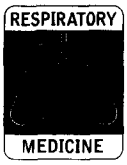
RESPIRATORY MEDICINE (1998) **92**, 467–472



The European Respiratory Society study on chronic obstructive pulmonary disease (EUROSCOP): recruitment methods and strategies

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The European Respiratory Society's study on chronic obstructive pulmonary disease (EUROSCOP) is a multicentre study performed initially in 12 countries to assess the effect of 3 years' treatment with inhaled corticosteroids on lung function decline in smokers with chronic obstructive pulmonary disease (COPD). It aimed at recruiting 50 subjects in 50 European centres. This study discusses the most successful, countrywise, recruitment strategies, an important issue since many multicentre European studies may follow in the future.

The total number of recruited subjects was 2147 in 39 participating centres. In total, at least 25 000 screening spirometries were performed, and about 80 000 hospital records were checked. The most effective way of recruiting subjects was to screen subjects by spirometry after mass media campaigns (eight out of nine countries). Others used workplace screenings and different types of population survey, and only a few centres successfully recruited participants by hospital records.

Inclusion criteria were slightly changed upon low initial accrual rate. Initial surveys in one country, where 2405 subjects were screened by spirometry, gave an important indication for the change of the inclusion criteria. Extension of the upper age limit from 60 to 65 yr considerably improved recruitment, as did a change of the upper limit of FEV_1 from below 80% predicted normal to below 100% predicted normal, while maintaining the FEV_1/VC ratio below 70%.

A tremendous effort is needed to recruit individuals with preclinical COPD, but this is certainly feasible with adequate strategies adjusted to each country.

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Introduction

It has been recognized for years that chronic obstructive pulmonary disease (COPD) has a slow onset and progression (1). Nowadays, COPD is increasingly common and an important cause of death worldwide (2). Especially in the early stages, there may be no symptoms, while airflow limitation may be present. Nevertheless, at this stage it is essential to prevent further deterioration of lung function. One important measure in this respect is to stop smoking, as this is the main cause of airflow limitation in the 15–20% of susceptible smokers (3–7). Cessation of smoking alleviates the rapid decline in lung function in initial and advanced disease (8,9), but the sustained success rate of even the most intensive trial of cessation, the Lung Health Study, is only 22% (9). As many smokers are unable to stop smoking, despite knowledge of the negative effects on their lungs and general health, other measures are necessary to prevent morbidity, mortality and the associated high costs of health care caused by the progressive loss of lung function.

The multicentre European Study on COPD (EUROSCOP), directed by the European Respiratory Society (ERS) was started in order to assess whether anti-inflammatory therapy might improve health in smokers with mild to moderate airway obstruction. The study is based on the hypothesis and circumstantial evidence that inflammation is the main underlying pathophysiological mechanism of COPD (10). Smokers who were not able to stop smoking within 3 months were randomized in a double-blind study to either budesonide (800 μg day^{-1}) or placebo during a 3-year period (9). To attain a sufficient number of participants – 500 randomized subjects per treatment arm – a multicentre study is required.

To date, only a few multicentre long-term studies have been performed in pulmonary medicine. One such

Received 11 June 1997 and accepted 11 June 1997.
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0954-6111/98/030467+06 $12.00/0

multicentre study (The Lung Health study in North America) has published its experiences in designing and conducting the study (11,12). However, as this was performed in only two countries with a common language, the EUROSCOP study is even more complicated in this respect. Twelve countries with different cultural, economic and social backgrounds had to recruit as many participants as possible. As it can be expected that in the future more multinational studies in the respiratory area will take place, especially concerning COPD, we now describe several aspects of the recruitment phase in different countries in Western Europe.

Material and Methods

GENERAL BACKGROUND

The aim of the EUROSCOP study is to investigate the hypothesis that airway inflammation plays an important role in the development of COPD. To test this hypothesis, the effect of 3 years' treatment with an inhaled glucocorticosteroid, budesonide, on the decline of post-bronchodilator FEV_1 in cigarette smokers who, despite cessation of smoking, continued to smoke after 3 months, will be compared to placebo treatment. Budesonide is given in a dose of 400 μg b.i.d via a Turbuhaler (Astra/Draco, Lund, Sweden).

The study is a parallel group, randomized, double-blind, multicentre study. Initially, 12 European countries and 47 centres were involved. The original goal was to recruit 50 subjects per centre.

