Appendix G Box 1. Overall Summary (Contextual Question 2)

- Major risk factors confirmed to be: older age, male sex, smoking, family history.
- Older adults have higher prevalence and risk of rupture but also higher surgical mortality and competing causes of mortality compared to younger adults. Screening is only rational for surgical candidates. Validated surgical prognostic models are available for decision-making although some issues around predictive accuracy have been raised.
- Women have lower prevalence, higher rupture risk at same diameter but at older age than men. Women have higher surgical morbidity and mortality compared to men. While women female smokers have prevalence approaching that of men in the trials, their surgical morbidity and mortality remain higher than men. A 2018 DA estimated NNIS for 65-70 year old women 1800-3900 (compared to 700 for men).
- With declining prevalence of AAA, male smokers and those with family history have AAA prevalence that approach that of men in the landmark screening trials. There is no available evidence to suggest that smokers or those with family history have different surgical outcomes.

Overall Risk by Demographic Characteristics and Smoking Status: Large Cohort Studies and Contemporary Trial

These cohorts and one contemporary screening trial confirm that older age, male sex, smoking and family history are the strongest risk factors for AAA development.

Lifetime AAA prevalence from contemporary US cohort for age, sex, smoking, race[30]

ARIC Cohort: This cohort reported women have half to one-third the prevalence of AAA as men. Female current smokers have a similar risk as male former smokers. This study is a prospective, community cohort of 15,792 individuals recruited in the U.S. between 1987-1989 and followed through 2013. It reported an overall lifetime risk of developing a clinically significant AAA was 5.6% (95% CI 4.8-6.1). Risk was higher for men (8.2%), whites (6.5%), current smokers (10.5%) and those in the top 2 tertiles of smoking pack-years (9.0% and 11.1%). There was a gradient effect identified for the length of smoking years.

AAA prevalence risk from US self-referred, self-pay screening cohort[29, 179]

Life Line Screening Cohort: A self-referred, retrospective cohort of 3.1 million participants was analyzed to assess risk factors for developing AAA (US, 2003-2008). This population was fairly young (20% <50 yrs), 65% female, and predominantly white (87%). This analysis confirmed that male, smoking, increasing age, family history, and cardiovascular disease are factors that increase risk for developing AAAs. Protective factors were frequent exercise and consumption of nuts, fruits and vegetables. Smoking cessation also reduced risk. This pattern of risk factors mirrors the analysis done on this same dataset examining predictors of large AAA (size ≥5.0cm)

Risk factors in contemporary Danish screening population[22]

VIVA trial: The VIVA trial is a contemporary RCT in Denmark which randomizes male participants aged 65-74 yrs to screening for AAA, PAD, and hypertension or to usual practice of no systematic screening. 18,749 men attended screening and AAA was identified in 619 men (3.3%). Current smoking and family history were strong risk factors for identification of AAA. Current smoker n=258/619 OR 3.25 (2.76 - 3.84). First-degree relative with AAA n=41/619 OR 2.45 (1.76 - 3.41).

Prevalence

Women

The best available evidence estimating AAA prevalence in women is derived from a new meta-analysis by the SWANN collaborative. There is an additional large UK Lifeline cohort that was published subsequent to the meta-analysis.

AAA prevalence in women from meta-analysis of screening cohorts[23]

Overall pooled prevalence of AAA > 3.0 cm estimated to be 0.74% (95% CI 0.53, 1.03) with a higher prevalence in ever-smokers 1.34% (95% CI 0.82, 2.19) and a lower prevalence in never smoking women of 0.28% (95% CI 0.09, 0.93). These estimates are far lower than reported prevalence in men. This is a systematic review and meta-analysis of eight cohort studies (population-based, self-referral, and physician-initiated screening) of AAA screening of 1.5 million women age 60 years and older in Ireland, Italy, Norway, Sweden, UK, US. The range of prevalence reported in these studies was 0.31 to 1.46%.

