each of the stated objectives in turn.

1. To set up and run a PPI group of women to inform the project and help disseminate its outputs.

We will establish a female PPI group to provide project-specific input and to help direct the dissemination of the outputs from this research project. Currently there are no aneurysm related projects in the NIHR INVOLVE database (www.invo.org.uk) and we will therefore maximize the long-term utility of the work performed here by ensuring the project-specific PPI activities become a generic future resource for research in this field. Therefore, in order to maximize both the speed at which we develop this resource and the reach of the resource, we will use conventional PPI approaches and also engage PPI groups via social media and the internet.

The NIHR Leicester Cardiovascular Biomedical Research Unit (BRU) has significant experience of using electronic media to promote PPI activities (SCAD, 2014) and we will adopt similar approaches for this project. At the centre of our PPI activities will be a website hosted on the NIHR Hub (NIHR Hub, 2014) with public-facing pages acting as the primary public project identifier. We will link this website to online events and fora utilizing 'Hangouts' and 'Groups'. We will also use media portals such as Twitter, LinkedIn and Facebook to advertise the website presence, as well as conventional media approaches to PPI to ensure that no demographic groups are disadvantaged.

Initial PPI group development will be performed by inviting female patients with AAA (pre- or post-operatively) in the Leicester Vascular Unit to a publicity event for the project. We will also invite the current Leicester BRU PPI group members to attend this meeting. We have experience using this approach and a previous event for male patients was over-subscribed (Leicester Mercury, 2014]. We will invite those women attending the meeting to register interest in joining the project PPI committee. Due to the older age of women affected by AAA we will also invite younger relatives of patients to join the committee. This committee will form the traditional PPI group for the project. We envisage that some members of the committee will participate in the online PPI activities, as skills or experience permit.

We will use our electronic resources to encourage PPI participation across a wide geographical area and form a virtual PPI group. We will advertise the project via patient groups, charities and the wider screening network. We will present project information to the virtual PPI group electronically for comments and review. As specific items arise over the duration of the project, we will obtain opinions from the virtual group, feed these back to the physical PPI committee at quarterly project meetings for further comment, and then provide onward feedback at the project management meetings.

We plan to use the PPI groups to respond reactively to PPI relevant project questions as they arise but also see that there will be the following specific times when input will be required:

1) Initial phase (months 1 to 6): Determination of patient priorities for project outputs.
2) Intermediate phase (months 7 to 12): Review of patient attitudes to screening, barriers to attendance, willingness to attend.
3) Final phase (months 13 to 20): Review of preliminary project outputs, dissemination and discussion of project results, and prioritization of future research areas.

2. To adapt a previously validated multi-state model of AAA screening in men as a more flexible individual simulation model.

The starting point will be the multi-state model structure (Figure 1) originally published in 2007 (Kim et al, 2007). In the figure, the ovals represent different possible states, the rectangles different events, and the arrows transitions between them. In its first form, the model's parameters were derived from the individual patient data for men in the MASS trial (MASS, 2002). Estimates of cost-effectiveness were later updated on the basis of more extensive follow-up data in the MASS trial (Thompson et al, 2009), and subsequently to reflect the parameters such as AAA prevalence and attendance rates being observed in NAAASP (Glover et al, 2014). This later work also updated unit costs to reflect current practice (2010/11 prices), and the increased use of endovascular (EVAR) rather than open repair for elective operations. The model was also adapted to study the cost-effectiveness of alternative surveillance strategies (Thompson et al, 2013).

This model was implemented in EXCEL, using 3-month cycles. For the purpose of this project where a range of different states and parameters need to be explored, it will be desirable to implement this model as an individual simulation model (ISM) in more flexible software. For this we will use the publicly available software R (R Core Team, 2011). For example, we will run the model for a synthetic population of 1,000,000 people, each invited to screening or not, to provide estimates of incremental costs and effects averaged over that population. In general, ISMs provide greater flexibility than aggregate

approaches like Markov Models and enable more accurate modeling when patients can be subject to a complex sequence of decisions and events. One immediate advantage of an ISM is that it will be easier to represent the heterogeneity in AAA growth rates between people (RESCAN, 2013), rather than having to make the transition rates time-dependent in a multi-state model; the latter was previously necessary to provide a sufficiently realistic model of the clinical situation (Thompson et al, 2013). To validate the re-programming of the model we will check that, given the same inputs, it provides virtually the same estimates of effects and costs as the original model implemented in EXCEL. We will also validate it against the 13-year MASS trial follow-up data now available (Thompson et al, 2012). The ISM will be designed to have a front-end that enables straight-forward modifications to be investigated, for example to undertake sensitivity analyses for parameter values or to address "what if" questions about the possible changes to the design of the screening programme.

