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## **The Safety of Device Registries for Endovascular Abdominal Aortic Aneurysm Repair: Systematic Review and Meta-regression**

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### **WHAT THIS PAPER ADDS**

The literature is full of papers examining outcomes for different types of stent grafts for repairing infrarenal abdominal aortic aneurysms. New stent grafts are released regularly with publications reporting their “safety” or superiority, but there is no consensus on how to report this. There is also no information on how many patients would be needed to prove non-inferiority to accepted devices. This is the first time that individual EVAR stent graft complication rates have been pooled in meta-analysis, a consensus performed, then the numbers of patients required for registry publications calculated from the results.

**Objectives:** New and re-designed stent grafts for endovascular aortic aneurysm repair (EVAR) are released regularly. Manufacturers use data from registries to assess stent graft performance, but little is known about the ability of such registries to detect rates of clinically relevant complications. The aim of this paper was to perform a systematic review and meta-analysis to determine pooled failure rates for EVAR stent grafts, to define an acceptable non-inferiority limit for these devices, and then to calculate the number of patients needed for a new device to achieve non-inferiority against published devices.

**Data sources and review methods:** MEDLINE and EMBASE were searched for studies reporting outcomes of specific EVAR grafts being used for intact infrarenal abdominal aortic aneurysms, from inception to November 2016. Meta-regression was performed to pool data and calculate the patient numbers needed to detect noninferiority of a future graft performance. An expert consensus was performed to define adequate standards for device safety.

**Results:** One hundred and forty-seven moderate quality papers involving 27,058 patients were included. Multiple outcomes were pooled. Of these, the estimated rate (standard error) of overall endoleak (excluding Type II) at 2 years was 5.7 0.6%.The pooled re-intervention rate was 11.1 0.7% at 2 years. There were differences in pooled endoleak rates between different stent graft types. Expert consensus defined non-inferiority as better performance than the worst performing 25% of stent grafts. The most popular outcome in the expert consensus was cumulative endoleak rate (excluding Type II). The number of patients who would need to be enrolled in a registry to demonstrate non-inferiority at this level was 525. Only two of 147 included studies achieved this. The second most popular choice in the expert consensus was re-intervention rate; 492 patients are required to demonstrate this.

**Conclusions:** Five hundred and twenty-five patients need to be entered into a registry to demonstrate noninferiority to previous stent grafts. Almost all previous publications have captured lower patient numbers. With performance varying between devices, and new devices being introduced regularly, there is an urgent need to capture higher quality long-term data on EVAR stent grafts.

**Keywords:** Abdominal aortic aneurysm, Endovascular procedures, Patient safety, Meta-analysis

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## INTRODUCTION

The incidence of abdominal aortic aneurysm (AAA) repair continues to increase in the western world.<sup>1</sup> Around 40,000 non-ruptured AAA are treated every year in the United States alone, with 80% being treated endovascularly. In the UK the proportion of AAA treated endovascularly has increased from less than 10% in 2005 to around 60% in 2012, and continues to grow.<sup>1</sup> An infrarenal stent graft for endovascular AAA repair (EVAR) costs around \$7000.<sup>2</sup>

This creates a lucrative market for device manufacturers, and new stent grafts for performing EVAR are released regularly. Commonly used, established stent grafts are given regular iterative updates, which often retain the same name for marketing purposes but may alter the graft design and structure.<sup>3,4</sup> The regulatory requirements for stent graft use vary by country or territory, and while not always available for scrutiny comprise a mixture of bench testing and limited clinical data. The “safety” and marketing data for these devices is therefore usually based on post-market surveillance registry publications; a recent Cochrane review highlighted that no randomised trials exist comparing one stent graft type with another.<sup>5</sup> Stent graft fixation, material, and stent design all vary between manufacturers, and different devices have appeared to suffer from different types of failure historically.<sup>6</sup> Most devices fail after more than 5 years, meaning long-term follow-up of EVAR stent grafts is especially important.

