

# JOHN WILEY & SONS, LTD., THE ATRIUM, SOUTHERN GATE, CHICHESTER P019 8SQ, UK

## \*\*\*PROOF OF YOUR ARTICLE ATTACHED, PLEASE READ CAREFULLY\*\*\*

After receipt of your corrections your article will be published initially within the online version of the journal.

# PLEASE AIM TO RETURN YOUR CORRECTIONS WITHIN 48 HOURS OF RECEIPT OF YOUR PROOF, THIS WILL ENSURE THAT THERE ARE NO UNNECESSARY DELAYS IN THE PUBLICATION OF YOUR ARTICLE

## □ READ PROOFS CAREFULLY

## ONCE PUBLISHED ONLINE OR IN PRINT IT IS NOT POSSIBLE TO MAKE ANY FURTHER CORRECTIONS TO YOUR ARTICLE

- This will be your only chance to correct your proof
- Please note that the volume and page numbers shown on the proofs are for position only
- ANSWER ALL QUERIES ON PROOFS (Queries are attached as the last page of your proof.)
  - List all corrections and send back via e-mail to the production contact as detailed in the covering e-mail, or mark all corrections directly on the proofs and send the scanned copy via e-mail. Please do not send corrections by fax or post

## □ CHECK FIGURES AND TABLES CAREFULLY

- Check size, numbering, and orientation of figures
- All images in the PDF are downsampled (reduced to lower resolution and file size) to facilitate Internet delivery. These images will appear at higher resolution and sharpness in the printed article
- Review figure legends to ensure that they are complete
- Check all tables. Review layout, title, and footnotes

## **COMPLETE COPYRIGHT TRANSFER AGREEMENT (CTA) if you have not already signed one**

Please send a scanned signed copy with your proofs by e-mail. Your article cannot be published unless we have received the signed CTA

## □ OFFPRINTS

 Free access to the final PDF offprint or your article will be available via Author Services only. Please therefore sign up for Author Services if you would like to access your article PDF offprint and enjoy the many other benefits the service offers.

#### Additional reprint and journal issue purchases

- Should you wish to purchase additional copies of your article, please click on the link and follow the instructions provided: <u>http://offprint.cosprinters.com/cos/bw/</u>
- Corresponding authors are invited to inform their co-authors of the reprint options available.
- Please note that regardless of the form in which they are acquired, reprints should not be
  resold, nor further disseminated in electronic form, nor deployed in part or in whole in any
  marketing, promotional or educational contexts without authorization from Wiley. Permissions
  requests should be directed to mailto: permissionsuk@wiley.com
- For information about 'Pay-Per-View and Article Select' click on the following link: <u>http://www3.interscience.wiley.com/aboutus/ppv-articleselect.html</u>

# Cost-effectiveness of traditional and endovenous treatments for varicose veins

# M. S. Gohel<sup>1</sup>, D. M. Epstein<sup>2</sup> and A. H. Davies<sup>1</sup>

<sup>1</sup>Imperial Vascular Unit, Charing Cross Hospital, London, and <sup>2</sup>Centre for Health Economics, University of York, York, UK *Correspondence to:* Professor A. H. Davies, Imperial Vascular Unit, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK (e-mail: a.h.davies@imperial.ac.uk)

**Background:** The aim of this study was to evaluate the cost-effectiveness of traditional and endovenous treatments for patients with primary great saphenous varicose veins.

Methods: A Markov model was constructed to compare costs and quality-adjusted life years (QALYs) for great saphenous vein (GSV) reflux. Eight popular treatment strategies were compared up to 5 years. Estimates for the effectiveness of treatments were obtained from published randomized studies and cost values were obtained from published National Health Service (NHS) healthcare resource group tariffs and device manufacturers. Parameter uncertainty was tested using sensitivity analysis and Monte Carlo simulation.

**Results:** Ultrasound-guided foam sclerotherapy (UGFS) had the lowest initial cost, but a higher requirement for further interventions. Day-case surgery (with concomitant treatment of varicosities), endovenous laser ablation (EVLA) and radiofrequency ablation (RFA) performed in an outpatient or office setting (with staged treatment of varicosities) were likely to be cost-effective treatment strategies. The incremental cost-effectiveness ratio (ICER) for UGFS (*versus* conservative care), EVLA (*versus* UGFS) and RFA (*versus* EVLA) were £1366, £5799 and £17350 per QALY respectively. The ICER for traditional surgery (performed on a day-case basis) was £19012 compared with RFA. Other strategies were not cost-effective using the NHS threshold of £20000 per QALY.

**Conclusion:** Day-case surgery or endovenous ablation using EVLA or RFA performed as an outpatient are likely to be cost-effective treatment strategies for patients with primary unilateral GSV reflux requiring treatment.

Presented in part to annual meetings of the Vascular Society of Great Britain and Ireland, Bournemouth, UK, November 2008, and the European Venous Forum, Copenhagen, Denmark, June 2009, and published in abstract form as *Br J Surg* 2009; **96**(Suppl 1): 14 and *Phlebology* 2009; **24**: 235 respectively

Paper accepted 14 July 2010

Published online in Wiley Online Library (www.bjs.co.uk). DOI: 10.1002/bjs.7256

# **1** Introduction

2 Varicose veins affect approximately 25 per cent of the 3 adult population, and complications arising from them 4 are a significant cause of patient morbidity and health 5 service expense<sup>1,2</sup>. The treatment of patients with 6 superficial venous reflux has changed in recent years 7 following the widespread acceptance of minimally invasive, 8 9 endovenous modalities including ultrasound-guided foam 10 sclerotherapy (UGFS)<sup>3</sup>, radiofrequency ablation (RFA)<sup>4</sup> 11 and endovenous laser ablation (EVLA)<sup>5</sup>. Although long-12 term outcomes for endovenous therapies are awaited, 13 clear technical, clinical and quality-of-life benefits have

14 been reported consistently for these new techniques<sup>6</sup>. 15 Although few randomized trials have shown superiority over traditional surgery, patient acceptance of endovenous 16 17 therapies is likely to be greater than for ligation and 18 stripping operations<sup>7</sup>. With a wide range of available 19 treatments and few comparative studies, treatment choices 20 are currently made on the basis of local availability 21 and clinician preference, rather than clinical evidence. 22 Moreover, the impression that endovenous, particularly 23 endothermal, therapies may be more expensive than 24 traditional treatments (because of costs of consumable 25 items) has limited their implementation in some National 26 Health Service (NHS) settings.