We will start with the same definitions of an aneurysm (aortic diameter of at least 3.0 cm), age at screening (65 years), threshold for consideration for surgery ('large' aneurysms of at least 5.5 cm), and surveillance intervals (yearly for 'small' aneurysms 3.0-4.4 cm in diameter, and three-monthly for 'medium' aneurysms 4.5-5.4 cm in diameter). Modified definitions that may be better for women will be explored later in the project.

3. To obtain information from the published literature, where possible, on input parameters for this model relevant to women rather than men.

The input parameters needed for the model are implicit in Figure 1, being the transition rates or probabilities corresponding to each of the arrows. The values of almost all of them will need to be changed to evaluate AAA screening in women (see examples in Table 1). For some parameters, information for women from systematic reviews or UK national statistics is readily available to us. These include AAA growth and rupture rates for small and medium AAAs from the RESCAN project (RESCAN, 2013), and the age-dependent competing (non-AAA) mortality from ONS statistics (ONS, 2014). We will also directly use the unit costs estimates (uplifted by inflation to 2014/15 prices) that were derived in costing the NAAASP programme in men in 2010/11 prices (Glover et al, 2014). The assumption here is that the unit costs of invitation, screening, surveillance, and surgery are the same in women and men (e.g. about £20,000 for emergency surgery, and £13,000 for elective surgery). This assumption, for example in terms of length of hospital stay after surgery, will be checked where possible.

For other parameters, information for women, often from outside the UK, will be available in published papers. These include the prevalence of AAA in women in Sweden (Svensjö et al, 2013) and operative mortality rates after rupture (De Rango et al, 2013; IMPROVE, 2014). The most recent systematic review of mortality following elective surgery was published in 2010 (Grootenboer et al, 2010) and will require updating to provide further evidence for endovascular repair. New systematic reviews to assess the proportion of women suitable for endovascular repair, with currently available endografts, and on the incidental detection rate of AAA in women may also be necessary.

The searching strategy will be implemented according to the advice received from the Cochrane Review Groups for Peripheral Vascular Diseases for the RESCAN Collaboration (Thompson et al, 2013). It is proposed to search Medline, Web of Science, EMBASE on OvidSP, Cochrane Register of Controlled Trials, ClinicalTrials.gov, and

controlled-trials.com. Ideally both estimates of parameters and their statistical uncertainty will be extracted. Where multiple studies provide information, meta-analyses of parameter estimates will be undertaken or alternative estimates will be used as the basis of deterministic sensitivity analyses.

4. To seek other information or data sources on input parameters for women which are not available in the published literature.

For some parameters, there may be little or no information published specifically for women. For example, we anticipate that this will apply to the proportion of elective and emergency AAA operations which are by EVAR rather than open repair (a key issue for costs, and maybe effects), as well as long-term mortality after repair. Here we will search out data sources that can provide relevant estimates, for example the Vascunet database and the National Vascular Registry (for both of which agreement has already been obtained), or Hospital Episode Statistics (HES) – see Table 1. Also we will request additional information specifically for women, for example on length of hospital stay, from published studies, such as the EVAR and IMPROVE trials (EVAR, 2012; IMPROVE, 2014). Since co-applicant JTP is coordinating the individual patient meta-analyses from the trials of endovascular versus open repair for both intact and ruptured AAA, additional information for women will be available by April 2015. Minimal information is available for the proportion of women turned down for elective repair, although this is likely to be higher in women than men (Karthikesalingam et al, 2011), and will require supplementation from local audit data in Leicester and London.

If no information at all can be obtained for certain parameters for women (for example this may be the case for how prevalence varies by ethnicity, drop-out rates from follow-up, and opportunistic detection rates), we will first use estimates for men. Then we will employ deterministic sensitivity analyses to explore the influence of alternative values on the final outcomes.

5. To run the adapted model for women to estimate both short-term and lifetime cost-effectiveness.

We will first provide cost-effectiveness estimates for women using the same screening design used in NAAASP. Given new values of the input parameters, it is a relatively simple task to re-run the model to obtain estimates of AAA-related mortality, all-cause mortality, surgical workload (both elective and emergency operations), life-expectancy, and costs. In addition, by using age-related population norms for quality of life (Kind et al, 1999), we can also estimate quality adjusted life-expectancy. It will be informative to look at the incremental effects and costs over both shorter timescales and the lifetime. Since the majority of the costs are incurred early on, while the benefits accrue later, cost-effectiveness is anticipated to improve markedly when viewed over longer time horizons (Kim et al, 2007). The principal results will be reported as incremental cost-effectiveness ratios (ICERs) of cost per life-year gained, and cost per QALY gained.