AAA prevalence in UK self-referred, self-pay screening cohort[247]

Life Line Screening Cohort: The first 50,000 women self-referring and self-paying to attend the Life Line Screening program in the UK and Ireland (2012-2013) were included. The prevalence of AAA in women 66 to 85 yrs was 0.29% (72/25,170). The prevalence in nonsmoking women was 0.26%. In women younger than 66 years of age, the prevalence was 0.02%. In women 66-85 years with a 40-pack year history of smoking, prevalence was 2.14% but there were few women in this category (3/140) so this estimate lacks precision.

Smokers

With declining overall prevalence of AAA over the past 2 decades, one VA study suggests that contemporary male smokers have similar AAA prevalence to those of participants in the 4 landmark screening trials.

AAA prevalence male smokers in a contemporary cohort[212]

This study shows that the prevalence of male ever smokers reaches the prevalence seen in the major screening trials even though overall prevalence is decreasing. A regional VA health care network identified male smokers 65 to 75 yrs of age who had smoked at least 100 cigarettes in their lifetime and screened them for AAA between 2007 and 2011 (n=8,751). The prevalence of for any aneurysm ≥ 3.0 cm was 7.2% with 77.9% of the aneurysms identified measuring between 3.0 – 4.4 cm.

Family history

New evidence from a contemporary Danish screening trial reports that men with a family history of AAA have prevalence similar to those of participants in the 4 landmark screening trials.

AAA prevalence in those with a family history

Reported estimates of prevalence of AAA in those with a family history vary widely and are obtained using a variety of methodology.

The prevalence of AAA in 65 to 74 year old men with at least one first-degree relative with AAA was 6.7%.[217] This is double the prevalence of those without a family history reported in VIVA (3.0%) and having a female relative with the disease had a higher association with AAA risk (OR

4.32 if female first degree relative; OR 1.61 if male relative). The screened arm of the Danish VIVA trial is the only analysis we identified estimating the prevalence of familial AAA based on population-based screening (N=18,614 screened; 569 with a positive family history based on a questionnaire).

The prevalence of AAA in women with a positive family history in the Life Line Screening cohort (self-referred, self-pay US), was reported to be 1%.[11] This is still much lower than the prevalence of men in the screening trials.

AAA Rupture Risk for Subgroups

An IPDMA and large UK population cohort demonstrate that older adults, women, current smokers and those with high MAP have higher risk of rupture when controlled for other risk factors.

Small AAA rupture risk from meta-analysis of international studies[69]
Women and current smokers have the highest risk of rupture when controlling for the diameter of the AAA. Individuals under surveillance for small AAAs (n=15,475; k=18; Australia, Canada, Denmark, Norway, Spain, UK, US) were monitored for AAA growth and rupture. The influence of risk factors on rupture was evaluated in an individual patient meta-analysis. Authors found higher rupture rates for women (HR 3.76 [95% CI 2.58, 5.47]), current smokers (HR 2.02 [95% CI 1.33, 3.06]), and those with higher mean arterial blood pressure HR 1.32 [95% CI 1.11, 1.56]).

Large UK population cohort AAA rupture risk[38]
The Oxford Vascular Study was a prospective, population-based cohort in the UK (n=92,728, 2002-2014) that looked at the effect of patient characteristics on acute AAA events (AAA rupture or the symptomatic AAA). Men accounted for 72.8% of the acute events and incidence per 100,000 population per year greatly increased with age although current smokers incurred events at younger ages than ex-smokers or never-smokers. Wide confidence intervals make comparing rates in current female smokers and past male smokers difficult.

Operative Mortality and Complications

Women

A new meta-analysis reports consistent evidence showing that women have higher post-operative complication rates following EVAR and open repair.

A systematic review (k= 8, n=19,247)[202] found women had higher 30-day mortality compared to men in both EVAR and open repairs. Women had higher 30-day mortality (2.31%) than men (1.37%) after EVAR procedures OR 1.67 (95%CI 1.38, 2.04) and open repair (5.37% vs 2.82%) OR 1.76 (95% CI 1.35, 2.30).

