Doing randomized controlled trials in a developing country: some practical realities

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Background. Formal randomized controlled trial results are often reported. The difficulties of doing such trials are not. Developing countries represent a new field in which trials can be undertaken. In this context even less is known about the practicalities involved.

Method and results. A randomized, double-blind, parallel study took significantly longer than expected to complete and subject recruitment and participation fell short of expectations. Different recruitment strategies were used and these performed differently in terms of enrolling trialists. Subjects most frequently left the trial in its early stages.

Conclusions. Possible explanations for these findings include the demography of the country, cultural factors, and the existence of an established doctor-patient relationship.

Keywords. Developing countries, drug treatment hypertension, randomized controlled trials, United Arab Emirates.

Introduction

Between September 1994 and July 1995 a Phase IIIb–Phase IV trial of a new antihypertensive agent was conducted in the United Arab Emirates (UAE). A randomized, double-blind, parallel study design was used to assess the safety and efficacy of the trial drug. The study was undertaken in the community among ambulatory patients with mild to moderate hypertension. Results of such trials are commonly reported in terms of the trial drug efficacy and safety profiles. Although such results are frequently published, a Medline search identified no published information on the practicalities of undertaking such research in a developing country. This report summarizes information acquired through doing the study, and will be of particular value to those who are considering undertaking similar work in developing countries.

Methods

The protocol required 20 individuals with mild to moderate hypertension to be enrolled in the study. Written, witnessed, informed consent was mandatory for entry. The subjects had to meet clearly defined inclusion and exclusion criteria. These are listed in Appendix 1. The study period was 16 weeks with a four week placebo controlled run-in period, randomization, and then a 12 week double-blind treatment period.

A potential pool of subjects was identified using three strategies. Strategy 1 identified known hypertensive patients from an existing chronic disease register kept at one Primary Health Clinic (PHC). Strategy 2 identified patients from consultation summary sheets kept at a second PHC, for whom hypertension was listed as the reason for the consultation. These two strategies resulted in a list of potential subjects who were then telephoned by a clinic administrator with the necessary language skills and invited to attend the clinic to discuss the study fully. Strategy 3 was to notify doctors working at these two PHCs of the trial, and seek their support in identifying potential patients from those consulting each session. In this strategy, the PHC doctor discussed the study with the individual subject face-to-face.

Together these three strategies resulted in a pool of trialists for the study. A fourth source of potential subjects comprising friends or relatives of the trialists developed during the course of the study and resulted in some additional enrolments.

For each potential subject, data was collected on: strategy used for identification; nationality; gender;
agreement to take part; enrolment in study; randomization status; last completed visit before leaving the study; extra visits directly related to the study; and reason for leaving the study. The time the principal clinical investigator spent on the study was measured in 3 hour "sessions". The data were collated and analysed using Microsoft Access 2.0.

Results
A total of 79 potential subjects were identified and of these 39 agreed to take part. Table 1 shows the strategy by which they were identified and the proportions for each strategy who agreed to enrol in the study. The nationalities of those involved in the study at each of four points—Potential Subject, Enrolled Subject, Randomized Subject and Completed Study Subject—are summarized in Table 2. Whether subjects went on to randomization by strategy used for selection is given in Table 3.

Figure 1 shows the points at which subjects from the 39 who enrolled in the study left it in relation to the point of randomization. The median of this range of values is Visit 2, the 25th and 75th percentile values Visits 1 and 6 respectively.

Summing the number of completed visits above gives the figure 124. To these were added an extra 51 visits which arose from one of three sources. These were: those determined by the protocol (e.g. to wean off...
medication, or check a high blood pressure reading); those arising from subject concerns; and those arising from the clinical investigator's concerns. The total number of study subject/clinical investigator contacts is thus 174.

Reasons for leaving the study are given in Tables 4 and 5.

The principal clinical investigator spent a total of 64 “sessions” of three hours each or 192 hours on the study. This time included subject contact time, and collating, checking and recording results. No attempt was made to quantify the time spent by the clinical administrator, the PHC doctors who helped recruit subjects or the principal investigators administrative input.

