Problems encountered in recruiting patients to an ophthalmic drug trial

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SUMMARY Two clinical trials to assess the efficacy of two topical beta-blocker preparations involved the recruitment of 60 and 40 patients respectively. The greatest obstacle encountered in carrying out the trials was recruiting patients. This difficulty is reported in detail and comparisons are made with the experience of others who have met similar problems.

All who have carried out clinical research will be aware that the recruitment of patients often poses major difficulties. It is only too easy to overestimate the number of patients who will both agree to take part in any study and will satisfy the inclusion criteria. However, in spite of this difficulty being commonplace, there is little information in the ophthalmic literature on the likely scale of the problem. We therefore took the opportunity of documenting the erosion of the number of patients originally identified as possibly being suitable for inclusion in two studies of the efficacy of two beta-blocker drugs. Our aim in quantifying the problems encountered is to give guidance to others undertaking similar studies.

The trials involved recruiting a statistically determined number of patients to allow comparison of the effects of the two preparations in the treatment of patients with either chronic open-angle glaucoma or ocular hypertension. The first study was a single-masked randomised crossover trial. The 60 patients were required to attend hospital on five occasions at three weekly intervals over a 12-week period. On three of these visits patients were required to arrive at the hospital at 9 am and stay until 5 pm. On the two remaining visits patients needed to spend no longer than half an hour in the hospital.

The second study was a randomised evaluation of both preparations in which the patients received only one of the drugs over a period of 12 months. The 40 patients were required to attend hospital for between 30 minutes and 2 hours on six occasions.

Materials and methods

The names of patients for possible inclusion in the

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studies were derived from three sources; the out-patients' diagnostic index, members of the medical staff, and the medical secretaries. Patients were

Fig. 1 Summary of steps in identification of patients.

Table 1 Definitions of chronic open-angle glaucoma and ocular hypertension

Definition of chronic open-angle glaucoma:	
(i)	Intraocular pressure >21 mmHg
(ii)	Glaucomatous cupping of the optic disc
(iii)	A glaucomatous visual field defect
(iv)	An open angle on gonioscopy
Definition of ocular hypertension:	
(i)	Intraocular pressure >21 mmHg
(ii)	Normal optic disc
(iii)	Normal visual field
(iv)	An open angle on gonioscopy

considered if they were diagnosed as having either chronic open-angle glaucoma or ocular hypertension or if they were suspected of having glaucoma for any reason other than a raised intraocular pressure.

The recruitment of patients was carried out in the following four stages:

Stage A. The patients' hospital records were retrieved and the relevant notes were scrutinised. The records of patients not fulfilling the inclusion criteria were rejected.

Stage B. A letter was then sent to those patients

Table 2 Exclusion criteria

(i)	Patients younger than 18 and older than 80 years of age
(ii)	Ocular diseases such as infection, inflammation, or corneal ulceration occurring within one month prior to the study
(iii)	Entry of foreign matter into the cornea within one month prior to the study
(iv)	Patients who wear contact lenses or who stopped wearing them within one month prior to the study
(v)	Intraocular operation or ocular injury within six months prior to the study
(vi)	All aphakic patients
(vii)	Patients with either secondary glaucoma or angle closure glaucoma
(viii)	History or evidence of a serious retinal condition
(ix)	History or evidence of bronchial asthma, chronic bronchitis, or other respiratory diseases
(x)	Cardiac insufficiency, myocardial infarction, cerebrovascular insufficiency, or aortic stenosis
(xi)	Sinoatrial or atrioventricular block as shown on an electrocardiogram
(xii)	Diabetes mellitus
(xiii)	Bradycardia (less than 55 beats per minute)
(xiv)	Melanoma or other malignancy that may give rise to ocular metastases
(xv)	Pregnant women or nursing mothers
(xvi)	History of intolerance to timolol
(xvii)	Patients who were judged by the attending investigator to be unsuitable for the studies
(xviii)	Prohibited drugs for concurrent medication were: other antiglaucoma agents apart from timolol; parasympathetic nerve stimulants; sympathetic nerve stimulants; carbonic anhydrase inhibitors; beta-adrenergic blocking agents; hypotensive agents (not including diuretics); tricyclic antidepressants; beta-adrenergic stimulants; oral and topical corticosteroids; monoamine oxidase inhibitors

Table 3 Reasons for rejecting the case records of 1195 patients (stage A)