6. To assess the impact of parameter uncertainty on the conclusions using probabilistic and deterministic sensitivity analyses.

Many of the parameter estimates will have uncertainty intervals which can be used in a probabilistic sensitivity analysis, thus providing an uncertainty interval for the estimated ICERs. These results will also be displayed as cost-effectiveness acceptability curves

(CEACs), which show the probability that AAA screening for women is cost-effective as a function of the willingness-to-pay per life-year or per QALY. Techniques to reduce the computational requirements for an individual simulation model when taking into account parameter uncertainty have been described (O'Hagan et al, 2007).

Some parameters may be based on little or no direct information in women. To address this, deterministic sensitivity analyses will be used, exploring the impact of different choices of these parameters on the incremental costs, effects and ICERs. Tornado plots (Epstein et al, 2014) will be used to assess the relative importance of the uncertainty in different parameters in driving the overall conclusion on cost-effectiveness.

7. For influential parameters, which are unknown or very uncertain for women, to estimate the expected value of obtaining information (EVI) on them to reduce the uncertainty of the conclusions.

An important question is whether the lack of information on some parameters in women makes it impossible to draw a reliable conclusion about the cost-effectiveness of screening women for AAA. If this is the case, then the next priority is to provide better information on these parameters, from appropriately targeted research studies, rather than trying to decide now whether or not to implement a national AAA screening policy for women. We will employ the methodology of expected value of information (EVI) to trade off the cost of such research, against the anticipated loss of making an early but incorrect decision about implementing AAA screening for women (Tappenden et al, 2004). Ensuring efficient computation will be important for an individual simulation model as here, and approximate techniques to reduce computation time will be used as necessary (Strong et al, 2014).

As a possible example, suppose we find that the incidental detection rate of AAA in women is an important factor: if it is high then the cost-effectiveness of a systematic approach to screening will be worsened, but if it low the cost-effectiveness will be improved. An audit study for incidental detection of AAA in women, according to age, could be based on hospital admission data and discharge diagnoses. This might be conducted through a bespoke study, covering hospitals in several regions, or through analysis of administrative datasets such as HES. An expected value of sample information (EVSI) analysis can be used to assess what cost could be reasonably dedicated to such research in order to lower the decision uncertainty about AAA screening in women.

8. To assess modifications of the AAA screening programme used for men that may be more appropriate and cost-effective for women.

The design of NAAASP followed the definitions and procedures employed in the MASS trial, which evaluated AAA screening in men. For women, some of these design characteristics might be altered to provide a more appropriate programme with potentially greater cost-effectiveness. A number of aspects will be considered:
(i) Aortic diameter which defines an aneurysm: This is 3.0 cm in men, but because women have typically narrower aortas (Rogers et al, 2013) a lower figure might be suitable. For example a figure of 2.5 cm might be considered for women. AAA growth rates in the range 2.5-2.9 cm may be available from published data (Wild et al, 2013), or by extrapolation from the RESCAN data (RESCAN, 2013).

(ii) Age at screening: This is 65 years in men. While women have a lower age-specific prevalence of AAA, they have a longer life-expectancy. Therefore there may be an argument for screening at a later age in women. So we will evaluate 70 years as an alternative to 65 years.
(iii) Threshold for considering elective surgery: This is 5.5 cm for men in NAAASP. The AAA rupture rates in women are about four times that in men, at a given AAA diameter. So a woman with a 4.5 cm diameter AAA has the same risk of rupture as a man with a 5.5 cm AAA (RESCAN, 2013). However, the outcomes after elective surgery appear to be worse for women than men, so reducing the threshold to 4.5 cm may be too drastic. So we will evaluate thresholds of 4.5 cm and 5.0 cm for women, and compare them to a threshold of 5.5 cm.
(iv) Surveillance intervals: If the surgical threshold is changed, it will be necessary to propose modified surveillance intervals. For example if the surgical threshold is lowered by 0.5 cm, then the surveillance intervals currently adopted in men could be applied in women to ranges of AAA diameter also all 0.5 cm lower. More generally, it would be possible to consider a wider range of surveillance options. By increasing surveillance intervals, costs would be reduced but the benefits of screening might be reduced because the rapid expansion of aneurysms in a few women would not be identified before rupture occurred. If the definition of an AAA in women is changed to an aortic diameter of at least 2.5 cm, new surveillance intervals for the 2.5-2.9 cm range need to be defined.
(v) Re-screening: A final aspect regarding 'surveillance' is whether re-screening of those originally screened as normal is justified. The latest follow-up of the MASS trial (Thompson et al, 2012) indicates that AAA ruptures in those men originally screened as normal start to occur and increase after about 8 years after screening. It was also noted that more than half of the men in whom these ruptures occurred had original screening aortic diameter measurements in the range 2.5-2.9 cm. The suggestion was that while re-screening men in the 2.5-2.9 cm range might be justified, re-screening of all men was unlikely to be so valuable. Similar questions will arise in women, whether or not the definition of an AAA is lowered to an aortic diameter of 2.5 cm, and need to be evaluated formally.