ENTRY CRITERIA

Final inclusion and exclusion criteria have been presented in an earlier report (10). In summary, participants had to be between 30 and 65 years of age, smoking more than five cigarettes per day at first visit, postbronchodilator FEV_1 had to be between 50 and 100% predicted, prebronchodilator FEV_1/VC <70% reversibility of FEV_1 <10% predicted normal, and variability in FEV_1 between visits two and three <15% predicted normal.

RECRUITMENT PHASE

The EUROSCOP Steering Committee and the EUROSCOP National co-ordinators were responsible for the recruitment phase. They remained in close contact with the centres. National meetings (one to six times per year, varying with country) and international meetings (once per year) were arranged in order to exchange ideas and to keep a good team spirit. Moreover, ideas were exchanged on recruitment strategies in order to keep enrollment high. Newsletters were sent four to six times each year to all participants with new ideas and results on recruitment strategies.

Recruitment strategies were deliberately not dictated before the study, as it was anticipated that the strategies would vary from country to country and from centre to centre.

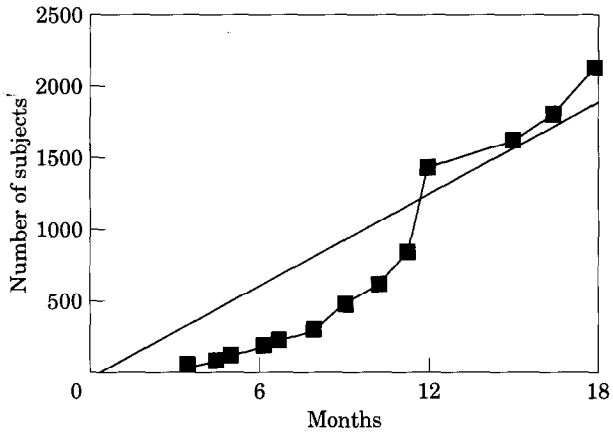

FIG. 1. Total actual recruitment over time in EUROSCOP (solid squares) compared to expected (continuous line) recruitment (50 subjects per centre).

To follow recruitment in the study, continuous reports on the recruitment status of each centre were sent to the monitoring centre, which also kept in contact with Local Monitors and National co-ordinators. The head of the EUROSCOP monitoring centre visited at least one national meeting in all countries, and some of the centres, personally. Moreover, all centres were visited by the supervising lung function co-ordinator of EUROSCOP and at regular intervals by the local monitors.

RECRUITMENT REPORTS

At the end of the recruitment period a questionnaire was sent to every centre on the recruitment methods used in the respective centres; it was answered by 29 of the 39 centres. The recruitment in two countries is presented in more detail. In The Netherlands, all subjects screened for the study were consecutively registered during the first part of the study. In one centre this registration was performed throughout the whole study. These registers have been used in the initial phase of recruitment to help in decision making on the adjustments of entry criteria. In Finland, a special telephone questionnaire was used after advertisements in the newspapers and data from all phone calls were registered.

Results

The original goal of the EUROSCOP study was to enroll a total of 2500 participants in 12 months. Twelve countries started to participate in the EUROSCOP study, and nine countries finally recruited subjects. Figure 1 shows the actual progress of recruitment which ultimately resulted in the enrollment of 2147 participants in 18 months. Thus, 86% of the recruitment goal has been reached in 50% longer time. Centres with a low recruitment rate have been

excluded, and final recruitment numbers range from 16 to 134 per centre.

As is evident from Fig. 1, early recruitment was slow, with an improvement in months 9–12, and a further increase during the prolonged recruitment phase between months 12 and 18. The final number of recruited subjects, 2147, divided by 39 centres, gives a mean which is somewhat higher than the expected 50 participants per centre. However, it did not reach the original goal of 2500 participants during the run-in period. According to the recruitment survey, at least 25 000 screening spirometries have been performed during the recruitment period, and at least 80 000 hospital records have been checked.

It finally appeared that mass media recruitment, including television, radio and newspapers, was the most successful strategy in almost all countries. One exception was Denmark, where most participants were derived from hospital clinics. The following recruitment strategies were applied:

1. *Mass media campaign.* This was the most efficient way of attracting participants to the study (see below for different countries).
2. *Workplace screening.* In Germany, workplace screening did not give the expected number of applicants for the study. In Newcastle it worked well, where spirometry was performed in smokers in a social security setting in collaboration with the health authorities. Screening took place over lunch time, and lunch was provided for all attenders. Thus, absenteeism from work was no problem.
3. *Shopping mall.* This was not effective in early trials in the Nottingham centre. It took screening of 809 individuals to select eight eligible participants, and occupied staff time in a very inefficient way.
4. *Hospital records.* Many centres started to screen their hospital records, but in most hospitals it became evident that very few subjects could be found this way as the desired study population most probably had not developed symptoms which were severe enough to cause them to contact their general practitioner.