1 The identification and use of cost-effective therapies 2 is desirable in all areas of healthcare, but of particular 3 relevance in the treatment of varicose veins. The debate 4 over which patients should be offered treatment for 5 varicose veins is ongoing and patients without skin changes 6 or ulceration may not qualify for treatment within the 7 NHS. These issues are pertinent in the current economic 8 climate where health budgets are likely to be under 9 considerable scrutiny for many years to come. Large 10 numbers of studies have evaluated technical and clinical 11 outcomes following endovenous interventions, but few 12 have assessed health economic outcomes, or the cost-13 effectiveness of these treatments. A greater understanding 14 of the costs of varicose vein treatment strategies may help to 15 guide service provision and improve consistency in clinical 16 practice when considered in conjunction with clinical and 17 patient-reported outcomes. The aim of this study was to 18 evaluate and compare the cost-effectiveness of traditional 19 and endovenous treatments for patients with primary great 20 saphenous varicose veins. 21

# 23 Methods

22

35

# <sup>24</sup><sub>25</sub> Model design and assumptions

26 The analysis was performed from the perspective of the 27 NHS, and the management of symptomatic patients with 28 primary unilateral great saphenous vein (GSV) reflux was 29 considered. A Markov model was constructed to compare 30 costs and quality-adjusted life years (QALYs) for eight 31 popular treatment strategies (Table 1). Details of the model 32 design are shown in Fig. 1; the time horizon of the model 33 was 5 years. 34

36 Table 1 Popular treatment strategies for great saphenous varicose
 37 veins evaluated in the decision model

38 39	Strategy	Treatment modality	Location	Type of anaesthesia
40 41	А	Traditional GSV surgery	Inpatient	General
42 43	В	Traditional GSV surgery	Day case	General
44	C D	UGFS	Office-based Office-based	Local Local/tumescent
45	E	EVLA	Day case	General
46	F	RFA	Office-based	Local/tumescent
47	G	RFA	Day case	General
48 49	Н	No surgery (conservative care)	Primary care	None

50 GSV, great saphenous vein; UGFS, ultrasound-guided foam

51 sclerotherapy; EVLA, endovenous laser ablation; RFA, radiofrequency
 52 ablation.

© 2010 British Journal of Surgery Society Ltd Published by John Wiley & Sons Ltd

#### M. S. Gohel, D. M. Epstein and A. H. Davies

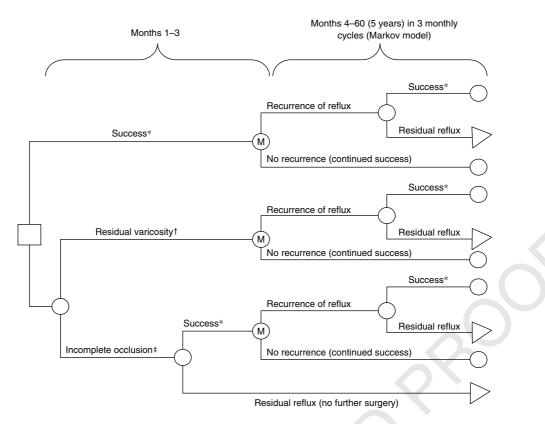
The structure of the model is illustrated in Fig. 1 for 53 the first two intervals (each of 3 months). By 3 months 54 55 after surgery, one of three outcomes is possible: (1) the initial intervention is considered successful if the GSV is 56 fully occluded and the patient has no residual varicosities; 57 58 (2) the GSV vein may be completely occluded but there 59 remain residual varicosities; and (3) there is residual reflux or incomplete occlusion of the GSV vein (with 60 or without varicosities). Patients with residual varicosities 61 62 after initial treatment (with a successfully occluded GSV) 63 were assumed to require at least one treatment of adjuvant 64 foam sclerotherapy in an office or outpatient setting (with 65 1 in 3 patients requiring a second treatment). All patients 66 with residual or recurrent GSV reflux after initial treatment 67 were treated with one repeat GSV intervention (specific 68 to that treatment strategy). This was assumed to have the 69 same success rate in treating GSV reflux as the primary 70 intervention. All patients treated under general anaesthetic 71 (GA) were treated with concomitant phlebectomy, with 72 the aim of removing varicosities. Patients who were 73 successfully treated at 3 months might develop recurrent 74 GSV reflux (and require a repeat GSV intervention) during 75 any subsequent interval. Recurrence of varicosities after the 76 first 3 months was not included in the model. 77

# Estimates of the effectiveness of treatments

80 Two recent systematic literature reviews have assessed the 81 effectiveness of varicose vein therapies. In 2009, van den 82 Bos and colleagues<sup>6</sup> estimated the proportion of patients 83 with anatomically successful outcome at 3 months, 1, 3 84 and 5 years after surgical ligation with stripping (Table 2). 85 They considered ultrasound-based outcomes resulting in 86 the obliteration or complete removal of the insufficient vein 87 such as complete occlusion, free of reflux and absence of 88 recurrent varicose vein to be equally successful. From these 89 data, it was estimated that the probability of incomplete 90 occlusion after ligation with stripping was 0.219 (SE 0.020) 91 in the first 3 months and the rate of recurrence of reflux was 92 0.004 (SE 0.003) per 3 months thereafter. In 2008, Luebke 93 and Brunkwall<sup>8</sup> conducted a systematic review and meta-94 analysis of randomized clinical trials (RCTs) to estimate 95 the odds ratios for incomplete occlusion of endovenous 96 laser therapy versus stripping, RFA versus stripping and 97 UGFS versus stripping (Table 3). The present authors 98 reviewed the studies included by Luebke and Brunkwall<sup>8</sup> 99 and excluded those that were not properly randomized 100 comparisons or did not compare these modalities from 101 the present analysis (Table 3). It was assumed that the 102 same odds ratios for occlusion applied to each treatment 103 modality regardless of the location (inpatient, day case 104

www.bjs.co.uk

78



**Fig. 1** Structure of the decision model for the management of patients with primary great saphenous vein (GSV) reflux. <sup>\*</sup>Defined as successful GSV occlusion without varicosities. <sup>†</sup> All patients with residual varicosities offered treatment at 3 months with office-based sessions of ultrasound-guided foam sclerotherapy, assumed to be successful. <sup>‡</sup> All patients with recurrent or residual GSV reflux offered one further treatment, with same probability of success as initial treatment. Squares indicate points where management decisions were made. Circles indicate chance events (M, Markov node). Triangles indicate absorbing states (patients remained in this state until the model ended)

# 1 Table 2 Probability of great saphenous vein occlusion after

#### 2 surgical ligation with stripping

3 4 5	Reference	Time after surgery	Probability of GSV occlusion*
6 7 8 9	van den Bos <i>et al</i> . <sup>6</sup> (meta-analysis)	3 months 1 year 3 years 5 years	0.80 (0.72, 0.87) 0.80 (0.72, 0.86) 0.78 (0.70, 0.84) 0.76 (0.68, 0.82)
9			

10 \*After one treatment with occlusion as defined by individual authors in11 published studies. GSV, great saphenous vein.

12 13

or office-based; *Table 1*). A further literature review was
undertaken to identify RCTs that compared sequential
with concomitant phlebectomy (*Table 4*). Meta-analyses
were carried out using STATA<sup>®</sup> 10 (StataCorp, College
Station, Texas, USA). The risks of incomplete occlusion
and of residual varicosities are unlikely to be independent.