These device failures lead to a significant late complication rate after EVAR, which includes treated AAAs rupturing, often leading to death.<sup>7</sup> Even though there is a perception that individual stent graft designs failed in different ways, these results have never been pooled and compared. The ability of stent graft registry publications to detect failures that could lead to patient death is unknown. Exactly which of these late failures is of most interest to surgeons and radiologists is also undefined. The aims of this paper were therefore threefold:

1. To perform a systematic review and meta-regression to determine pooled failure rates for EVAR stent grafts. As part of this process, to examine individual factors leading to stent graft failure where available.
2. To define an acceptable non-inferiority limit for EVAR stent grafts via expert survey.
3. To calculate the number of patients needed for a new device registry to achieve non-inferiority against previous devices.

## MATERIALS AND METHODS

### Systematic review and meta-regression

**Search methods.** A systematic review of published work was conducted as per the protocol specified by the Cochrane collaboration,<sup>8</sup> and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for the conduct of meta-analyses of intervention studies.<sup>9</sup> The following sources were searched: Medline via PubMed, Embase, and the Cochrane Library Database (Cochrane Central Register of Controlled Trials) for studies comparing stent graft types for endovascular repair of intact abdominal aortic aneurysms (AAAs). All studies describing results from more than 10 patients were included. Non-English language papers were excluded. Studies arising from duplicate publications and review articles were excluded. Studies were excluded

if the subjects included non-degenerative AAAs, thoracic, thoraco-abdominal, or isolated iliac aneurysms. Studies of only emergency or complex aneurysms (fenestrated, extreme anatomy, e.g. angled neck, short neck) were excluded, though if these were case cohort studies, data from the control group (non-emergency, non-complicated) were extracted. Studies of endovascular sealing devices were excluded. As a result, stent grafts (and manufacturers) included were Zenith (Cook Medical, Bloomington, IN, USA); Zenith Low Profile (Cook Medical); Endurant (Medtronic, Minneapolis, MN, USA); Excluder (W.L. Gore, Newark, DE, USA); AFX (Endologix, Irvine, CA, USA); Anaconda (Vascutek, Inchinnan, Glasgow, UK); Aorfix (Lombard, Didcot, UK); Powerlink (LeMaitre, Burlington, MA, USA); Talent (Medtronic); AneuRx (Medtronic); Incraft (Cordis, Milpitas, CA, USA). For each stent graft the heading “Aneurysm” and the specific stent graft name, e.g. “Excluder”, were used as search terms.

Articles were also identified by hand searching of references and extensive use of the related articles function in PubMed. The last search date was November 24, 2016.

**Data extraction.** Data were extracted independently by two authors (F.K. and D.B.). Data extraction was initially trialled on 10 papers, and then refined. Extracted demographic data included stent graft studied, company sponsored study, on or off label use, years over which graft studied, study design, number of patients, and duration of follow-up.

Outcome data collected included endoleak rates and types, re-intervention rates, and late rupture rates. Data on Type IV and V endoleaks were initially collected, but due to the extremely low reported rates of Type IV leaks, and the heterogeneity inherent in Type V leak definition, results for these types of leaks were not further examined, though they are pooled within total cumulative endoleak rates. Study quality was assessed using the NewcastleOttawa scale.<sup>10</sup> Further details of extracted data are given in Appendix 1. Where short and long-term results from the same patient cohort were published separately, relevant data were retrieved from both publications preferentially using the latest.

### **Statistical analysis**

Type I-III endoleaks were modelled using weighted linear regression modelling, with constant term representing initial “failure to seal” and linear term representing subsequent development of leak over time:  $\text{leak rate} \frac{1}{4} \text{late leak rate} \text{ mean follow-up time} \beta \text{ failure to seal}$ .

