

# Multicentre randomised study of computerised anticoagulant dosage

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## Summary

**Background** The demand for anticoagulant treatment is increasing. We compared the benefits of computer-generated anticoagulant dosing with traditional dosing decided by experienced medical staff in achieving target international normalised ratios (INRs).

**Methods** In five European centres we randomly assigned 285 patients in the stabilisation period and stabilised patients to the computer-generated-dose group (n=137) or traditional-dose group (n=148). Centres had a specialist interest in oral anticoagulation but no previous experience with computer-generated dosing. The computer program calculated doses and times to next visit. Our main endpoint was time spent in target INR range (Rosendaal method).

**Findings** For all patients combined, computer-generated dosing was significantly beneficial overall in achieving target INR ( $p=0.004$ ). The mean time within target INR range for all patients and all ranges was 63.3% (SD 28.0) of days in the computer-generated-dose group compared with 53.2% (27.7) in the traditional-dose group. For the stabilisation patients alone, computer-generated doses led to a non-significant benefit in all INR ranges ( $p=0.06$ ), whereas in the stable patients the benefit was significant ( $p=0.02$ ).

**Interpretation** The computer program gave better INR control than the experienced medical staff and at least similar standards to the specialised centres should be generally available. Clinical outcome and cost effectiveness remain to be assessed.

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## Introduction

A worldwide increase in oral anticoagulant treatment has followed studies showing the value of these drugs in a wide range of clinical disorders.<sup>1</sup> Improved benefit/risk ratio has resulted from lower doses, pioneered in the UK and the Netherlands, and with the introduction of WHO's international normalised ratio (INR) system of laboratory control. The INR is the prothrombin-time ratio that would have been obtained if the WHO international first primary reference thromboplastin (67/40 human combined) had been used to perform the test on the blood sample with the traditional technique.

With the increase in demand for oral anticoagulant treatment, medical, technical, nursing, and administrative staff in hospitals and clinics in many countries are being overwhelmed, and devolution of management to community-based control is becoming more common. Baglin<sup>2</sup> has calculated that if all patients in the UK were to attend hospital anticoagulant clinics, the current number of such clinics would need to increase by five to ten times.

One possible way of maintaining the present standards achieved in specialist centres is by computerisation of the anticoagulant dosing. Good results from computer programs designed to generate doses have been claimed<sup>3-5</sup> but not confirmed by randomised studies. Our previous small single-centre randomised study showed that computer-generated dosing achieved INR targets similar to experienced medical staff.<sup>6</sup> In the present study, the European Concerted Action on Anticoagulation (ECAA) did a multicentre randomised assessment of the safety and efficacy of computer-generated anticoagulant doses in patients at different stages of anticoagulant administration. Multicentre studies enable assessment of more patients and give more reliable comparisons between doses generated by computer and medical staff or individual centres, since success in INR control by traditional dose decisions made by medical staff varies from centre to centre and may not be representative.

## Methods

### Study design

We selected study centres on recommendations from ECAA national directors. The centres were interested in introducing a computerised anticoagulant dosing system, but none had previously used such a program. Participating centres had to have sufficient numbers of patients to guarantee adequate recruitment during the study. The five centres selected were the Royal Infirmary, Manchester, UK; St Bartholomew's Hospital, London, UK; Aker Sykehus Hospital, Oslo, Norway; Centralsygehuset, Esbjerg, Denmark; and Centro Hospitalar, V N Gaia, Portugal.

The computer program, DAWN AC anticoagulant therapy management system (version 407), was used in parallel with the traditional dose decisions made by experienced medical staff at each centre.

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Results	
<b>Computer-dose group (n=27)</b>	
Number of INRs	40
Proportion of time in target range	42%
Mean time between visits (days)	7
Proportion dose changes	55%
Proportion traditional interventions	35%
Proportion low INRs	28%
Proportion high INRs	38%
Mean INR	3.0
<b>Traditional-dose group</b>	
Number of INRs	195
Proportion time in target range	45%
Mean time between visits (days)	7
Proportion dose changes	65%
Proportion traditional interventions	0
Proportion low INRs	36%
Proportion high INRs	28%
Mean INR	2.7

Table 1: Results of first 3 weeks' treatment for stabilisation patients in computer-dose and traditional-dose group

The program has two main modules—the induction module for starting warfarin therapy over the first 4 days to reach a dose within 1 mg of eventual maintenance dose, and the maintenance module (version 4 only was used) for finely tuning the dose to the therapeutic range and sustaining it.