COUNTRIES WITH RECRUITMENT FAILURE

Three countries dropped out for different reasons. In one country, approval of the medical ethics committee came late, far beyond approval in other countries, and despite local and national mass media campaigns the response was very low. In a second country, recruitment was started at post offices, where screening was carried out on all attendants, not only smokers. This huge amount of work finally resulted in only a small number of individuals who were both eligible and consented to participate. Finally, in a third country local organization was not optimal for successful recruitment, and factory-related recruitment did not work out as expected.

RECRUITMENT IN REMAINING COUNTRIES

Figure 2 shows the recruitment in the nine countries finally continuing in the study.

In Belgium, the four centres had a very slow start, and during month 10 an extensive mass media campaign started, preceded by the organization of the centres to take immediate care of the subjects who wanted to be screened in the study. A good response was seen in a short time.

In Denmark, where three centres had very good registers of spirometries performed in the hospitals, subjects fulfilling the spirometric entry criteria were contacted. In one centre, where 300 were called for spirometry check-up, 100 subjects showed up and 50 subjects were recruited. This recruitment was started early, and the rate of inclusion was relatively stable throughout the inclusion period.

In Finland, early recruitment from hospital records was very slow, and after 11 months it was decided at a National meeting to start an advertisement campaign to recruit subjects. There was an immediate response with very high recruitment during one month. Most patients were interviewed on the telephone, using a simple questionnaire. Figure 3 shows the result of 1534 telephone interviews, 365 individuals being excluded on telephone, not fitting into criteria for inclusion. Of the 988 who were immediately given an appointment for spirometry, 82% showed up, and of these 172 fulfilled all inclusion criteria. Thus, 21% of the performed spirometric tests were within the limits for inclusion.

The centres in Italy showed a slow recruitment rate, in spite of using various ways to recruit subjects. Mass media campaigns of different kinds were tried with varying results. However, in one centre 400 subjects were screened by spirometry after a newspaper advertisement campaign, and 43 were included.

Centres in The Netherlands had an early start trying to recruit from hospital records and by posters – for example, in hospitals. Soon they started to use newspaper advertisements, with increasing success. The data are presented separately below as they were also used in the evaluation of the inclusion criteria, and the changes made during the study.

In Norway, different methods were used. Some centres working in occupational medicine checked their earlier records as well as performing new spirometry screening among the staff.

In Spain there was a slow onset, due partly to the delay in approval by the ethical committee. Some centres used advertisements with about 10% inclusion of performed spirometries. In one centre, the screening of 5000 hospital records showed 300 subjects fulfilling inclusion criteria, of which 150 came for spirometry and 35 were included.

In Sweden, subjects were recruited mainly by means of two methods. Newspaper advertisements were used in some centres with very good and rapid response in inclusion rate. Subjects were also recruited from a population study in the Northern part of the country.

In the United Kingdom, the very early efforts, for example, in a shopping mall, were very disappointing. Contacts with general practitioners with computerized lists of patients were effective in one centre. Some 16 900 mailshots were sent to patients, with 5000 answers. A total of 456 patients were screened, and 21 entered the study. Screening in a working place was effective in one