	Number of case records	
	Number excluded	Number remaining
Original number of case records		1388
Glaucoma suspects	449	939
Multiple treatment	252	687
Notes missing	176	511
Serious eye disease	53	458
Narrow angles	45	413
Trabeculectomy	35	378
Lived too far away	27	351
On prohibited drugs	26	325
Respiratory problems	23	302
Diabetes mellitus	19	283
Secondary glaucoma	19	264
Cerebrovascular disease	16	248
Aphakia	15	233
Cardiac disease	12	221
Died recently	10	211
Low-tension glaucoma	8	203
Malignancies	7	196
Thyroid disease	3	193

Number of case records rejected=1195 (1388-193). 193 patients were then invited for interview, 120 patients agreed to be interviewed, 96 patients were found unsuitable (see Table 4).

who were thought suitable for inclusion in the studies. This set out the aims of the projects, and the patients were asked to return a slip indicating whether or not they wished to be contacted by telephone to be given further particulars.

Stage C. The returned slips were collected and the contents of the replies noted. The patients who indicated an interest in participating in the studies were invited to the hospital and interviewed.

Stage D. The patients were subsequently examined. After a full medical and surgical history had been taken, perimetry and electrocardiography were performed and the pulse and blood pressure were recorded.

This routine is summarised in the flow chart (Fig. 1). The definitions of chronic open-angle glaucoma and ocular hypertension as applied in these studies are given in Table 1. The exclusion criteria are set out in Table 2.

Results

The reasons for rejecting the case records of 1195 patients from an original 1388 (stage A) are shown in Table 3. Of the remaining 193 patients who were invited to take part in the studies (stage B) 120 agreed to be interviewed. At interview (stage C) 96 patients were excluded from the trials for the reasons shown in Table 4. Table 5 shows the reasons for a further

Table 4 Reasons for 96 patients being excluded after being interviewed (stage C)

	Number of patients	
	Number excluded	Number remaining
Number of patients		96
Prohibited drugs	25	71
Extensive field loss	14	57
Cerebrovascular disease	12	45
Respiratory disease	11	34
Diabetes mellitus	7	27
Unable to take time off work	5	22
Cardiac disease	5	17
Not actually instilling timolol	4	13
Unwilling to take part in study	3	10
On multiple treatment	3	7
Trabeculectomy	3	4
Bradycardia	2	2
Unreliable perimetry	2	0

nine patients being excluded after they were examined (stage D). Hence, only 15 patients were recruited from an original 1388 case records—a ratio of 1:92–5.

Discussion

The problems we encountered will be recognised by any one involved in clinical research. As Hamilton put it, 'In any investigation involving human subjects the most difficult part is getting hold of them.'¹ It was a great boon having an outpatient diagnostic index to which to refer in the first instance.²

In his review of the practical problems encountered in carrying out collaborative clinical trials Ederer³ refers to the so called Muench's third law,⁴ which states that the number of patients promised for a clinical study must be divided by a factor of at least 10. Several studies from other disciplines have documented the progressive loss of patients who were initially identified as likely to be suitable for inclusion in the trials. In the National Diet Heart Study⁵ only

899 entrants to the trial were found after almost 20 000 people had been screened—a ratio of 1:22.

Other workers have had results even more akin to our own. In one component of the Hypertensive Detection and Follow-up Study⁶ 5314 entrants were discovered among 436 679 contacts—a ratio of 1:82. In the Coronary Primary Prevention Trial⁷ 3810 individuals took part out of the 436 679 people originally considered (1:115). Similarly, in the Veterans Administration Mild Hypertensive Study⁸ 1012 participants were recruited from the 120 000 who were first approached (1:119). Finally, the recruitment to the pilot study of the Systolic Hypertension in the Elderly programme⁹ was no more than 551 individuals from approximately 75 000 people originally contacted—a ratio of 1:136.

In view of our experience, and that of many others,¹⁰ we suggest that the prudent research worker should divide by 100 the number of individuals he initially thinks may be eligible for a trial rather than by 10 as previously suggested. In this way later embarrassment will be more often avoided and fewer promises will be broken.

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Table 5 Reasons for nine patients being excluded after being examined (Stage D)

Cardiac abnormalities diagnosed on electrocardiogram	3
Bradycardia	1
Changed to multiple treatment	1
Using hydrocortisone ointment for psoriasis	1
Over 80 years of age	1
Pathology identified on chest x-ray	1
Patient thought unlikely to complete study	1
Total	9