Terms were weighted in the regression analysis according to the number of patients in the study. Overall endoleak rates, re-intervention rates, and rupture rates were modelled in the same way. The reason that meta-regression was chosen over fixed point meta-analysis was that different studies included different follow-up times, so attempting to consider these rates at one or more time points would have meant discarding an enormous amount of the published data. Negative “failure to seal” estimates were set to zero. Confounder adjustment was performed using multivariate linear regression for mean patient age, proportion of male patients and mean aneurysm diameter if these terms were significant based on calculation of Akaike’s Information Criterion. Akaike’s Information Criterion (AIC) is a standard statistical tool for model selection. The AIC penalises complex models, so minimisation of AIC is a way of ensuring that predictors that improve the fit of a model more than they increase its complexity are included. Separate regression models were also fitted for graft types with data from at least 10 studies. R (<https://www.r-project.org>) was used for all statistical analysis.

### **Definition of non-inferiority**

**Expert survey.** No formal guidance exists to define inferiority of endovascular devices. Numerous outcomes could potentially be selected when comparing new endografts with existing products.

Furthermore, how non-inferiority should be defined (in terms of deviation from previously published outcome rates) has not previously been stipulated.

In order to decide how to define clinically significant failure rates for use in determining the appropriate sample size for a new device registry, medical members of the British Society for Endovascular Therapy (BSET) Council (<https://www.bset.co.uk/about-bset/council-members>) were surveyed for a consensus. The survey was pre-defined using feedback and iteration by the authors and the research subcommittee of BSET. The council includes high volume EVAR practitioners (surgeons and radiologists) and actively publishing EVAR academics. The council were asked what statistical definition of non-inferiority should be used for a power calculation, and what they felt was the most relevant complication of EVAR stent grafts on which to base that calculation. The questionnaire was performed before any analyses. The full survey, with multiple choice options and answers, is given in Supplementary Table I.

### **Number of patients needed to achieve non-inferiority in new studies**

**Statistical analysis.** A Bayesian approach was used to investigate the number of patients required in a registry for a new device to detect leak, re-intervention, or late rupture rates (“rates”) which were inferior by a defined, “clinically significant” quantity  $\epsilon$  determined by the expert survey. Rates were modelled using a Beta prior,<sup>16</sup> with parameters estimated from the meta-regression above. A binary search strategy was then used to find the number of patients for a new registry which would be required, under this model, to show inferior rates with 80% power determined by the predefined “clinically relevant” rate. These patient numbers were calculated for 2 and 5 years of follow-up using a Monte Carlo technique.

Attrition rates for EVAR treated patients were needed to adjust the numbers of patients required for entry into a registry to produce enough patients at 2 and 5 years to detect late complications. This length of time was chosen based on previous randomised data picking up the majority of early complications in this timeframe. Rates were calculated by pooling attrition rates for the EVAR arms of all randomised control trials on EVAR versus open repair or conservative management for AAA,<sup>11e15</sup> as these were felt to be more likely to accurately reflect true attrition rates with high quality follow-up than cohort studies.

## **RESULTS**

### **Systematic review and meta-regression**

**Literature search and study characteristics.** Database searches identified 1584 unique studies and searching through references revealed 17 further studies (Fig. 1). A total of 1601 abstracts were screened and 213 full articles were obtained. One hundred and forty-seven papers involving 27,058 patients were included in analysis. This included no randomised controlled trials (RCTs), 22 registries/Phase II clinical trials, 46 cohort studies, and 79 case series. Seventy (48%) studies were prospective. The median NewcastleOttawa score was 4 (range 3e8; Supplementary Table II). The weighted mean follow up was 24 months (range 1e120 months), and the median patient number enrolled on the studies was 111 (IQR 49e214). The pooled mean patient age was 73 years, and 89% of patients were male. The mean aneurysm diameter was 57 mm. Full details of all included studies are given in Supplementary Table II.