Age

A new meta-analysis reports consistent evidence showing that octagenarians have higher post-operative complication rates following EVAR compared to younger adults.

Meta-analysis comparing surgical outcomes in ≥80 yr olds to <80 yr olds[180]
A systematic review and meta-analysis (k=9, n=25,723) of surgical outcomes in EVAR procedures

in patients ≥ 80 yrs compared to younger patients. Octogenarians had a higher 30-day mortality (3.7% vs 1.7%; OR 2.372 [1.992, 2.825]) and a higher rate of 30-day endoleak (25.83% vs 21.31%; OR 1.281 [1.183, 1.388]). Although, octogenarians had higher harms, the authors state that the absolute rates are acceptable.

Family History

A retrospective review of a large US surgical registry did not indicate that individuals with a family history have worse surgical outcomes than individuals without a family history.

Vascular Quality Initiative registry comparing surgical outcomes for those with and without a family history of AAA. [248]

Surgical outcomes were compared for patients with or without a family history of AAA in the VQI registry from 2003-2017. 1997 individuals were identified to have a family history and 18,815 were without a family history. Procedures included open repair and EVAR. No differences were identified in postoperative complications (p=0.510), 30-day mortality (p=0.177), or long-term mortality (p=0.259).

Current Clinical Practice: Surgical Threshold

New data from national registries demonstrate that AAA repair thresholds are lower in clinical practice for both men and women in the US compared to the UK; the US has lower AAA related deaths compared to the UK.

UK v US comparative data of contemporary surgical practice comparing surgical approaches and threshold for intervention in men and women[104]

It is much more common for men and women in the US to undergo repair prior to reaching the indicated surgical thresholds of 5.5 cm for men (39.21% vs 8.82%) and 5.0 cm for women (17.19% vs. 4.72%) compared to the UK. A review of registry data in England and US was undertaken to identify the frequency of AAA repair along with the aortic diameter at the time of repair (2005-2012; n=29,300 in England; n=278,921 in US). Repairs in the US were undertaken at a smaller diameter (5.83 cm vs 6.37 cm, p<0.001) although AAA-related death and hospitalization due to AAA rupture were more common in England.

Outcomes Table for Screening Women

A new decision-analysis with CEA reports that screening women is not cost effective and estimates NNIS of 3,900 to prevent 1 AAA death in women.

Decision-analysis of screening women (outcomes table)[210]

A decision analysis assessing AAA screening in women. If women were screened at age 65 years, 3,900 women would need to be invited to be screened to prevent one AAA-related death with an overdiagnosis rate of 33%. A second strategy of screening women at age 70 years would require 1,800 invitations to screen to prevent one AAA-death with an overdiagnosis rate of 55%. Uncertainty around the AAA prevalence in women makes it difficult to accurately estimate the effects of screening.

Appendix G. Additional Contextual Question 2 Evidence

Appendix G Table 1. Odds ratios of risk factors associated with developing AAAs (based on adjusted multivariate analyses)

Factors Associated With AAA	Any AAA ≥3 cm[29]	Any AAA ≥5 cm[179]
Male sex (vs. female sex)	5.71	7.70
Female sex (vs. male sex)	NR	NR
Age (vs. <55 years)		
55–59	2.76	3.20
60–64	5.35	8.10
65–69	9.41	13.20
70–74	14.46	20.70
75–79	20.43	32.0
≥80	28.37	53.10
Hispanic/black/Asian (vs. white)	0.69 to 0.72	0.70
Family history of AAA	3.80	3.20
Smoking: years (<10 years, 10 to 35 years, or >35 years) + PPD (≤0.5, 0.5 to 1, >1)	2.61 to 12.13	2.60 to 14.50
Smoking cessation (5 to 10 years, >10 years)	0.42 to 0.87	0.50 to 0.80
Diabetes	0.75	0.70
CVD morbidities	1.1 to 1.7	1.10 to 1.70

Abbreviations: AAA = abdominal aortic aneurysm; CVD = cardiovascular disease; NR = Not reported; PPD = packs per day.