This software calculates whether a dose adjustment is necessary from a user-defined table of trend rules for each therapeutic range, the current INR result, and a set number of INR and dose history. All user-defined tables were defined before the start of trial and could not be changed.

If the program recommends a change to the dose, the current INR measurement is compared to the set target INR for therapeutic range, and the difference and a simple empirical proprietary equation are used to create a new dose.

The time to the next test is calculated from a user-defined table of variables, the current INR value, and the interval between the last two tests. Other variables such as the number of previous non-changes to the dosage or the number of previous INRs within target range were not used.

Before the start of the study, we trained computer operators for each study centre for 1 day at the ECAA Central Facility in Manchester, UK.

We obtained approval from the local ethics committees for each centre before the start of the study, and informed consent from each patient before randomisation.

### Patients

We recruited as many patients as possible for the stabilisation group. These patients had been discharged from hospital within 6 weeks of the start of anticoagulation. A minimum of 6 days

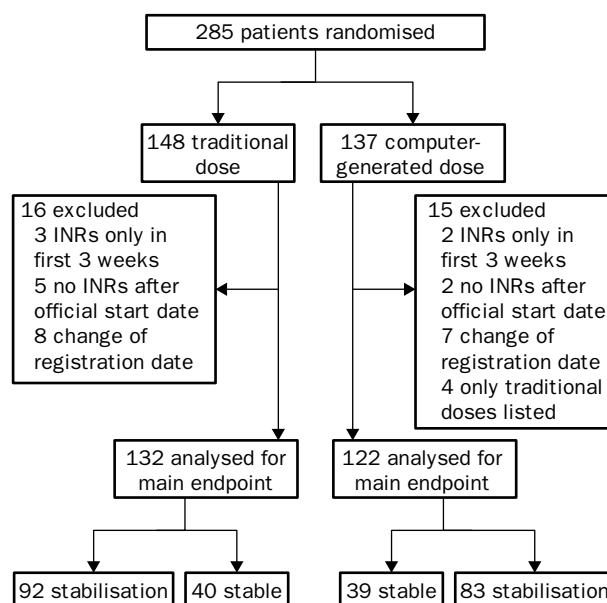


Figure 1: Trial profile

after starting on warfarin or alternative drug was required as a safety measure to ensure that the patient had achieved close to their maintenance dose. The DAWN AC maintenance module requires for safety reasons at least two previous doses to be entered to show stability. For some patients already on warfarin some doctors still require these two doses to judge the maintenance dose, and they can be administered during the first 2–3 weeks of therapy. During this period, the software records these as traditional doses and computer calculation is done. Since none of the centres had previous experience of computer doses, we left the date of entry into the study and the acceptance of the computer-generated doses and instructions to the discretion of the participating centre to win the confidence of the medical staff. Follow-up of at least 3 months for each patient from entry into the study was required.

In the second group we enrolled patients already stabilised on long-term anticoagulant therapy. Nearly all had received a minimum of 22 weeks' anticoagulation.

### Randomisation

All patients were given a study number and randomly assigned to receive traditional doses or computer-generated doses. Randomisation was done according to computer-generated order at each centre. Each new patient was given an appointment for first attendance within 1 week of discharge from hospital. After