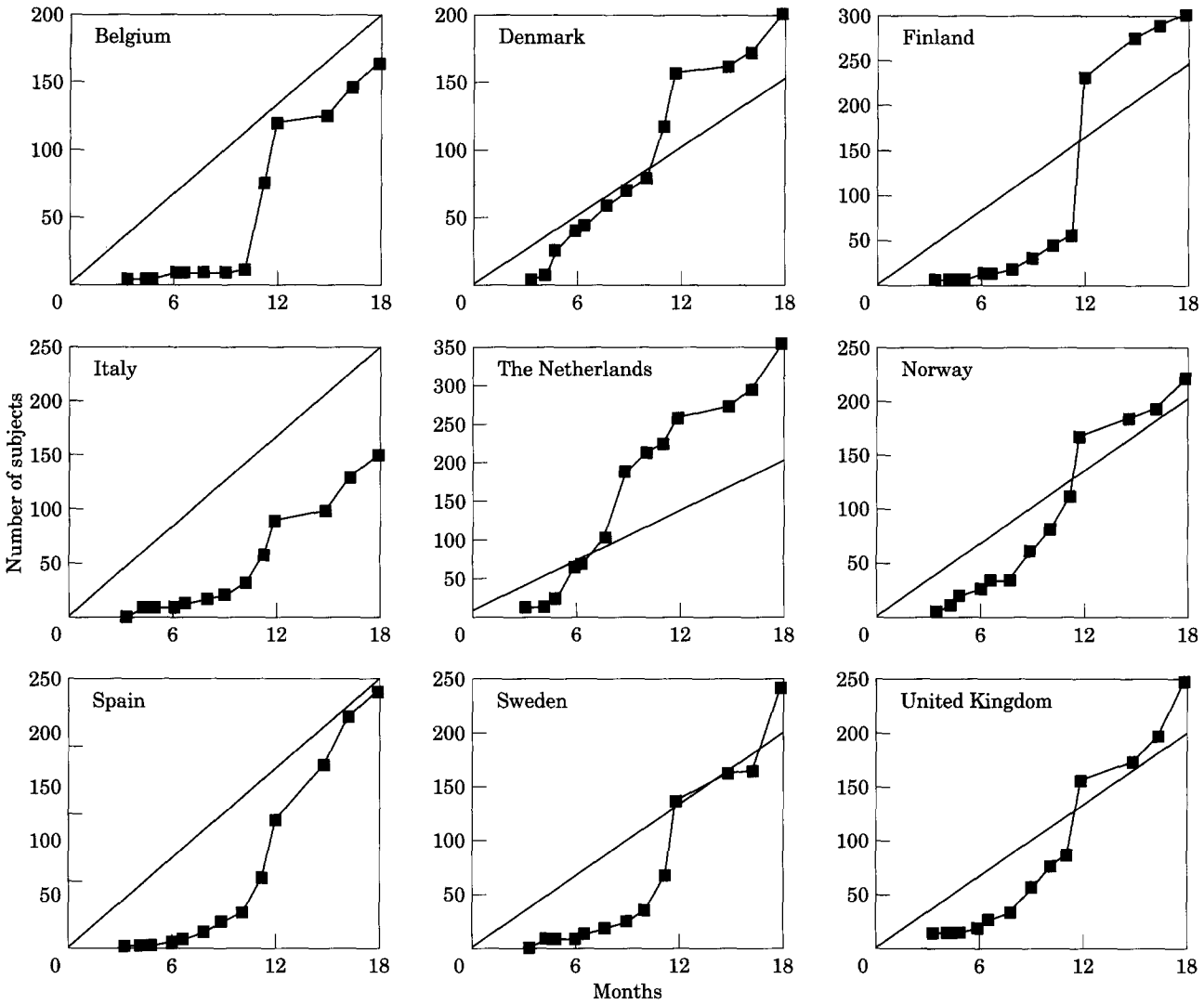

FIG. 2. Total actual recruitment over time per country in EUROSCOP, compared to expected (straight line) recruitment (50 subjects per centre).

centre, and newspaper advertisements were effective in two centres.

In summary, and using a questionnaire to assess the success rate of different recruitment strategies, 26 out of 39 centres considered mass media campaigns – especially advertisements – to be the most successful strategy. Occupational health survey was the most effective for five centres. Also, five of 39 centres preferred checking through hospital records. Finally, three centres preferred contacts with general practitioners.

USE OF RESULTS OF RECRUITMENT STRATEGIES IN THE STUDY

As many centres complained about the problem of finding candidates for the study, the steering committee looked at the country that had the quickest start and had collected data on all individuals screened. In the four centres involved, a total of 2405 patients had been screened. Extending the upper age limit to less than 65 years considerably increased the number of patients in the study, as shown in Fig. 4. For the criterion used for inclusion (FEV_1/VC ratio <70%) the extension from FEV_1 <80% predicted normal to FEV_1 <100% predicted normal increased the number eligible from 8 to 16% (Fig. 5). The major reason for not accepting subjects for the study was a normal lung function value.

Discussion

Recruitment in this study was successful, although 18 months were needed instead of 12 months. This is a relatively common experience in clinical trials and can be anticipated in the secondary agenda of a steering team managing a trial. Thus, a rate of 208 participants per month had to be enrolled in EUROSCOP according to the protocol. It can easily be seen in Fig. 1 that the enrollment