Appendix G. Additional Contextual Question 2 Evidence

Trial Identifier	Study Name	Location	Participants N	Intervention	Outcome Measures	Status Aug 2018
NCT01756833	Non-Invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial (N-TA^3CT) Michael Terrin	US	Men and women age 55 years and older N=261	Doxycycline 100 mg po bid for 2 years vs. placebo	AAA growth	Active, expected completion 2019. Protocol published 2016
NCT01683084	Study of the Effectiveness of Telmisartan in Slowing the Progression of Abdominal Aortic Aneurysms (TEDY) (Ronald L Dalman)	US	Adults ages 50 to 85 years N=22	Telmisartan 40 mg daily for 24 mo vs. placebo	Rate of AAA growth, AAA diameter, AAA biomarkers, QoL	Completed 2016. No result publication found. Protocol published 2015
NCT02717481	Using US to Evaluate Aortic Aneurysm Size Based on 3D Co-registration to Previous CT Scan (Diana Gaitini)	Israel	Men and women age 18 years and older diagnosed with AAA or following invasive repair N=120	Ultrasound	Primary: Exact and reliable evaluation of the aneurysm size Secondary: The size difference between systolic and diastolic aneurysm; aneurysm neck size and changes following an invasive procedure to repair it (EVAR); evaluation of the pressure on the aneurysmal wall	Not yet recruiting, expected completion 2018
NCT01205945	The Effect of Abdominal Aortic Aneurysm Screening on Mortality in Asian Population (Jin Hyun Joh)	South Korea	Men and women ages 50 to 85 years with CVD risk factors, family history of AAA N=12,000	Ultrasound	Benefits of screening older population	Ongoing, estimated completion 2017. No publications found.
NCT02345590	Eplerenone in the Management of Abdominal Aortic Aneurysms (Leah Isles)	Australia	Men and women ages 60 to 90 years with AAA 30 to 49 mm N=172	Eplerenone 25mg/day vs. placebo	AAA maximum orthogonal diameter	Ongoing, estimated completion 2019.
NCT02229006	Sodium Fluoride Imaging of Abdominal Aortic Aneurysms (SoFIA3) (Rachael O Forsythe)	UK	Men and women age 50 years and older in MA3RS study with AAA >40 mm N=100	Radiation: 18F-NaF PET-CT	Primary: Change in AAA anteroposterior diameter at 6 and 12 months measured with CTA Secondary: Co-localization of 18F-NaF with USPIO uptake on MRI scanning	Completed 2017. No publications found.