	Stabilisation						Stable					
	Centre 1	Centre 2	Centre 3	Centre 4	Centre 5	All sites	Centre 1	Centre 2	Centre 3	Centre 4	Centre 5	All sites
<b>Computer-dose group</b>												
Number of patients	5	46	8	2	22	83	..	6	17	14	2	39
Number of INRs	19	327	50	12	211	619	..	26	120	149	19	314
Proportion time in range	81%	60%	82%	71%	71%	68%	..	80%	75%	73%	45%	72%
Mean time between visits (days)	31	13	27	15	19	17	..	21	24	16	25	20
Proportion dose changes	26%	39%	22%	25%	46%	39%	..	19%	30%	38%	74%	36%
Proportion traditional interventions	0	16%	10%	17%	40%	23%	..	8%	8%	28%	68%	21%
Proportion low INRs	32%	31%	18%	25%	28%	29%	..	31%	22%	24%	37%	25%
Proportion high INRs	11%	17%	6%	0	13%	14%	..	8%	17%	19%	37%	18%
Mean INR	2.5	2.7	2.6	2.3	2.5	2.6	..	3.1	2.8	2.6	2.9	2.7
<b>Traditional-dose group</b>												
Number of patients	10	47	10	3	22	92	..	10	15	13	2	40
Number of INRs	80	306	71	41	195	693	..	71	152	145	19	387
Proportion time in range	48%	58%	69%	44%	49%	55%	..	58%	70%	45%	26%	59%
Mean time between visits (days)	17	13	21	14	20	16	..	27	22	10	20	18
Proportion dose changes	44%	54%	49%	45%	71%	57%	..	44%	46%	45%	58%	46%
Proportion traditional interventions	0	0	0	0	0	0	..	0	0	0	0	0
Proportion low INRs	43%	33%	25%	37%	42%	36%	..	18%	20%	39%	32%	27%
Proportion high INRs	10%	16%	7%	20%	21%	16%	..	27%	16%	16%	47%	19%
Mean INR	2.2	2.8	2.4	2.3	2.5	2.6	..	3.2	2.7	2.4	2.9	2.7

Table 2: Results from study centres for computer-dose and traditional-dose groups

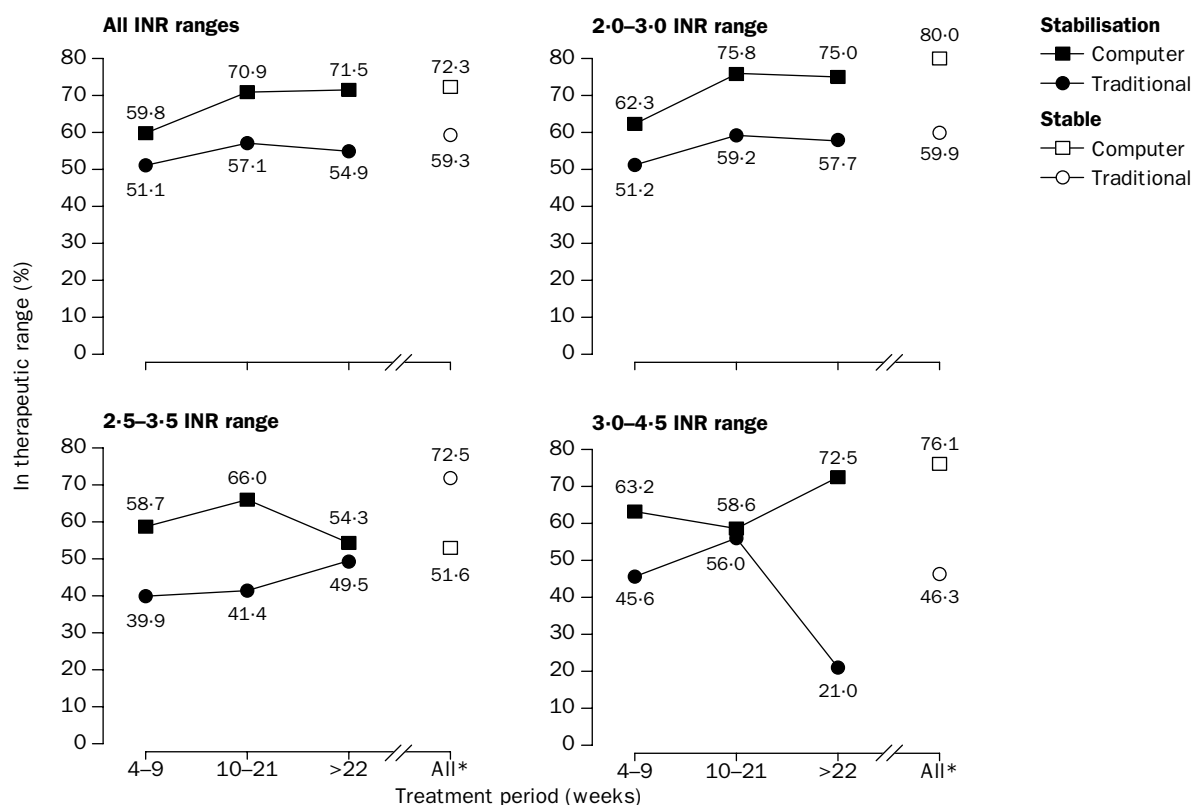


Figure 2: Proportion time in INR ranges

\*INR results for all weeks, including first 3 weeks.

being counselled about the aims and objectives of long-term anticoagulation treatment, patients were informed of the study design and invited to take part. Patients were assured that computer-generated doses would be monitored by medical staff, who would continue to be responsible for their treatment.