The correlation between these outcomes was estimated by20the authors to be 0.40 (range 0.20-0.80). Probabilities of21complete treatment success and each of the other outcomes22were calculated using the method described by Rodgers and23co-workers<sup>23</sup>. The correlation coefficient was varied in the24sensitivity analysis.2526

# Costs

Costs were estimated from NHS healthcare resource group 29 (HRG) reference costs 2008-2009<sup>24</sup>, supplemented by 30 additional information from device manufacturers and 31 published list prices for the latest available laser and 32 radiofrequency devices (excluding potential discounts) 33 (Table 5). The mean NHS cost of a day-case primary 34 varicose vein procedure was £980 and that of an inpatient 35 primary varicose vein procedure was £1583, which was 36 assumed to correspond to the cost of ligation with stripping 37 under GA. Although HRG tariffs represent a mean cost 38

27

		Incomplete occlusion	
Reference	Stripping*	Ablation or sclerotherapy*	Pooled odds ratio
Stripping versus EVLA†			0.97 (0.21, 4.43)
de Medieros and Luccas <sup>9</sup> ‡	1 of 20	0 of 20	<b>x</b>
Rasmussen <i>et al</i> . <sup>10</sup> §	2 of 49	3 of 51	
Stripping versus RFA			0.84 (0.37, 1.93)
Hinchliffe et al. <sup>11</sup> ‡	2 of 16	3 of 16	
Lurie et al. <sup>12</sup> §	8 of 36	6 of 44	
Perälä <i>et al</i> .¹³¶	3 of 13	5 of 15	
Rautio <i>et al</i> . <sup>14</sup> ¶	1 of 13	0 of 15	
Stotter et al. <sup>15</sup> ¶	0 of 20	0 of 20	
Stripping versus UGFS#			3.01 (1.55, 5.85)
Wright <i>et al</i> . <sup>16</sup> ¶	13 of 94	58 of 178 (UGFS)	

Table 3 Odds ratio of incomplete occlusion for stripping versus ablation or sclerotherapy

Values in parentheses are 95 per cent confidence intervals. \*Number with event of the total number randomized and available at follow-up. †Belcaro et al.<sup>17,18</sup> were excluded from the evidence synthesis because they used ligation without stripping as the comparator surgery; Lurie et al.<sup>19</sup> was excluded as the same patients were used in Lurie et al.<sup>12</sup>; Kianifard et al.<sup>20</sup> was excluded because it was a non-randomized study (patients in the intervention group were compared pairwise with an age- and sex-matched control group). ‡Included only patients with bilateral great saphenous vein (GSV) reflux; each patient was operated on using both the intervention and control, one on each leg, using a lottery to make the choice. §Included unilateral and bilateral GSV interventions; over 85 per cent of patients had unilateral GSV reflux; the unit of analysis was the leg. Included only unilateral GSV interventions. #Bountouroglou et al.<sup>21</sup> was excluded because the study compared ultrasound-guided foam sclerotherapy (UGFS) with saphenofemoral ligation versus surgery with ligation and stripping. EVLA, endovenous laser ablation; RFA, radiofrequency ablation.

1 Table 4 Odds ratio of residual varicosity requiring reintervention 2 for sequential versus concomitant phlebectomy

2				
3				
4		Reinte	ervention for resi	dual varicosity
5	Reference	Sequential*	Concomitant*	Pooled odds ratio
6 7	Carradice et al.22†	16 of 24	1 of 25	48.00 (5.50, 422.00)

8 Values in parentheses are 95 per cent confidence intervals. \*Number with 9 event of the total number randomized and available at follow-up.

†Included only unilateral great saphenous vein interventions. 10

11 12 over several kinds of varicose vein procedure, these values 13 corresponded fairly closely to day-case and inpatient 14 costs of surgery estimated by other published UK-based 15 studies<sup>21,25</sup>, taking account of inflation. The additional 16 costs of RFA and EVLA under GA included the use of the 17 generator, a catheter, plus the staff and equipment costs of 18 using ultrasonography. It was assumed that the costs of RFA 19 and EVLA under local anaesthetic comprised an outpatient 20 attendance (£154) plus the use of the generator, catheter 21 and ultrasound machine, as above. The cost of UGFS 22 was the cost of a vascular surgery outpatient attendance, 23 plus the use of sclerosant and ultrasonography. It was 24 assumed that the cost of conservative care to the NHS was 25 negligible, without the option of future surgery $^{25}$ .

26

#### 27 Health-related quality of life 28

29 Health-related quality of life (HRQOL) was measured 30 using the EQ-5D index, where a value of 1 represented full health and 0 a health state that the general population consider to be equivalent to death<sup>26</sup>. In a previous randomized study, the estimated HRQOL using the EQ-5D<sup>TM</sup> (EuroQol Group, Rotterdam, The Netherlands) was 0.77 (SE 0.02) before traditional varicose vein surgery and 0.87 (SE 0.02) 1 year after surgery, with little change in a comparator group that had conservative care<sup>27</sup>. It was assumed that patients with residual varicosities and incomplete occlusion had the HRQOL of patients before surgery during the time in which the condition was unresolved. Traditional surgery tends to have a longer and more painful recovery than other treatments<sup>10,14</sup>. Based on the results from these studies for •Short Form 36 bodily pain, a diminution of HRQOL of 0.1 was assumed for 2 weeks after traditional surgery.

31

32

33

34

35

36 37

38

39

40

41

42

43

44

45

46

47

48

# **Cost-effectiveness analysis**

The decision model was constructed in Microsoft® 49 50 Excel (Microsoft Corporation, Mountain View, California, USA). The uncertainty in the mean value of each 51 parameter was represented using a probability distribution 52 and the model was analysed by running 1000 Monte 53 Carlo simulations<sup>28</sup>. The results were presented in two 54 ways. First, mean costs and QALYs over 5 years for the 55 56 eight strategies were reported and their cost-effectiveness 57 was compared, estimating incremental cost-effectiveness ratios (ICERs) using standard decision rules<sup>29</sup>. Briefly, the 58 alternative strategies were ranked by mean cost. Strategies 59 that were more costly than another but offered no greater 60

#### Table 5 Cost items used in model

Cost item	Details	Cost per patient (£)*	Source	Comments
Traditional surgery	Unilateral (inpatient)†	1583 (1172–1922)	NHS costs <sup>10</sup>	
	Unilateral (day case)	980 (706–1196)	NHS costs <sup>10</sup>	
Catheter	EVLA	395	List prices‡	Biolitec AG, Jena, Germany
	RFA	495	List prices‡	VNUS ClosureFAST <sup>™</sup> (VNUS <sup>™</sup>
				Medical Technologies, San Jose,
				California, USA)
Generator	EVLA‡	111	List prices‡	Biolitec 980-nm laser; acquisition cost
	554	22		
	RFA‡	89	List prices‡	VNUS <sup>™</sup> Medical Technologies; acquisition cost £7995
Ultrasonography		38	NHS costs <sup>10</sup>	Mobile intraoperative ultrasonography
Outpatient attendance	First attendance	154 (115–168)	NHS costs <sup>10</sup>	Consultant-led multiprofessional clinic
Sclerosant	Fibro-Vein <sup>™</sup> 3%	10	List prices§	105-ml vials, £102.65

\*Values are mean (interquartile range); mean cost per patient was calculated using an annuity formula for the economic cost of depreciation of capital, assuming an asset life of 5 years, 20 patients per year and a discount rate of 3.5 per cent per year. †One overnight stay assumed. ‡Manufacturer's list prices for 2008–2009; §STD Pharmaceutical Products, Hereford, UK, May 2010. NHS, National Health Service; EVLA, endovenous laser ablation; RFA, radiofrequency ablation.