Total number of hours spent divided by total number of subject/clinical investigator contacts is 192/175. This is close to one contact completed per hour of work.

### Discussion

When this study was first proposed, the researchers were hopeful of a prompt completion of the task. This hope was based on their local knowledge of the community and primary health system. Hypertension is an increasing and common problem in the UAE although the exact prevalence is not known. The PHC clinics have chronic disease registers and a summary of all consultations by date and reason for presentation. The PHC clinic doctors are very willing to assist in research. All these factors meant the study began with hopes of easily enrolling 20 subjects and finishing it within five months.
Neither hope was realized. Only nine subjects fully completed the study and it ran for 10 months.

Utilizing the two strategies based on records to identify patients had the theoretical advantage of providing a pool of patients at the start of the study. As Table 1 shows, approaching patients from the hypertension register resulted in just under two thirds of them declining to take part. Strategy 2 resulted in over three quarters of those contacted declining to take part. The large number of people who declined when telephoned meant that the process of telephoning continued over several weeks, and those agreeing to take part did so over a similar time course. Entry to the trial occurred at a rate of 1–2 trialists per week, rather than with a large group enrolling at the same time. Strategy 3 resulted in 100% enrolment. This identification process also took place over several months because these people presented for a consultation rather than being contacted.

There are several factors which may contribute to this finding. The first is illustrated in Table 2. The UAE population is made up of people from many different cultural and socio-economic backgrounds. Although both English and Arabic are spoken widely, those for whom these are not primary languages tend to have conversational abilities only. The person who telephoned was fluent in Arabic and English, but despite this may have had difficulty presenting the invitation in a way which attracted the person to seek more information. The telephone call was from a stranger, inviting participation in a study run by another stranger. This would seem likely to discourage a positive response.

Neither the hypertension register, nor review of the last three months’ doctor–patient contacts give information about the individual concerned except in a generic sense. The PHC doctor has a much more complete sense of what makes this particular person suitable or not suitable, and this is reflected in the 100% enrolment which resulted from such recommendations. The PHC doctor is not a stranger to the patient, but has been a trusted adviser over time so that a recommendation from the doctor is more likely to be followed. The value of the doctor–patient relationship is demonstrated by this finding.

Friends and relatives are similarly likely to be trusted by potential subjects, and so have their advice acted on. However, these people may lack the clinical knowledge necessary to make a recommendation to be part of the trial, so that although the subjects enrol, they have a high drop out rate. This is borne out by studying Table 3 which shows that no patients identified by friends or relatives were randomized.

Figure 1 shows that a large amount of work is done enrolling patients in the trial who drop out before randomization. It was not possible to predict who these people would be when they enrolled in the study. It is discouraging for the researcher to have subjects leave the study after spending significant time with them. Those planning similar research should be prepared for such discouragement, especially early in the study.

As seen in Table 4, between enrolment and randomization seven patients had a blood pressure measurement below that required in the protocol. This was a larger number than may have been anticipated given that all the potential subjects had hypertension previously confirmed as a diagnosis. One explanation is the exclusion criteria which were strictly adhered to. Even one slightly low blood pressure reading meant exclusion, despite several later readings again being high. Six patients who agreed to participate did not attend despite being reminded on three separate occasions. The authors consider that there may be a cultural factor operating in these cases, in which participation is agreed in order to “please”, but that the intention always was not to participate.

In two cases renal impairment as defined by the exclusion criteria was discovered. This had not been previously identified despite treatment being given for hypertension.

Table 5 shows that those who were randomized were most likely to complete the study. One reason for this may be the establishment of a good therapeutic relationship between the clinical researcher and the subject.

Obviously comparing this experience with similar research conducted elsewhere would be of interest. Despite an extensive literature search, no comparative data on these issues were found making such comparison impossible.