To ensure true randomisation and that the trial was prospective, we deleted all doses and INR entries before Nov 30, 1996, the official start date of the study. Entry to the study was staggered because of training and practice in the use of the computer program. We agreed a fixed start date so that the study could be carried out simultaneously in all centres and that it was not unnecessarily long. We took into account only INRs entered after registration. Any changes in the demographic data that are normally part of anticoagulant records, such as name, address, age, sex, clinical information, and current medication, resulted in a change in the registration date. To ensure that the trial was prospective and sites had not added data retrospectively, the registration date for each patient was checked. We excluded patients whose registration date had been changed.

We did not compare computer-generated and traditional doses for the first 3 weeks since we found that 79% of doses for this period in the computer group were decided by medical staff (table 1). The proportion was high partly because of the two priming doses required by the computer and partly because of an apparent initial lack of confidence in the computer program. By weeks 4-9, 81% of patients in the computer group had received computer-generated doses. We took this period to be the first 6 weeks of comparison. Any traditional doses recorded after the first 3 weeks in this group were excluded. We also compared doses for a second period of 12 weeks from weeks 10 to 21 and for a third period from week 22 onwards. We chose week 22 onwards because most of the stabilised patients had been on warfarin for the whole of this period.

Patients randomised to the traditional-dose group were reviewed in the normal way by the doctor who supervised doses. For patients in the computer-generated-dose group, laboratory INR values were entered on to the computer. The computer calculated the dose of oral anticoagulant and time to next visit. The computer-generated instructions were reviewed at each

centre by an experienced doctor before being passed to the patient. If either instruction was thought to be potentially harmful, a second opinion from another member of the medical staff was sought. In cases of overanticoagulation, treatment was stopped for the advised number of days. We chose a maximum upper limit of 6 weeks between visits. At each visit for patients in the computer-generated-dose group we recorded the INR and whether or not it was within the target range, the suggested dose, the recommended time between visits, any alteration to computer-generated instructions and any clinical events. We also recorded the proportion of time patients were within the target therapeutic dose range<sup>7</sup> and proportion of INRs lower and higher than the target range (underanticoagulated and overanticoagulated).

The INR target ranges were decided by the individual centre, based on one of: the guidelines on oral anticoagulation of the British Society of Haematology,<sup>8</sup> the Leuven Group,<sup>9</sup> and the ACCP Consensus. Three different ranges of INR resulted; 2.0-3.0, 3.0-4.5, and 2.5-3.5.<sup>1</sup>

We planned that the study would be of 6 months' duration, with a minimum of 3 months' follow-up for each patient. At each centre, the maximum recruitment number was 100 patients.

Although most experience with computerised programs has been for warfarin, other oral anticoagulant drugs, such as acenocoumarol could be accommodated on the Dawn program. Different dose instructions, such as tablets per day, mg per week, or once or twice daily, could be used.

#### Statistical analysis

We analysed results by site, traditional or computer-generated dose, and whether patients were stabilisation patients or stable. For stabilisation patients, doses were compared for the periods 4-9 weeks, 10-21 weeks, and 22 weeks and beyond. We analysed all patients by all INR ranges (2.0-3.0, 2.5-3.5, and 3.0-4.5) for all sites and by individual range.

The endpoint for all groups and subgroups was proportion of time within target INR range, according to the Rosendaal