1 expected benefit were known as 'dominated' and excluded. 2 Strategies that were dominated by a linear combination 3 of other strategies were considered subject to 'extended 4 domination' and were also excluded. ICERs were then 5 calculated for each of the remaining strategies, compared 6 with the next best alternative. The strategy with the lowest 7 ICER may not be the most cost effective. Conventionally 8 in the UK, a strategy is likely to be considered cost 9 effective if the ICER is less than £20000 per QALY, 10 and unlikely to be considered cost effective oif the ICER is more than £30000 per QALY<sup>30</sup>. Costs and QALYs 11 12 were discounted by 3.5 per cent per year<sup>30</sup>. Second, the 13 decision uncertainty was shown as the probability that 14 each intervention was the most cost effective for a given 15 cost-effectiveness threshold<sup>28</sup>. 16

#### 17 18 **Results**

AQ4

# <sup>19</sup> Clinical effectiveness

The results of the pooled meta-analyses of the odds ratios 21 for occlusion from nine RCTs identified by Luebke and 22 Brunkwall<sup>8</sup> are shown in *Tables 3* and *4*. Compared with 23 surgical ligation with stripping, incomplete occlusion tends 24 to be more likely with UGFS, and tends to be less 25 likely with RFA and EVLA, although only the results 26 27 for UGFS were significant at the 5 per cent level. The RCTs reported results at different intervals of follow-28 29 up, from 1 week to 2 years, but the data suggested that the odds ratios for incomplete occlusion did not differ 30 during follow-up. One RCT was identified that reported 31 relative risks of reintervention for residual varicosities 32

© 2010 British Journal of Surgery Society Ltd Published by John Wiley & Sons Ltd after concomitant versus sequential phlebectomy (Table 4). 33 Sequential phlebectomy was associated with higher 34 rates of secondary intervention<sup>22</sup>. The estimated mean 35 36 probabilities for each of the outcomes 3 months after treatment are shown in Table 6. These estimates changed 37 only slightly in response to different assumptions about the 38 correlation between occlusion and residual varicosity after 39 treatment. 40

#### **Cost-effectiveness**

The initial cost of surgery, cost of reinterventions, total44costs, QALYs and ICERs for each strategy are shown in45Table 7. UGFS has the lowest initial cost, but this was partly46offset by the costs of reintervention for recurrent reflux and47residual or recurrent varicosities over 5 years. Relative to48

 
 Table 6 Estimated probabilities for outcomes at 3 months after treatment

Treatment	Complete occlusion with residual varicosity	Incomplete occlusion (with or without varicosity)	Success (complete occlusion without varicosity)
Surgery (GA)	0.04	0.19	0.77
EVLA (LA)	0.22	0.18	0.60
EVLA (GA)	0.04	0.18	0.77
RFA (LA)	0.22	0.16	0.62
RFA (GA)	0.04	0.16	0.79
UGFS (LA)	0.38	0.47	0.16

GA, general anaesthetic; EVLA, endovenous laser ablation; LA, local anaesthetic; RFA, radiofrequency ablation; UGFS, ultrasound-guided foam sclerotherapy.

www.bjs.co.uk

41

42

43

49

50

51

62

63

Treatment	Cost of initial surgery (£)	Reinterventions for residual varicosity at 3 months (£)	Reinterventions for GSV reflux over 5 years (£)	Total cost over 5 years (£)	QALYs over 5 years	Incremental cost (£)	Incremental QALY	ICER per QALY	Probability that treatment is cost-effective at threshold of £20 000 per QALY
Conservative	0	0	0	0	3.522	_	_	_	< 0.01
UGFS (LA)	202	101	125	429	3.836	429	0.314	1366	0.10
EVLA (LA)	698	161	173	1031	3.940	602	0.104	5799	0.35
RFA (LA)	776	166	168	1110	3.944	78	0.005	17 350	0.24
Surgery (DC)	980	12	251	1242	3.951	133	0.007	19012	0.29
EVLA (GA)	1524	12	380	1915	3.954	_	_	ED	0.01
RFA (GA)	1602	12	351	1964	3.958	722	0.007	100451	< 0.01
Surgery (IP)	1583	12	405	2000	3.951	_	_	D	0.00

Table 7 Results of cost-effectiveness analysis

GSV, great saphenous vein; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; UGFS, ultrasound-guided foam sclerotherapy; LA, local anaesthetic; EVLA, endovenous laser ablation; RFA, radiofrequency ablation; DC, day case; GA, general anaesthetic; ED, extendedly dominated; IP, inpatient; D, dominated.

1 conservative care (if no alternative treatment was available),

2 all treatments were cost effective. However, in order to
3 identify the most cost-effective strategy (using the National
4 Institute for Health and Clinical Excellence cost-per5 QALY threshold), the aim of this study was to perform
6 an incremental cost-effectiveness analysis, assuming that
7 all treatments were feasible strategies.

8 UGFS had an ICER of about £1400 per QALY relative 9 to conservative care. EVLA (local anaesthetic, LA) had 10 an ICER of about £5800 per QALY relative to UGFS. 11 RFA (LA) had an ICER of £17350 per QALY relative to 12 EVLA (LA), and the ICER for day-case surgery versus RFA 13 (LA) was about £19000 per QALY. The ICER for RFA 14 (GA) versus day-case surgery was more than £100 000 per 15 QALY. Other treatments were dominated or extendedly 16 dominated, and not cost effective on average at any cost-17 per-QALY threshold.

18 Fig. 2 shows that there is considerable uncertainty 19 surrounding these results. At a threshold of £20000 per 20 QALY, the probability that EVLA (LA) was cost effective 21 was 0.35, the probability for RFA (LA) was 0.24, and that 22 for day-case surgery 0.29; the probabilities that the other 23 treatments were cost effective were very low. Univariable 24 sensitivity analyses were performed on plausible values 25 of the uncertain parameters, including the costs of the 26 alternatives and their relative effectiveness in terms of GSV 27 reflux and residual varicosities. Results were substantially 28 changed compared with the base case in four of these 29 scenarios. 30

First, if the probability of occlusion of the GSV 3 months after UGFS was the same as that for surgery (odds ratios of 1.00), then UGFS was cost effective, with an ICER of about £1000 per QALY *versus* conservative care, and other treatments were not cost effective.