9. To compare population-based AAA screening of women with targeted screening of at-risk groups, in terms of overall life-years gained and costs.

The recent US guidelines on screening for AAA focus on men who have ever smoked, because they have a higher prevalence of AAA, rather than all men (USPSTF, 2014). It will therefore be important to attempt to evaluate screening approaches targeted at higher risk groups of women in this project. These might be, for example, ever-smokers or the sisters of men with an AAA. The evaluation will be in terms of the mortality, costs and cost-effectiveness for the targeted group (e.g. per women who is an ever-smoker), as well as an evaluation in population terms (e.g. what proportion of all AAA-related mortality in older women would be averted).

There are two main challenges. The first is the variety of ways a "higher risk" group could be defined. We will already investigate different ages at screening, as above, and here we could consider smokers, those with a family history of AAA, those without diabetes, or those with hypertension. The costs of identifying individuals in these groups (through primary care data or otherwise), as well as the costs of screening, have to be included. The second challenge is the paucity of information (or its poor quality) likely to be available to be able address such questions. For example, whereas AAA growth and

rupture rates in smokers can be estimated from the RESCAN Collaboration (RESCAN, 2013), sources of information may not be available for female smokers alone for many other parameters. If this is the case, it will still be important to state that any absence of conclusions about targeted screening arises through lack of reliable data rather than because the issue was not considered.

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Figure 1 Original Markov multi-state model of AAA screening in men (reproduced from Kim et al, 2007). Ovals represent states, rectangles are events, and arrows show possible transitions between them.