Appendix G. Additional Contextual Question 2 Evidence

Trial Identifier	Study Name	Location	Participants N	Intervention	Outcome Measures	Status Aug 2018
NCT02604303	A Prospective Analysis on the Expansion Rates of Abdominal Aortic Aneurysms (Eugene S. Lee)	US	Veteran men and women age 21 years and older screened for AAA by VA N=200	Observational using screening	Primary: aortic expansion rate measured with ultrasound Secondary: RhoA levels	Ongoing, expected completion Nov 2018.
NCT02070653	The Efficacy of Ticagrelor on Abdominal Aortic Aneurysm (AAA) Expansion (TicAAA) (Anders Wanhainen)	Sweden	Men and women ages 50 to 85 years with AAA 35 to 49 mm N=145	Ticagrelor 180 mg/day vs. placebo	Primary: AAA volume growth measured with MRI Secondary: AAA diameter growth measured with ultrasound and MRI; need for surgery; rupture	Completed 2018. No publications found.
NCT02548546	Estimation of Biomechanical Aortic Wall Properties in Healthy and Aneurysmal Aortas Using Novel Imaging Techniques (Houssam Farres)	US	Men and women age 21 years and older with AAA ≥1.5x normal diameter N=30	Surveillance vs. open repair vs. EVAR	Primary: ECHO imaging Secondary: ECG-gated MRA imaging	Ongoing (recruiting), expected completion Aug 2018.
NCT02225756	Cyclosporine A in Patients With Small Diameter Abdominal Aortic Aneurysms (ACA4) (Eric Allaire)	France	Men with AAA 30 to 49 mm, women with AAA 25 to 44 mm, 50 to 85 years N=360	Cyclosporine vs. placebo	Primary: AAA diameter evolution on CT-scanner 12 months after treatment interruption Secondary: AAA diameter evolution on duplex-scanner 12 months after treatment interruption; all-cause CV mortality/morbidity	Ongoing (recruiting), expected completion Sep 2018.
NCT02022436	Evaluation of Predictors of Aortic Aneurysm Growth and Rupture (Rabih Chaer)	US	Men and women age 21 years and older diagnosed with AAA N=148	Contrast ultrasound	Primary: time to growth and/or rupture of abdominal aortic aneurysm Secondary: AAA biomarkers	Ongoing (recruiting), expected completion Jul 2020.
NCT02179801	Screening Cardiovascular Patients for Aortic aNeurysms (SCAN) (Hans-Henning Eckstein, Karl-Ludwig Laugwitz)	Germany	Men any age with 1 or more risk factors for AAA and coronary artery intervention N=1,000	Ultrasound screening	Primary: prevalence of AAA Secondary: prevalence of AAA in the cohort requiring treatment; correlation of risk factors for AAA with risk factors for CAD; distribution of risk factors	Ongoing (recruiting), expected completion Apr 2018. No publications found.

Appendix G. Additional Contextual Question 2 Evidence

Trial Identifier	Study Name	Location	Participants N	Intervention	Outcome Measures	Status Aug 2018
NCT02846883	Safety and Efficacy of Allogeneic MSCs in Promoting T-regulatory Cells in Patients With Small Abdominal Aortic Aneurysms (VIVAAA) (Michael Patrick Murphy, Richard L. Roudebush)	US	Men and women ages 40 to 80 years diagnosed with AAA 35 to 45 mm	Intravenous infusion of 1 or 3 million allogeneic MSCs/kg vs. placebo	Primary: incidence of treatment-related adverse events at 12 months Secondary: changes in inflammatory AAA biomarkers; change in aortic inflammation measured by 18-FDG PET/CT	Ongoing (recruiting), expected completion 2021.
ISRCTN10945166	Abdominal Aortic Aneurysm Screening by Ultrasonography in Primary Care (Ana Claveria)	Spain	Men ages 65 to 74 years N=3,348	Screening	Primary: impact of early diagnosis on overall/CV mortality with incidental AAA Secondary: CV mortality; surgery for AAA; type of hospital discharge	Ongoing, expected completion 2021.
NCT01420991	Brain and Abdominal Aneurysm Study (BAAS) (James Meschia)	US	Men and women age 18 years and older diagnosed with intracranial aneurysm N=81	Opportunistic screening	Primary: prevalence of AAA Secondary: functional outcomes at 30 days	Ongoing, expected completion 2024.
NCT00662480	Randomized Preventive Vascular Screening Trial of 65-74 Year Old Men in the Central Region of Denmark (VIVA)	Denmark	40,000	Screening for hypertension, lower limb atherosclerosis, and abdominal aortic aneurysm	All-cause mortality, cardiovascular events	Active, expected completion Dec 2023. Median (4.4 year) results published in 2017.[146]
ISRCTN12157806	The Danish Cardiovascular Screening Trial (DANCAVAS) (Jes Lindholt)	Denmark	45,000	Large population-based, randomized, clinical multicenter trial testing combination cardiovascular screening in men ages 65 to 74 years	All-cause mortality, costs, and cost-effectiveness after 3, 5, and 10 years to assess possible health and/or societal benefits of the screening; nationwide registry-based information on health care consumption	Ongoing, expected completion Jan 2026. Protocol published 2015.