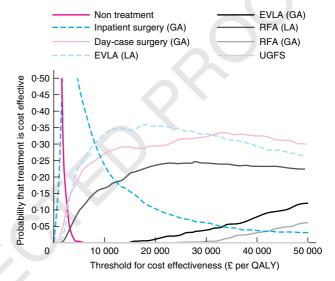


Fig. 2 Probability• that each treatment is cost effective for different threshold costs per quality-adjusted life year (QALY). GA, general anaesthetic; EVLA, endovenous laser ablation; LA, local anaesthetic; RFA, radiofrequency ablation; UGFS, ultrasound-guided foam sclerotherapy

Second, if the odds ratio of a reintervention for 36 residual varicose vein after sequential *versus* concomitant 37 phlebotomy was 5.50 (the lower value of the 95 per cent 38 confidence interval of the odds ratio), then UGFS, RFA 39 (LA) and EVLA (LA) were approximately equally likely 40 to be cost effective and day-case surgery was dominated 41 (fewer QALYs and greater cost). 42 Third, if the cost of day-case surgery was £700, then 43

Third, if the cost of day-case surgery was £700, then day-case surgery was the most cost-effective strategy, with an ICER of about £4000 per QALY *versus* UGFS.

www.bjs.co.uk

British Journal of Surgery 2010; 97: 00-00

49 50

48

44

45

46 47 AQ5

© 2010 British Journal of Surgery Society Ltd

- 50 51
- 52 53 54

Fourth, if the cost of day-case surgery was £1200, the
 ICER for surgery increased to £58000 per QALY, and
 UGFS, RFA (LA) and EVLA (LA) were about equally
 likely to be cost effective.

### 5 6

# 7

# <sup>7</sup> Discussion

9 This study suggested that either RFA or EVLA, performed 10 under local/tumescent anaesthesia in an outpatient or office-based setting, or day-case traditional GSV surgery 11 12 were likely to be cost-effective strategies for the treatment 13 of primary GSV reflux at a conventional threshold for a cost 14 per QALY in the UK. Interestingly, despite the perceived 15 high costs of EVLA and RFA, both of these treatments 16 were likely to be as cost effective as traditional GSV surgery 17 when performed in an office-based setting, with staged 18 foam sclerotherapy for residual varicosities. Both EVLA 19 and RFA are promoted as being ideal for office-based 20 ambulatory procedures and a recent survey<sup>31</sup> showed that 21 the majority of venous specialists offer endovenous ablation 22 procedures using only local or tumescent anaesthesia. In 23 published randomized studies, RFA and EVLA had similar 24 rates of occlusion compared with traditional surgery, and 25 the initial cost savings were only partly offset by higher 26 costs of reinterventions for residual varicosities. In this 27 model, the presence of residual or recurrent varicosities 28 had only a modest impact on HRQOL, as it was assumed 29 that reinterventions for varicosities after the initial surgery 30 were undertaken promptly and successfully in outpatient 31 clinics. Concomitant phlebectomy may be performed 32 under local/tumescent anaesthesia<sup>22</sup> and, although this 33 specific treatment strategy was not evaluated in the present 34 study, it would seem logical to assume that even greater 35 economic advantages may be present with this approach. 36

UGFS was the least expensive initial cost, but this 37 advantage was partly offset by high expected rates 38 of reintervention at 3 months for residual reflux or 39 varicosities, with a corresponding loss in HRQOL for 40 the patient, and cost to the health service. Although the 41 ICER was lowest, at less than £1400 per QALY, other 42 treatments may offer greater expected benefits for the 43 additional cost and may be considered better value for 44 money. Consequently, in the base-case analysis UGFS had 45 a low probability of being cost effective. This conclusion 46 was based on the results of a single RCT<sup>16</sup> which showed 47 that foam sclerotherapy was less effective in occluding the 48 49 GSV than surgery; UGFS would be cost effective if the strategies were equally effective for this outcome. Potential 50 cerebral and other complications of UGFS have received 51 considerable recent publicity<sup>32,33</sup>, although the cost or 52

quality-of-life impact of these were not considered in the 53 present model. 54

55 Unilateral endothermal ablation may also be performed under GA, allowing additional phlebectomies for promi-56 nent varicosities. However, the additional costs of laser 57 58 or radiofrequency consumables mean that this approach is 59 probably more expensive than traditional venous surgery. 60 Although the model found that endothermal ablation under 61 GA was not cost effective on average, some patients may be 62 best treated with unilateral GSV intervention under GA, 63 particularly when multiple venous segments require abla-64 tion, there are large numbers of superficial varicosities or 65 the patient is averse to treatment under LA. Although indi-66 vidual practice varies between venous specialists, bilateral 67 endothermal ablation under LA alone is not commonly 68 performed. As both legs may be treated at the same 69 time (including phlebectomy for varicosities) and the costs 70 of multiple treatment visits may be avoided, the cost-71 effectiveness of superficial venous interventions under GA 72 may be greatest in patients who need bilateral surgery 73 or ablation of multiple venous segments. In view of the 74 lack of published studies, the cost-effectiveness of bilateral 75 treatment was not modelled in the present study. 76

It should be recognized that economic modelling has 77 limitations arising from the assumptions required and 78 uncertainty in the data. Although eight commonly offered 79 treatment strategies for GSV reflux were assessed in this 80 model, others may be used. Moreover, as the published 81 studies used numerous different laser and radiofrequency 82 devices, with different definitions of treatment success, 83 there was considerable heterogeneity in the data combined 84 to generate the probability estimates. This model did not 85 consider the recurrence of varicosities beyond 3 months, 86 but did take account of recurrent GSV reflux. Recurrent 87 varicosities alone (without GSV reflux, excluding de novo 88 small saphenous vein reflux) are uncommon, and would 89 be unlikely to affect the conclusions of this analysis. The 90 unit cost data may not be representative, particularly as 91 many institutions may have negotiated reduced consumable 92 prices with device manufacturers. However, reductions in 93 the costs of EVLA and RFA consumables will further 94 increase the cost-effectiveness of these interventions. This 95 model made inferences only about the relative effectiveness 96 of treatments based on RCT evidence<sup>30</sup>, addressing the 97 major methodological weakness of other comparative 98 reviews<sup>6,8</sup>. However, there is a lack of large RCTs 99 comparing traditional and endovenous interventions. 100 The available RCTs have compared EVLA or UGFS 101 or RFA with traditional surgery, requiring indirect 102 comparisons between the treatments<sup>34</sup>. A large Health 103 Technology Assessment-funded multicentre randomized 104

#### M. S. Gohel, D. M. Epstein and A. H. Davies

study comparing traditional surgery, EVLA and foam 2 sclerotherapy (Comparison of LAser, Surgery and foam 3 Sclerotherapy, CLASS study)<sup>35</sup> is currently recruiting, and 4 may help to address some of these deficiencies.

The cost-effectiveness of varicose vein surgery varies widely, depending on the choice of treatment and location. Despite initial concerns about the expense of EVLA and RFA treatments, these interventions are likely to be cost effective at the conventional threshold of the cost per QALY in the UK when offered as an outpatient procedure. Day-case surgery is also likely to be cost effective. There is greater uncertainty about UGFS and further comparative trials are needed. Inpatient surgery and endothermal ablation performed under GA are unlikely to be cost effective for treating unilateral primary GSV reflux except in specific circumstances.