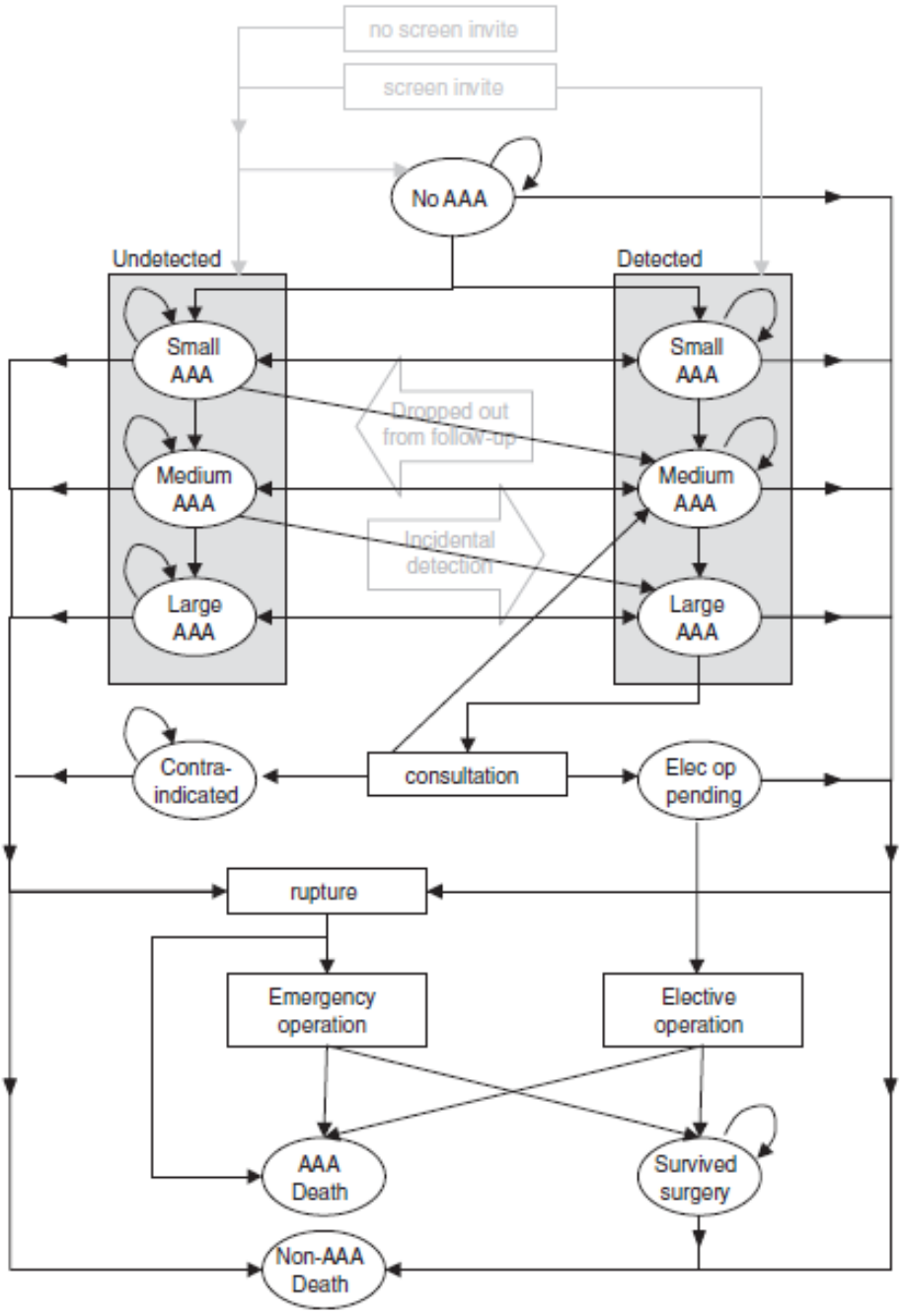

Table 1 Examples of parameters required and possible sources of estimates in women

Parameter	Sources	Availability
Acceptance rate for ultrasound screening	Chichester and Uppsala screening programmes	Published
Prevalence of AAA (3+cm at age 65 or 70, or alternative definitions)	Some in Chichester, Uppsala and Lifeline screening programmes; others not yet known	Some published, but dated; others require literature review
AAA size distribution at screening	Chichester and Uppsala screening programmes; Framingham study	Likely to be available by personal communication
AAA (<5.5cm) growth rates	RESCAN	Published / available through co-applicants
AAA (<5.5cm) rupture rates	RESCAN	Published / available through co-applicants
Rate of drop out from AAA surveillance	Uppsala screening programme	Likely to be available by personal communication
Rate of incidental detection of AAA	Published literature	Systematic review needed
Rate of contraindication for surgery for large AAAs	Some published (e.g. Karthikesalingam et al, 2011)	Needs to be supplemented by local UK audits
Age-specific AAA-related and CVD mortality rates in contraindicated patients	Unlikely to be in published literature	Local UK audit data, supplemented by HES data
Proportion of elective surgery done by EVAR	NVR and other publications from sources outside UK	Systematic review could provide further information
Elective surgical mortality rate (EVAR and open repair)	NVR; EVAR and similar trials	Needs updated systematic review
Long-term AAA-related mortality after elective EVAR	EVAR trial 15-year follow-up, and up to 8 years in linked HES-ONS data	Trial data available through co-applicants. Requires extraction of HES data.
Proportion of AAA ruptures reaching operating theatre alive	IMPROVE trial; linked HES-ONS data	Trial data available through co-applicants. Requires extraction of HES data.
Proportion of emergency surgery done by EVAR	IMPROVE trial; HES data	Trial data available through co-applicants. Requires extraction of HES data.
Emergency surgical mortality rate (EVAR and open repair)	IMPROVE trial; Ruptured aneurysm trialists collaboration	Available through co-applicants
Long-term AAA-related mortality after emergency EVAR and open repair	3-year data from IMPROVE trial	Available in July 2016
Age-specific CVD mortality (excluding AAA-related) in	Possibly by personal communication from Pujades	Also available as a relative risk from UK Small

patients with AAA	et al, 2014.	Aneurysm Study
Age-specific non-CVD mortality	ONS	Published

Acronyms and sources / references for Table 1

Chichester screening programme: Ashton et al, 2007

CVD: Cardiovascular disease

EVAR trials: Brown et al, 2012

Framingham Study: Rogers et al, 2013

HES (Hospital Episode Statistics): http://www.hscic.gov.uk/hes

IMPROVE trial: IMPROVE, 2014

Lifeline screening programme: www.lifelinescreening.co.uk

NVR (UK National Vascular Register): http://data.gov.uk/dataset/national-vascular-registry-aaa-unit-mortality-report-2013-results

ONS (Office of National Statistics): http://www.ons.gov.uk/ons/datasets-and-tables/index.html

RESCAN: Thompson et al, 2013

UK Small Aneurysm Study: UKSAT, 2007

Uppsala screening programme: Svensjö et al, 2013