	Stabilisation				Stable			Total
	Weeks 4-9	Weeks 10-21	Weeks ≥22	Total	Weeks <22	Weeks ≥22	Total	
<b>Computer-dose group</b>								
Number of patients	60	69	48	83	..	39	39	122
Number of INRs	191	248	174	619	..	314	314	933
Proportion time in range	60%	71%	72%	68%	..	72%	72%	70%
Mean time between visits (days)	13	17	20	17	..	20	20	18
Proportion dose changes	49%	38%	29%	39%	..	36%	36%	38%
Proportion traditional interventions	26%	21%	21%	23%	..	21%	21%	22%
Proportion low INRs	31%	30%	25%	29%	..	25%	25%	28%
Proportion high INRs	16%	13%	13%	11%	..	18%	18%	15%
Mean (SD) INR	2.6 (0.8)	2.5 (0.8)	2.7 (0.9)	2.6 (0.8)	..	2.7 (0.9)	2.7 (0.9)	2.6 (0.9)
<b>Traditional-dose group</b>								
Number of patients	76	79	51	92	2	39	40	132
Number of INRs	220	246	212	693	5	382	387	1080
Proportion time in range	51%	57%	55%	55%	58%	59%	59%	56%
Mean time between visits (days)	14	18	17	16	13	18	18	17
Proportion dose changes	60%	57%	52%	57%	0	47%	46%	53%
Proportion traditional interventions	0	0	0	0	0	0	0	0
Proportion low INRs	37%	37%	33%	36%	60%	27%	27%	33%
Proportion high INRs	12%	17%	19%	16%	0	20%	19%	17%
Mean (SD) INR	2.6 (0.8)	2.7 (1.6)	2.5 (0.7)	2.6 (1.1)	2.6 (0.4)	2.7 (0.9)	2.7 (0.8)	2.6 (1.0)

Patients can be in more than one time period.

Table 3: Results from all ranges, all sites

method.<sup>7</sup> This analysis takes into account the time between tests since the percentage of therapeutic INR results alone may be misleading because tests are done more frequently in unstable patients. We calculated proportion of time in range for all patients in the two dose groups, and tested the significance of the mean of the group's results with the Student's *t* test.

## Results

285 consecutive patients were entered into the study at the five centres. 16 were excluded from the traditional-dose group and 15 from the computer-generated-dose group. 254 patients were analysed (figure 1). Results by dose groups and centres are shown in table 2.

23 (8% of all patients) patients used acenocoumarol. All other patients used warfarin.

In the stabilisation period, the number of INRs was slightly less in the computer group than in the traditional group. The proportion of time in range was, however, higher throughout the study (figure 2). The time between doses was similar in the two groups, but the proportion of dose changes was lower in the computer-dose group. There were fewer low and high INRs in the computer-dose group than in the traditional-dose group despite marginally higher mean INR values in all three treatment periods (table 3). Among the stabilised patients, the number of INRs was also slightly fewer in computer-generated dose group than in the traditional-dose group, but they spent more time within target INR range and had fewer dose changes. For stabilisation and stable patients, more INRs higher and lower than the target range were seen in the traditional-dose group than in the computer-dose group for INR ranges 2.0-3.0 and 3.0-4.5. For INR range 2.5-3.5 the number of INRs in range was higher with computer than traditional dosage in the stabilisation group patients but not in the stable

patients. The number in the stable group was small, however (16 patients in the traditional and ten in the computer group), and the proportions of high and low INRs reflected these differences between stabilisation and stable patients (table 4). The mean INRs were similar in the two groups.

Patients in the computer-generated-dose group spent more time within target INR range than those in the traditional group, which showed a significant benefit when the combined mean results for stabilisation and stable patients were analysed ( $p=0.004$ , table 5). When the dose groups were tested separately, the stabilised patients fared significantly better with computer dosage than with traditional dosage ( $p=0.02$ ) but the benefit in the stabilisation group did not quite achieve significance ( $p=0.06$ ).

The mean proportion of dose changes in the computer-generated-dose group was 22%. In these patients, the magnitude of the change was small, with a mean dose change of 0.34 mg against the mean warfarin dose of 4.4 mg.

The study centres' performances were variable for success in INR control in the two dose groups (range 60-80% computer group, 44-68% traditional group).

## Discussion

Our results for computerised oral anticoagulant doses are encouraging. If the success in achieving target INRs with computerised dosing had been merely similar to that of the experienced medical staff, the results would have made a sufficient case for the use of the computer program. The computer program could be made available to hospitals and community clinics in which nurses, laboratory technicians, and pharmacists are becoming increasingly involved in control of anticoagulant dosage. Our results,