## **Acknowledgements**

This study was funded by a European Venous Forum pump priming grant. The authors declare no conflict of interest.

# References

- 1 Callam MJ. Epidemiology of varicose veins. Br 7 Surg 1994; 81: 167-173.
- 2 Evans CJ, Allan PL, Lee AJ, Bradbury AW, Ruckley CV, Fowkes FG. Prevalence of venous reflux in the general population on duplex scanning: the Edinburgh vein study. J Vasc Surg 1998; 28: 767-776.
- 3 Jia X, Mowatt G, Burr JM, Cassar K, Cook J, Fraser C. Systematic review of foam sclerotherapy for varicose veins. Br J Surg 2007; 94: 925-936.
- 4 Gohel MS, Davies AH. Radiofrequency ablation for uncomplicated varicose veins. Phlebology 2009; 24(Suppl 1): 42-49.
- 5 Darwood RJ, Gough MJ. Endovenous laser treatment for uncomplicated varicose veins. Phlebology 2009; 24(Suppl 1): 50 - 61.
- 6 van den Bos R, Arends L, Kockaert M, Neumann M, Nijsten T. Endovenous therapies of lower extremity varicosities: a meta-analysis. J Vasc Surg 2009; 49: 230-239.
- 7 Shepherd AC, Gohel MS, Lim CS, Hamish M, Davies AH. The treatment of varicose veins: an investigation of patient preferences and expectations. Phlebology 2009; 25: 54-65.
- 8 Luebke T, Brunkwall J. Systematic review and meta-analysis of endovenous radiofrequency obliteration, endovenous laser therapy, and foam sclerotherapy for primary varicosis. 7 Cardiovasc Surg (Torino) 2008; 49: 213-233.
- 9 de Medeiros CA, Luccas GC. Comparison of endovenous treatment with an 810 nm laser versus conventional stripping of the great saphenous vein in patients with primary varicose
- veins. Dermatol Surg 2005; 31: 1685-1694.

© 2010 British Journal of Surgery Society Ltd

Published by John Wiley & Sons Ltd

10	Rasmussen LH, Bjoern L, Lawaetz M, Blemings A, Lawaetz B, Eklof B. Randomized trial comparing	53 54
	endovenous laser ablation of the great saphenous vein with high ligation and stripping in patients with varicose veins:	55 56
	short-term results. <i>J Vasc Surg</i> 2007; <b>46</b> : 308–315.	57
11	Hinchliffe RJ, Ubhi J, Beech A, Ellison J, Braithwaite BD. A	58
	prospective randomised controlled trial of VNUS closure	59
	<i>versus</i> surgery for the treatment of recurrent long saphenous varicose veins. <i>Eur J Vasc Endovasc Surg</i> 2006; <b>31</b> :	60
	212–218.	61
12	Lurie F, Creton D, Eklof B, Kabnick LS, Kistner RL,	62
	Pichot O et al. Prospective randomised study of endovenous	63
	radiofrequency obliteration (closure) versus ligation and vein	64
	stripping (EVOLVeS): two-year follow-up. <i>Eur J Vasc</i>	65
13	Endovasc Surg 2005; <b>29</b> : 67–73. Perälä J, Rautio T, Biancari F, Ohtonen P, Wiik H,	66 67
15	Heikkinen T <i>et al.</i> Radiofrequency endovenous obliteration	67 68
	versus stripping of the long saphenous vein in the	69
	management of primary varicose veins: 3-year outcome of a	70
	randomized study. Ann Vasc Surg 2005; 19: 669-672.	71
14	Rautio T, Ohinmaa A, Perälä J, Ohtonen P, Heikkinen T,	72
	Wiik H <i>et al.</i> Endovenous obliteration <i>versus</i> conventional stripping operation in the treatment of primary varicose	73
	veins: a randomized controlled trial with comparison of the	74
	costs. <i>J Vasc Surg</i> 2002; <b>35</b> : 958–965.	75
15	Stötter L, Schaaf I, Bockelbrink A. Comparative outcomes of	76
	radiofrequency endoluminal ablation, invagination stripping,	77
	and cryostripping in the treatment of great saphenous vein	78
16	insufficiency. <i>Phlebology</i> 2006; <b>21</b> : 60–64. Wright D, Gobin JP, Bradbury AW, Coleridge-Smith P,	79
10	Spoelstra H, Berridge D <i>et al.</i> Varisolve <sup>®</sup> polidocanol	80 81
	microfoam compared with surgery or sclerotherapy in the	82
	management of varicose veins in the presence of trunk vein	83
	incompetence: European randomized controlled trial.	84
17	<i>Phlebology</i> 2006; <b>21</b> : 180–190. Belcaro G, Nicolaides AN, Ricci A, Dugall M, Errichi BM,	85
17	Vasdekis S <i>et al.</i> Endovascular sclerotherapy, surgery, and	86
	surgery plus sclerotherapy in superficial venous	87
	incompetence: a randomized, 10-year follow-up trial – final	88
	results. Angiology 2000; 51: 529-534.	89
18	Belcaro G, Cesarone MR, Di Renzo A, Brandolini R,	90
	Coen L, Acerbi G <i>et al.</i> Foam-sclerotherapy, surgery, sclerotherapy, and combined treatment for varicose veins: a	91
	10-year, prospective, randomized, controlled, trial (VEDICO	92 93
	trial). Angiology 2003; <b>54</b> : 307–315.	93 94
19	Lurie F, Creton D, Eklof B, Kabnick LS, Kistner RL,	95
	Pichot O et al. Prospective randomized study of endovenous	96
	radiofrequency obliteration (closure procedure) versus	97
	ligation and stripping in a selected patient population (EVOLVeS Study). <i>J Vasc Surg</i> 2003; <b>38</b> : 207–214.	98
20	Kianifard B, Holdstock JM, Whiteley MS. Radiofrequency	99
	ablation (VNUS closure) does not cause neo-vascularisation	100
	at the groin at one year: results of a case-controlled study.	101
2.	8 ,	102
21		103
	TOUND T, GETOWARDS G. OTHASOUND-BUILDED TOAM	104

www.bjs.co.uk

British Journal of Surgery 2010; 97: 00-00

1

#### Cost-effectiveness of traditional and endovenous therapy

sclerotherapy combined with sapheno-femoral ligation
compared with surgical treatment of varicose veins: early
results of a randomised controlled trial. <i>Eur J Vasc Endovasc</i>
Surg 2006; <b>31</b> : 93–100.