Conclusions

This phase IIIb/IV study was able to be done in an ambulatory setting in the UAE. It proved more difficult to obtain 20 subjects than had been expected, and the study took twice as long as was initially planned for. The multi-cultural nature of the community gave rise to language and cultural barriers which may have operated to detract from enrolment and participation. A personal approach to the patient by the PHC clinic doctor was a more effective strategy for patient enrolment compared to review of patient registers. Two-thirds of those who began the study withdrew before randomization which was discouraging for the researchers. This study suggests that further Phase IIIb/IV trials can be undertaken in the UAE, but that those contemplating such research should not underestimate the difficulties involved.

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References

5. Data from United Arab Emirates Ministry of Health, Al-Ain Medical District Statistics. PO Box 1006 Al-Ain, UAE.

Appendix 1

Inclusion criteria

1) The patient is a male or a female of at least 18 years old
2) The patient has no other concurrent medical conditions that might of themselves or their treatment affect the patient’s blood pressure
3) The patient has a trough Sitting Diastolic Blood Pressure (average of 3 readings)
   • between 90–115 mmHg at Visit 1 (Week -4)
   • between 95–115 mmHg at Visit 2 (Week -2)
   • between 95–115 mmHg at Visit 3 (Week 0)
   • The difference between the mean value at Visit 2 and the mean value at Visit 3 is £7 mmHg

If the answer to any of the above is NO, the patient is not eligible to enter the study.

Exclusion criteria

1) Patient is a pregnant or lactating female
2) Patient has secondary hypertension of any etiology, such as unilateral or bilateral renal disease coarctation of the aorta or pheochromocytoma
3) Patient has malignant hypertension
4) Patient has known renal artery stenosis, primary aldosteronism or other reversible forms of hypertension
5) Patient has a diagnosis of acute renal failure, chronic glomerulonephritis, polycystic kidneys
6) Patient gives evidence of significant renal impairment as indicated by
   • serum creatinine > 150 mol/l
   • proteinuria > 2+ by dipstick
   • hematuria by dipstick
7) Patient had congestive heart failure, cerebrovascular accident, transient ischemic attacks or hypertensive encephalopathy within the past year
8) Patient had a myocardial infarction within the last six months, or angina pectoris
9) Patient had uncontrolled diabetes mellitus (fasting blood glucose > 11 mmol/l)
10) Patient has an untreated thyrotoxicosis or hypothyroidism
11) Patient has a history of clinically important hepatic, hematological, pulmonary or neurological disorders
12) Patient has any other medical condition which might interfere with optimal participating in the study or produce significant risk to the patient
13) Patient shows any clinically important abnormal laboratory findings including:
   • serum potassium < 3.5 mmol/l or > 5.5 mmol/l
   • ASAT/ALAT twice the upper limit of normal
14) Patient has obesity such that arm circumference is > 41 cm
15) Phase V of Korotkoff sounds cannot be detected
16) Patient has bleeding or platelet disorder
17) Patient uses concomitant drugs such as beta-blockers (except ophthalmic preparations), or any agent that may cause an alteration of blood pressure (e.g. diuretics, nitrates, angiotensin converting enzyme inhibitors or other calcium channel blockers)
18) Patient uses concomitant drugs such as steroids, adrenocorticotropic hormone (ACTH), or lithium
19) Patient is mentally or legally incapacitated
20) Patient uses any other investigational drugs other than those used in this study
21) Patient has any other condition or therapy which, in the opinion of the investigator, might pose a risk to the patient when he/she enters the study, or might confound the results of the study
22) Patient has a history (or suspicion) of alcohol or drug abuse, or other factor which in the judgment of the investigator might detract from or complicate participation in the study.

23) Patient has known hypersensitivity or contraindication to captopril or other calcium channel blockers.

24) Patient has any other concurrent severe disease which could preclude participation or survival, such as neoplasm or Acquired Immunodeficiency Syndrome (AIDS).

If the answer to any of the above is YES, patient is not eligible to enter the study.