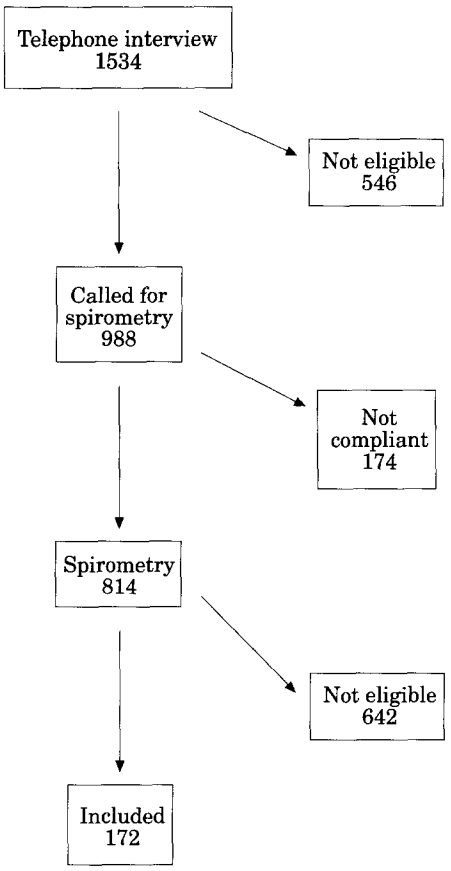

FIG. 3. Results of telephone interviews after newspaper advertisements in Finland.

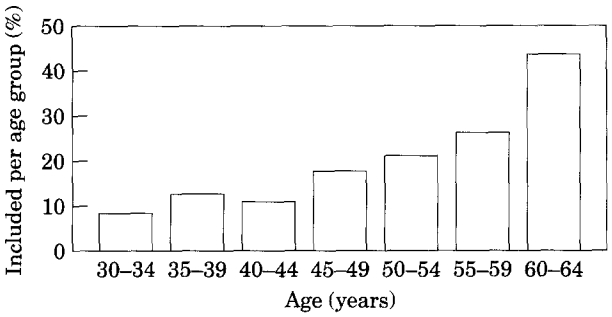

FIG. 4. Percentage of screened population, depending on age, meeting the inclusion criteria of EUROSCOP in The Netherlands. Total number of screened subjects: 2405. Numbers below the bars show the absolute number included in each age class.

rate was not uniform. This has been due largely to choice of recruitment strategies. Mass media screening has been the most successful strategy. As these individuals were screened as quickly as possible to prevent 'dropouts', the result was many eligible participants within 1 or 2 weeks in some centres. This also explains the slow enrollment at other times.

The second most successful screening programme was occupational health screening and health-care facilities. The latter was really successful only in Denmark, thus showing

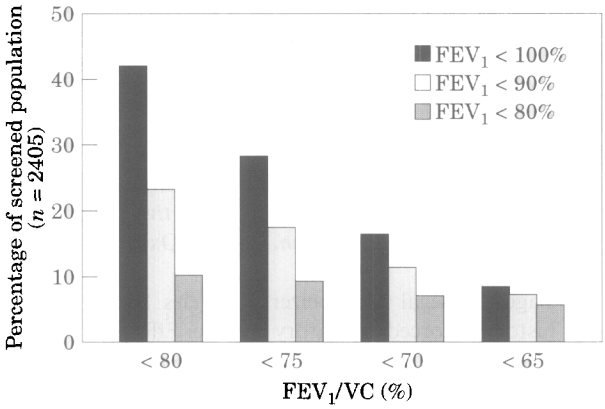

FIG. 5. Percentage of screened population, depending on extension of FEV_1 % predicted inclusion criteria. Increase in FEV_1 % predicted enhanced recruitment numbers with FEV_1 % VC <70%.

different attitudes between countries toward patient referral to hospital clinics. This contrasts with the Nocturnal Oxygen Therapy Trial, where 78% of the patients were enrolled via physicians due to the fact that they had to be severely affected patients in need of oxygen. Thus, in studies in which mild or pre-clinical disease has to be investigated, physician-related accrual can be anticipated to be low.

Some guidelines for multicentre cross-Europe recruitment strategies can be derived from our study in mild and pre-clinical COPD. Advertisement and articles in newspapers appeared to be the best strategy for recruitment of patients in most countries (eight out of nine). Participants who responded to media strategies have a large component of self-motivation as they also have to make contacts themselves and travel for their screening. It appears that an active, positive attitude is essential for participation in a study, especially a long-term one in individuals who are even sometimes not known to any doctor as having a disease.

In practice, it was found that a telephone number which differs from that of the hospital is essential for quick answering, and a sufficient number of telephone lines and personnel have to be available after mass media campaigns. A screening questionnaire is helpful to exclude those individuals who do not fulfill inclusion criteria – for example, out of age range, other concomitant serious diseases, wrong additional treatment. A quick appointment for the first screening is essential to promote enthusiasm in the future participant, and is essential for the whole study.

Finally, it can be concluded that a tremendous effort is needed to recruit subjects in an early phase of COPD, as is the case in the EUROSCOP study.

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