- 22 Carradice D, Mekako AI, Hatfield J, Chetter IC. Randomized clinical trial of concomitant or sequential phlebectomy after endovenous laser therapy for varicose veins. Br 7 Surg 2009; 96: 369-375.
- 23 Rodgers M, Epstein D, Bojke L, Yang H, Craig D, Fonseca T et al. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess 2010 (in; press).
- 24 Department of Health. NHS Reference Costs, 2007-08. Department of Health: London, 2009.
- 25 Ratcliffe J, Brazier JE, Campbell WB, Palfreyman S, 15 MacIntyre JB, Michaels JA. Cost-effectiveness analysis of 16 surgery versus conservative treatment for uncomplicated 17 varicose veins in a randomized clinical trial. Br J Surg 2006; 18 93: 182-186. 19
  - 26 Szende A, Oppe M, Devlin N (eds). EQ-5D Value Sets: Inventory, Comparative Review and User Guide Series. EuroQol Group Monographs. Springer: London, 2007.
- 22 27 Michaels JA, Campbell WB, Brazier JE, Macintyre JB, 23 Palfreyman SJ, Ratcliffe J et al. Randomised clinical trial, 24 observational study and assessment of cost-effectiveness of 25 the treatment of varicose veins (REACTIV trial). Health 26 Technol Assess 2006; 10: 1-196, iii-iv.

9

53

54

<ol> <li>Spiegelhalter DJ, Abrams K, Myles JP. Bayesian Approaches Clinical Trials and Health Care Evaluation.: John Wiley: Chichester, 2004.</li> <li>Johannesson M, Weinstein M. On the decision rules of cost-effectiveness analysis. 7 Health Econ 1993; 12: 459–46</li> </ol>	29 30 31 34. 32 33
<ul><li>Clinical Trials and Health Care Evaluation.: John Wiley: Chichester, 2004.</li><li>29 Johannesson M, Weinstein M. On the decision rules of</li></ul>	29 30 31 34. 32 33
29 Johannesson M, Weinstein M. On the decision rules of	30 31 64. 32 33
-	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$
cost-effectiveness analysis. 7 Health Econ 1993; 12: 459-46	$   \begin{array}{cccc}             34. & 32 \\             32. & 33 \\             3. & 33   \end{array} $
	33
30 National Institute for Health and Clinical Excellence	֥
(NICE). Guide to the Methods of Technology Appraisal. NICE	
London, 2008.	25
31 Shepherd AC, Gohel MS, Hamish M, Lim CS, Davies AH	1.
Endovenous treatments for varicose veins – over-taking or	. 36
over-rated? Phlebology 25: 38-43.	37
32 Ceulen RP, Sommer A, Vernooy K. Microembolism durin	
foam sclerotherapy of varicose veins. N Engl J Med 2008;	39
<b>358</b> : 1525–1526.	40
33 Bush RG, Derrick M, Manjoney D. Major neurological	41
events following foam sclerotherapy. <i>Phlebology</i> 2008; 23:	42
189–192.	43
34 Song F, Altman DG, Glenny AM, Deeks JJ. Validity of	44
indirect comparison for estimating efficacy of competing	45
interventions: empirical evidence from published	46
meta-analyses. <i>BMJ</i> 2003; <b>326</b> : 472. 35 National Institute for Health Research Health Technology	. 47
Assessment programme. Randomised controlled trial	<sup>y</sup> 48
comparing foam sclerotherapy, alone or in combination wi	ith 49
endovenous laser therapy, with conventional surgery as a	50
treatment for varicose veins. ISRCTN 51995477.	51
http://www.hta.ac.uk/project/1728.asp [accessed	52
10 August 2010].	53

## Commentary

# Cost-effectiveness of traditional and endovenous treatments for varicose veins (Br J Surg 2010; ??: ????-???)

This investigation of the costs of varicose vein treatments is a very useful analysis of the factors that contribute to the hospital costs of treatment. It is clear that saphenous stripping and phlebectomies is one of the more expensive options, with no clear advantages as far as the long-term outcome is concerned. This study did not include the potential societal costs of treatment for varicose veins - only the costs of treatment and benefit to health were analysed. The different treatments may lead to greatly differing times away from work, especially when comparing the most and least invasive treatments. Absence from work in the range of 1-4 weeks following surgical treatment has been reported in several studies, whereas minimally invasive treatments usually lead to absence from work of a few days. Failure to consider such costs does not fully reflect the advantage of less invasive treatments.

AQ1

AQ2

5

6

7

8

9

10

11

12

13

14

20

21

27

The authors acknowledge that many of the crucial parameters in their model have wide ranges reported in published literature. They have analysed the effect of using a range of values. This results in substantially different conclusions being reached depending upon the initial assumptions. Thus, •it all hinges on the reliability of the information in Table 6, where each treatment strategy is compared concerning its 3-month outcome. In fact, all the data are very similar except for that for ultrasound-guided foam sclerotherapy (UGFS). So why is the outcome here so poor? The authors have referred to the paper by Wright and colleagues<sup>1</sup>, which is one of few randomized controlled trials comparing UGFS with surgery. In fact, the data used by the authors (•UGFS 68 per cent, surgery 87 per cent success rate at 3 months) represent only half

#### M. S. Gohel, D. M. Epstein and A. H. Davies

of the study – that performed by surgeons. When sclerotherapists performed the foam sclerotherapy (in the same study) they obtained 94 per cent occlusion with foam and 88 per cent with liquid at 3 months. Data from clinical series published recently by Coleridge Smith<sup>2</sup> and Darvall and co-workers<sup>3</sup> showed 12-month occlusion of saphenous trunks and freedom from varices in 90-95 per cent of cases. The authors have therefore been inadvertently disingenuous about the outcome of foam sclerotherapy. Surgeons naive to the methods of UGFS may have poor results, but skilled practitioners can equal or exceed the reported outcomes of surgery, laser and radiofrequency ablation. I would recommend assuming that all treatments achieve the same clinical success rate, thus substantially modifying the existing conclusions in this paper. P. Coleridge Smith AQ •Department of Surgery, UCL Medical School, The Middlesex Hospital, Mortimer Street, London W1N 8AA, UK (e-mail: p.coleridgesmith@ucl.ac.uk) DOI: 10.1002/bjs.7281 References 1 Wright D, Gobin JP, Bradbury AW, Coleridge-Smith P, Spoelstra H, Berridge D. Varisolve® polidocanol microfoam compared with surgery or sclerotherapy in the management of varicose veins in the presence of trunk vein incompetence: European randomized controlled trial. Phlebology 2006; 21: 180-190. 2 Coleridge Smith P. Chronic venous disease treated by ultrasound guided foam sclerotherapy. Eur J Vasc Endovasc Surg 2006; 32: 577-583. 3 Darvall KA, Bate GR, Silverman SH, Adam DJ, Bradbury AW. Medium-term results of ultrasound-guided foam sclerotherapy for small saphenous varicose veins. Br 7 Surg 2009; 96: 1268-1273. 

© 2010 British Journal of Surgery Society Ltd Published by John Wiley & Sons Ltd

# QUERIES TO BE ANSWERED BY AUTHOR

IMPORTANT NOTE: Please mark your corrections and answers to these queries directly onto the proof at the relevant place. Do NOT mark your corrections on this query sheet.