	Proportion low INRs			Proportion high INRs		
	2.0-3.0	2.5-3.5	3.0-4.5	2.0-3.0	2.5-3.5	3.0-4.5
<b>Stabilisation</b>						
Computer dose (n=83)	22.8%	34.5%	35.4%	15.7%	9.1%	9.4%
Traditional dose (n=92)	32.2%	44.3%	44.7%	17.7%	19.7%	10.5%
<b>Stable patients</b>						
Computer dose (n=39)	19.7%	32.2%	42.1%	16.2%	25.3%	5.3%
Traditional dose (n=40)	23.0%	23.3%	46.4%	19.4%	18.3%	7.1%

Table 4: Proportion of INRs lower and higher than target ranges

	Stabilisation			Stable			Both		
	Computer	Traditional	p	Computer	Traditional	p	Computer	Traditional	p
Mean (SD) time in target range days	61.8 (27.1)	54.0 (27.5)	0.06	66.4 (29.9)	51.2 (28.4)	0.02	63.3 (28.0)	53.2 (27.7)	0.004

Table 5: Mean proportion of time in target range

favoured computerised dose control. These results were not attributable to more frequent testing since the times between appointments were similar for the computer-generated-dose and traditional-dose groups. The percentage of dose changes was substantially lower in the computer-dose group than in the traditional-dose group, and a smaller proportion of INRs were higher or lower than the therapeutic range, which are additional measures of safety.

We found in our own earlier single-centre study of three computer programs<sup>6</sup> that results for computer-generated and traditional dosing did not differ significantly, except for in the INR range 3.0–4.5, for which there was a significant benefit in the computer-generated-dose group. A report of an earlier version of the DAWN AC system in a randomised single-centre study showed that among 100 patients the computer and traditional doses gave similar results for target INRs, but there were fewer dose changes for computer-dose patients than traditional-dose patients.<sup>10</sup>

Our present results therefore seem more favourable than those for previous reports, despite the fact that it was not feasible to mask investigators to treatment group, as it was in our previous study. In the present study, the medical staff may have been influenced in their decisions about dose because they thought they were in direct competition with the computer. We will discuss the question of whether the non-masked nature of the study affected the standard of dose decisions in the traditional group in a separate report, in which therapeutic quality control in the traditional-dose group at one of the five centres before and after the start of this will be compared.

The variability of success with traditional dose in achieving target INRs between centres supports the case for multicentre investigations to assess the value of benefit of computerised dose decisions. Nevertheless, success with a computer program depends on the confidence of the medical staff in its use. The lack of confidence or initial reluctance of specialist medical staff to trust the computer dose was shown by the high proportion of traditional dose decisions made in the first 3 weeks after computer dosing began. Confidence increased at the later stages and the rate of intervention decreased, although the overall intervention rate of 22% was much higher than that encountered for staff who have previous experience of computer-assisted dose, which is reported to be about 5%.<sup>11</sup> None of the medical staff in our study had previous experience of computerised doses. In our previous study,<sup>6</sup> a pilot familiarisation study preceded the main investigation and intervention with traditional doses was rarely seen. The medical intervention may, however, have limited the advantages of computerisation.

Databases and computerised dose programs vary, so the success of individual programs must be assessed separately. Some programs exclude many patients or have limited clinical application. Our only criterion for exclusion of patients on clinical grounds was that there

should be a minimum of 6 days' treatment with warfarin before entry into the computer-dose group and not because of clinical disorder or concomitant therapy.

We assumed that improved INR control has implications in clinical outcome. We did not study clinical outcome since we would have needed a much larger database that could not have been justified on ethical grounds before the reliability of INR control was shown.

We did not assess the cost-effectiveness of the DAWN AC program but the introduction of computerised dose could substantially save medical, nursing, and administrative time. With the computerised dose, attention could be concentrated on the few patients who present unusual difficulties for anticoagulant control. In addition, such a program would have administrative advantages including large databases of anticoagulant records, provision of written dose schedules, records of concomitant treatments clinical instructions on duration of therapy, clinic diaries, and support documentation and letters.

#### European Concerted Action on Anticoagulation Advisory Committee

S G Weston-Smith, P Rose, M Gilbert, D Houghton, and S Stewart assisted the ECAA project leader with the planning of the study, and D Houghton advised on the statistical analysis.

#### Contributors

The design, co-ordination and analysis of the study were undertaken from the ECAA Central Facility. L Poller prepared the paper. C R Shiach, P McCallum, A M Johansen, A M Münster, J Jespersen, and A Magalães were responsible for carrying out the study at the individual study centres.

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