Fifteen per cent were company funded registries and 22% of the remaining papers declared company sponsorship. The median patient number enrolled on company sponsored registries was significantly larger (236, IQR 80e357) than non-company sponsored registries (100, IQR 44e178;

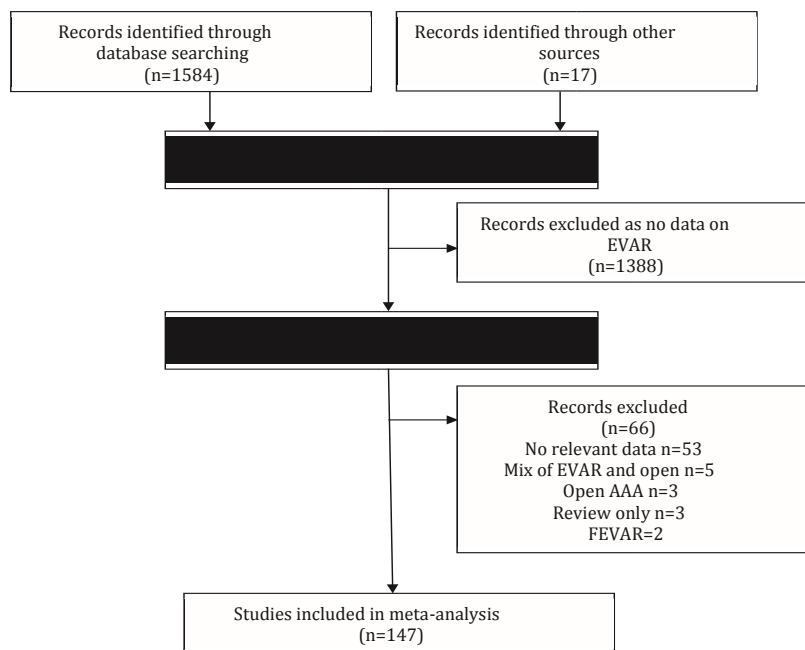


Figure 1. Identification process for eligible studies.

$P=0.001$ ), although the median follow up was shorter (12, IQR 8e22, vs. 22, IQR 12e36;  $p \frac{1}{4} .01$ ). Company sponsorship had no relationship to endoleak ( $p \frac{1}{4} .77$ ) or reintervention rates ( $p \frac{1}{4} .22$ ). Thirty-seven per cent of studies included only patients treated according to the manufacturer's instructions for use (IFU).

The weighted mean attrition rate from all included studies at 30 days was 2%. By 1 year it was 29%. The attrition rate from EVAR RCTs was lower than this at 1.9% and 8.5% respectively.

**Endoleak rates.** Table 1 shows pooled results from metaregression after EVAR. Type I, II, and III endoleak rates (standard error) at 2 years were 3.4 0.3%, 13.0 1.0%, and 0.8 0.1% respectively. The overall endoleak rate at 2 years was 18.9 1.2%, and was 5.7 0.6% when Type II endoleaks were excluded. Fig. 2 shows the fitted regression model for overall endoleak rate (excluding Type II) and shows weighting by study size and stent graft type.

**Graft specific outcomes.** Six grafts (Zenith, Talent, Endurant, Excluder, Anaconda and AneuRx) had data from at least 10 separate studies (23, 24, 23, 28, 10, and 21 respectively). Zenith could not be subdivided into Zenith and Zenith Low Profile (LP) because of the 23 studies (5754 patients) reporting on Zenith, only one19 included a cohort with Zenith LP (101 patients). Endurant could also not be subdivided in this way: of 25 studies (4783 patients), only one study reported outcomes from Endurant II (64 patients),<sup>20</sup> and there were no studies of the current Endurant IIs.

Predicted endoleak, re-intervention, and late rupture rates at 2 years for the different grafts are given in Table 1. Stent grafts performed significantly differently. For example the Endurant graft from Medtronic performed significantly better for cumulative endoleak rate (excluding Type II) than its predecessor the Talent graft, with rates of 3.5 1.2% vs. 8.4 1.6% ( $p < .01$ ) respectively.