7 8	Queries from the Copyeditor:
9	AQ1 By "Thus, it all hinges.", do you mean: "Thus, the validity of the conclusions depends upon the reliability of the information"?
10	AQ2 These data (UGFS 68 per cent, surgery 87 per cent success rate at 3 months) do not appear to be given in the
11 12	paper by Gohel et al. Please check with data in the proof (?Table 6).
13 14	AQ3 Proofreader: As the author was unable to tell from the original papers which version of SF-36 had been used, I have just used the full version without the name of the "manufacturer" (Alex).
15	AQ4 Should this be " if the ICER is more than $\pounds 20000$ per QALY <sup>30</sup> "?
16	AQ5 For <i>Fig. 2</i> , please check carefully on the proof that the curves have been shown correctly with respect to the key.
17 18	AQ6 Please check that this correspondence address, as amended, is correct.
19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	
37	
38 39	
40	
41	
42	
43	
44 45	
45 46	
47	
48	
49	
50	
51	



# WILEY AUTHOR DISCOUNT CLUB

We would like to show our appreciation to you, a highly valued contributor to Wiley's publications, by offering a **unique 25% discount** off the published price of any of our books\*.

All you need to do is apply for the **Wiley Author Discount Card** by completing the attached form and returning it to us at the following address:

The Database Group (Author Club) John Wiley & Sons Ltd The Atrium Southern Gate Chichester PO19 8SQ UK

Alternatively, you can **register online** at <u>www.wileyeurope.com/go/authordiscount</u> Please pass on details of this offer to any co-authors or fellow contributors.

After registering you will receive your Wiley Author Discount Card with a special promotion code, which you will need to quote whenever you order books direct from us.

The quickest way to order your books from us is via our European website at:

# http://www.wileyeurope.com

Key benefits to using the site and ordering online include:

- Real-time SECURE on-line ordering
- Easy catalogue browsing
- Dedicated Author resource centre
- Opportunity to sign up for subject-orientated e-mail alerts

Alternatively, you can order direct through Customer Services at: <u>cs-books@wiley.co.uk</u>, or call +44 (0)1243 843294, fax +44 (0)1243 843303

So take advantage of this great offer and return your completed form today.

Yours sincerely,

Verity Leaver Group Marketing Manager <u>author@wiley.co.uk</u>

#### **\*TERMS AND CONDITIONS**

This offer is exclusive to Wiley Authors, Editors, Contributors and Editorial Board Members in acquiring books for their personal use. There must be no resale through any channel. The offer is subject to stock availability and cannot be applied retrospectively. This entitlement cannot be used in conjunction with any other special offer. Wiley reserves the right to amend the terms of the offer at any time.



# **REGISTRATION FORM** For Wiley Author Club Discount Card

To enjoy your 25% discount, tell us your areas of interest and you will receive relevant catalogues or leaflets from which to select your books. Please indicate your specific subject areas below.

Accounting • Public	[]	Architecture	[]
<ul><li>Corporate</li></ul>	[]	Business/Management	[]
<ul> <li>Chemistry</li> <li>Analytical</li> <li>Industrial/Safety</li> <li>Organic</li> <li>Inorganic</li> <li>Polymer</li> <li>Spectroscopy</li> </ul>	[ ] [ ] [ ] [ ] [ ] [ ]	<ul> <li>Computer Science</li> <li>Database/Data Warehouse</li> <li>Internet Business</li> <li>Networking</li> <li>Programming/Software Development</li> <li>Object Technology</li> </ul>	
<ul> <li>Encyclopedia/Reference</li> <li>Business/Finance</li> <li>Life Sciences</li> <li>Medical Sciences</li> <li>Physical Sciences</li> <li>Technology</li> </ul>	[ ] [ ] [ ] [ ] [ ]	<ul> <li>Engineering</li> <li>Civil</li> <li>Communications Technology</li> <li>Electronic</li> <li>Environmental</li> <li>Industrial</li> <li>Mechanical</li> </ul>	
Earth & Environmental Science Hospitality	[]	<ul> <li>Finance/Investing</li> <li>Economics</li> <li>Institutional</li> <li>Personal Finance</li> </ul>	[ ] [ ] [ ] [ ]
<ul> <li>Genetics</li> <li>Bioinformatics/ Computational Biology</li> <li>Proteomics</li> <li>Genomics</li> <li>Gene Mapping</li> <li>Clinical Genetics</li> </ul>		Life Science Landscape Architecture Mathematics Statistics Manufacturing Materials Science	[] [] [] []
<ul> <li>Medical Science</li> <li>Cardiovascular</li> <li>Diabetes</li> <li>Endocrinology</li> <li>Imaging</li> <li>Obstetrics/Gynaecology</li> <li>Oncology</li> <li>Pharmacology</li> <li>Psychiatry</li> </ul> Non-Profit		<ul> <li>Psychology</li> <li>Clinical</li> <li>Forensic</li> <li>Social &amp; Personality</li> <li>Health &amp; Sport</li> <li>Cognitive</li> <li>Organizational</li> <li>Developmental &amp; Special Ed</li> <li>Child Welfare</li> <li>Self-Help</li> </ul> Physics/Physical Science	
	[]	riysics/ riysical Science	[]

Please complete the next page /



I confirm that I am (\*delete where not applicable):

a **Wiley** Book Author/Editor/Contributor\* of the following book(s): ISBN:

ICRN	I٠	
TODIN		

a **Wiley** Journal Editor/Contributor/Editorial Board Member\* of the following journal(s):

SIGNATURE:	Date:
SIGNATORE:	

# PLEASE COMPLETE THE FOLLOWING DETAILS IN BLOCK CAPITALS:

TITLE: (e.g. Mr, Mrs, Dr) FULL NAME:
JOB TITLE (or Occupation):
DEPARTMENT:
COMPANY/INSTITUTION:
ADDRESS:
TOWN/CITY:
COUNTY/STATE:
COUNTRY:
POSTCODE/ZIP CODE:
DAYTIME TEL:
FAX:
E-MAIL:

## YOUR PERSONAL DATA

We, John Wiley & Sons Ltd, will use the information you have provided to fulfil your request. In addition, we would like to:

- Use your information to keep you informed by post of titles and offers of interest to you and available from us or other Wiley Group companies worldwide, and may supply your details to members of the Wiley Group for this purpose.
   Please tick the box if you do **NOT** wish to receive this information
- 2. Share your information with other carefully selected companies so that they may contact you by post with details of titles and offers that may be of interest to you.
  - [] Please tick the box if you do **NOT** wish to receive this information.

#### **E-MAIL ALERTING SERVICE**

We also offer an alerting service to our author base via e-mail, with regular special offers and competitions. If you **DO** wish to receive these, please opt in by ticking the box [].

If, at any time, you wish to stop receiving information, please contact the Database Group (<u>databasegroup@wiley.co.uk</u>) at John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, PO19 8SQ, UK.

#### **TERMS & CONDITIONS**

This offer is exclusive to Wiley Authors, Editors, Contributors and Editorial Board Members in acquiring books for their personal use. There should be no resale through any channel. The offer is subject to stock availability and may not be applied retrospectively. This entitlement cannot be used in conjunction with any other special offer. Wiley reserves the right to vary the terms of the offer at any time.

## PLEASE RETURN THIS FORM TO:

Database Group (Author Club), John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, PO19 8SQ, UK <u>author@wiley.co.uk</u> Fax: +44 (0)1243 770154