**Table 1. Results of pooled meta-regression**

	Total no. of patients	Number of studies	Mean follow up time (years)	Estimated rate at 2 years' follow-up (%)	Standard error	Adjusted R <sup>2</sup>	Numbers needed to show non-inferiority	
							2 years	5 years
Type I endoleak	17,068	106	2.10	3.39	0.29	0.24	903	1190
Type II endoleak <sup>a</sup>	17,900	110	1.84	13.04	0.96	0.04	298	278
Type III endoleak	16,116	98	1.87	0.76	0.13	0.25	964	1597
Cumulative endoleak	16,035	104	2.09	18.86	1.23	0.09	225	212
Cumulative endoleak rate excluding Type II	13,636	89	1.88	5.67	0.55	0.28	525	720
Re-intervention rate <sup>b</sup>	21,595	126	2.26	11.12	0.68	0.23	492	500
Re-intervention for Type II	15,586	101	2.05	3.08	0.28	0.15	970	1273
Late rupture <sup>c</sup>	20,999	100	2.13	0.60	0.07	0.20	2773	3759

Note. Numbers in the final two columns are the number of patients needing to be entered into a registry to show non-inferiority for the stated outcome. Numbers needed to show non-inferiority have been adjusted to allow for attrition rates similar to those seen in randomised controlled trials, which were 17% at 2 years and 41% at 5 years.

a Adjusted for the proportion of male patients.

b Adjusted for median patient age and mean aneurysm size.

c Adjusted for mean aneurysm size.

### Definition of non-inferiority

Expert survey. Thirteen responses from 16 polled experts were received. All of these responded to both questions. The majority (7 respondents) felt that a new device could be declared non-inferior if the registry were large enough to show with reasonable power that complication rates were at least as good as those pooled from 75% of existing devices. Regarding the most important outcome for

calculating sample size, five respondents selected “endoleak rate excluding Type II endoleaks”, four respondents selected “reintervention rates”, while two thought “Type I endoleak rate” was most important. Full results are given in Supplementary Table I.

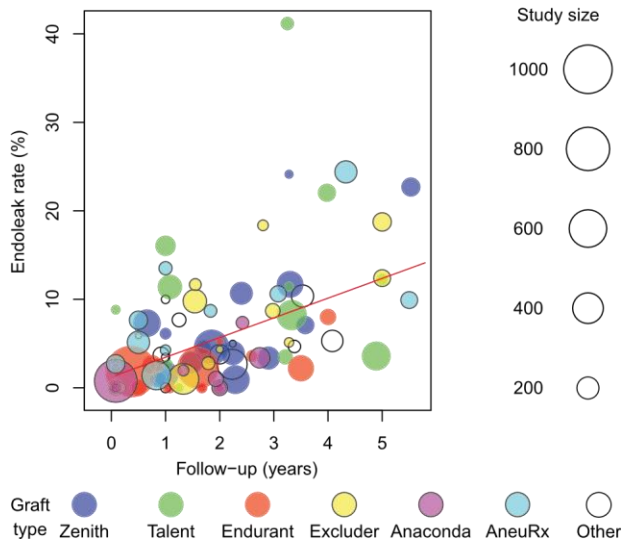


Figure 3. Bubble plot showing fitted meta-regression model for reintervention rate

### Number of patients needed to achieve non-inferiority in new studies

The number of patients required for a registry to detect non-inferiority for total endoleak rate (excluding Type II) was calculated as 525 patients at 2 years, taking attrition rates into account (Table 1). Only two of the 147 studies (1.4%) published in the literature<sup>17,18</sup> had sufficient numbers of patients and duration of follow-up to satisfy the requirements of the expert survey.

**Re-intervention and rupture rates.** The second most popular choice in the expert consensus was re-intervention rate. This was 11.1 0.7% at two years, of which 3.1 0.3% was for Type II endoleak. Four hundred and ninety-two patients would be required to detect noninferiority for re-intervention rates at 2 years. Fig. 3 shows the fitted regression line for re-intervention rates as well as data from the available studies and shows weighting by study size and stent graft type.

Late rupture rates were 0.6 0.1% at 2 years. Far larger numbers would be needed for a registry to detect late rupture rates; 2773 patients would need to be enrolled in order to show non-inferiority for late rupture at 2 years. None of the included studies enrolled patient numbers this large.

## DISCUSSION

This study has shown that 525 patients are required for a registry to show acceptable non-inferiority at 2 years for new or altered EVAR stent grafts at the consensus level. Only two of 147 studies in the literature met this retrospective requirement.<sup>17,18</sup> One was a company sponsored registry.<sup>17</sup> Both of these stent grafts have subsequently been redesigned to be mounted on low profile delivery devices, which means although they are marketed under similar names they differ in both stent and graft material design. Neither of the re-designs have publications with enough patients to satisfy the non-inferiority definition.



To put the primary outcome measure of non-inferiority into context, cumulative endoleak rate (excluding Type II) means that all graft related failures (Type I, III, IV, and V endoleaks) are included. Type II endoleaks are thought to be patient related and therefore representative of patient selection rather than the stent graft itself.<sup>21</sup> Type II endoleaks are also more variably detected and reported, intervened for, and are thought to be less clinically relevant than the others.<sup>22</sup> This perception is reinforced by cumulative endoleak (excluding Type II) having the best fit of all meta-regression models run (Table 1; adjusted R<sup>2</sup> = 0.28). The model fit improved significantly (0.09e0.28) when Type II endoleak was removed, and the fit for Type II endoleak re-intervention was relatively poor (0.15), further implying agreement. Stent graft limb occlusion rates could also be included in a composite endpoint like this; however, they are also variably re-intervened for, and almost never lead to patient death. The numbers needed for patients to define safety by different endoleak types including Type II are included in Table 1.

Attrition rates were particularly high in these studies. This is highlighted by the 29% pooled attrition rate at 1 year. This compares badly to the EVAR arms of RCTs, and even to the EVAR 2 trial (21% attrition at 1 year), which included medically unfit patients and had a higher mortality than RCTs of representative AAA patients.<sup>11</sup> Attrition in the included studies is therefore likely to have poor follow-up, which needs addressing in future registries. The other concern is that the high attrition rates will mask higher stent graft failure rates than those found at 1 year. This is a problem with the EVAR and aneurysm literature in general, and can only be compensated for by more robust follow up regimens.

The importance of follow up after EVAR has recently been highlighted by the late results of the EVAR 1 randomised trial, which randomised patients fit for open repair to either that or EVAR. This has shown a significant late (>5 years) complication rate in the EVAR arm, to the extent where the initial survival benefit in the EVAR arm was reversed at 8 years.<sup>7</sup> Although stent graft designs have changed over this time, and complications reduced (Table 2), length of follow-up remains a concern, especially as the median follow-up from these data was only 24 months. Pragmatically, the cost of entering enough patients and maintaining registries for between 5 and 10 years makes this unlikely, but other data sources should be considered. For example, the National Vascular Registry in the UK captures data on all EVARs performed in the UK, and stent graft type could easily be added as a field.<sup>23</sup> Registries can be powerful for detecting device related complications as shown by the metal on metal hip implant scandal which was first detected by the National Joint Registry of England and Wales.<sup>24,25</sup> This is urgently required for EVAR stent grafts as different designs performed significantly differently from one another in the analysis when comparing graft related endoleaks, and national registries which do not routinely capture anatomical considerations and linked endoleak/re-intervention rates should consider doing so. Table 2. Graft specific endoleak, re-intervention and late rupture rates for the six grafts with data from at least 10 studies

Table 2. Graft specific endoleak, re-intervention and late rupture rates for the six grafts with data from at least 10 studies

	Type I endoleak	Type II endoleak	Type III endoleak	Cumulative endoleak	Cumulative endoleak rate excluding Type II	Re-intervention rate	Re-intervention for Type II	Late rupture
Zenith	3.5 0.6	17.9 1.8	0.9 0.3	25.9 2.8	5.7 1.2	11.6 1.8	4.7 0.6	0.9 0.2
Talent	5.3 0.8	10.8 2.1	1.1 0.4	18.4 3.5	8.4 1.6	11.9 1.7	2.3 0.7	0.8 0.2
Endurant 1	2.0 0.6	11.3 2.0	0.5 0.3	11.7 3.2	3.5 1.2	9.5 1.9	2.3 0.6	0.3 0.2
Excluder	2.5 0.7	11.6 2.1	0.1 0.3	23.0 3.9	7.0 1.8	10.2 1.8	3.1 0.7	0.4 0.2
Anaconda	2.2 1.0	14.8 3.0	0.5 0.5	15.1 4.1	3.4 1.8	8.7 3.5	0.8 1.3	0.4 0.3
AneuRx	6.1 0.9	11.9 2.4	2.4 0.5	19.2 3.7	8.7 1.7	15.4 1.5	4.2 0.8	0.7 0.2

Study quality was poor in this field but could be improved in the future by powering studies using the numbers in this analysis, more thorough follow-up regimens, and improved data collection. There was also significant variability in outcome reporting between studies, so future datasets could be standardised using the outcomes reported here. Aneurysm related survival could also be reported, but would need a huge number of patients to have any power to detect poor performance, and is difficult to collect outside a randomised control trial. The survey was predefined by a consensus, but a larger (e.g., Delphi) process would have made it more robust.

Because of a lack of reporting within studies, data could not be adjusted or analysed by adherence to the manufacturer's IFU. This would have been interesting because adherence to the IFU is known to produce better clinical results.<sup>26</sup> However, in real world studies only 30e70% of stent grafts are actually inserted in anatomy adhering to IFU,<sup>27</sup> so this analysis remains a valid, pragmatic representation of the use of stent grafts during EVAR. It was impossible to subdivide grafts by iterative updates under the same or a similar name because the current generation of updated grafts had too few data available.

The definition of non-inferiority used was from an expert consensus, but it is acknowledged that there are many other ways to define non-inferiority in this setting; there is no standard. For that reason, analyses are included which would allow other researchers to calculate patient numbers based on other definitions of non-inferiority. This would potentially range from 225 to 2773 patients depending on the outcome of choice. The consensus was taken before analysis but examining the results the outcome chosen appears reasonable; the regression model fit was the best for this outcome and the number of patients needed to power was between the lowest and highest for other outcomes.

## CONCLUSION

Five hundred and twenty-five patients need to be entered into a registry to demonstrate non-inferiority to previous stent grafts for EVAR in a 2 year time period. Current registries had serious limitations, with only 1% of included studies including enough patients. With performance varying between devices, and the majority of grafts included in this analysis now being last generation, there is an urgent need to capture higher quality long-term data on EVAR stent grafts.

**CONFLICT OF INTEREST**

None.

**FUNDING**

None.

## Appendix 1

### Extracted data.

<b>Study design</b>	<b>Cohort and graft characteristics</b>	<b>Baseline demographics and patient factors (number of patients unless stated)</b>	<b>Outcomes (number of patients unless stated)</b>
Type of study (RCT/cohort/case series)	Number of patients	Age (median/mean)	Length of procedure in minutes (mean/median)
Data analysis (retrospective/prospective)	Graft type	Sex	Endoleak rate (separate for each Types I-III)
Company sponsored (yes/no)	Company	ASA (median)	Total endoleak rate
Publication year	Graft generation	Aneurysm width	Total re-intervention rates
Midpoint of study year	Graft used on IFU (yes/no)	Follow up time (mean/median)	Late rupture rate
Ruptures included (yes/no)			
Newcastle Ottawa Score			

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