create an infrastructure which could enable the new material to be put to best use.

No one doubts the critical importance of clinical effectiveness, and the NHS Executive is right to make it the concern of both purchasers and providers, but the use of contracting to change clinical practice will need evaluation (just as any other intervention requires evaluation). Stipulating that purchasing authorities should divert investment towards effective interventions and away from ineffective ones has a mechanistic feel to it. Purchasers need to have a more interactive role than this: they need to establish dialogue with local hospital doctors, general practitioners, and patients. In addition, hospital doctors need to talk to each other about policy and practice, and purchasers should insist that they do so.

At this stage the role of the contracting mechanism should perhaps be to tie providers to this dialogue; to ensure that clinicians address issues of clinical policy and practice with their colleagues (including the local adaptation of evidence based clinical guidelines); and to enable local users of health services to have an informed voice. That would give all parties sufficient freedom for local collaboration, while ensuring the commitment of providers.

JOHN HAYWARD
Medical director

Camden and Islington Family Health Services Authority,
London NW1 2LJ

1 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;**308**:81-106.
2 Fibrinolytic Therapy Trialists' Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of over 1000 patients. *Lancet* 1994;**343**:311-22.
3 Ketley D, Woods KL. Impact of clinical trials on clinical practice: example of thrombolysis for acute myocardial infarction. *Lancet* 1993;**342**:91-4.
4 Lincolnshire Medical Audit Advisory Group. *Audit of management of suspected heart attacks.* Lincoln: Lincolnshire Medical Audit Advisory Group, 1994.
5 NHS Management Executive. *Improving clinical effectiveness* Leeds: NHS Management Executive, Leeds 1993. (EL(93)115).
6 NHS Executive. *Priorities and planning guidance for the NHS: 1995/96.* Leeds: NHS Executive, 1994. (EL(94)55).
7 NHS Executive. *Improving the effectiveness of the NHS.* Leeds: NHS Executive, 1994. (EL(94)74).
8 Grimshaw JM, Russell T. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. *Lancet* 1993;**342**:1317-22.
9 Haines A, Jones R. Implementing the findings of research. *BMJ* 1994;**308**:1488-92.
10 Sackett DL, ed. *The Cochrane Collaboration handbook 1994.* Oxford, 1994.

Evening primrose oil

Currently used in many conditions with little justification

Oil extracted from seeds of the evening primrose (*Oenothera biennis*) contains linoleic acid, γ linolenic acid, and vitamin E. γ Linolenic acid is a precursor of prostaglandin E and several other active substances and is said to be the constituent of the oil responsible for its therapeutic effects. Disorders for which evening primrose oil has been tested in controlled clinical trials include atopic dermatitis, rheumatoid arthritis, diabetic neuropathy, multiple sclerosis, various cancers, Raynaud's phenomenon, ulcerative colitis, pre-eclampsia, the premenstrual syndrome, menopausal flushing, breast cysts, mastalgia, Sjögren's syndrome, schizophrenia, and hyperactivity.[1] What are the results of these clinical trials?

Many of the studies have been crossover trials, which is a pity for two reasons. Firstly, crossover trials are really suitable only for assessing drugs whose effects fade rapidly after treatment has been stopped. Any persistent effects will disappear provided there is a "washout" period before the crossover. Secondly, if the explanation given to patients before their informed consent is obtained includes the timing of the crossover their expectations may become a major source of bias. The treatment, the natural course of the disease, and placebo effects will induce changes that the patient may or may not have expected. For example, patients who receive active treatment in the first period and who notice improvements will have low expectations for the next period; and patients who notice no improvement in the first period will assume that they were taking placebo. These expectations would result in a bias, increasing the measured difference. Evening primrose oil is claimed to have effects that are both sustained and subjective, and so parallel trials should be used to assess its effects.

Turning to the published work, for atopic dermatitis Wright and Burton reported positive effects from a double blind crossover trial of evening primrose oil in 99 patients (60 adults and 39 children).[2] Bamford *et al* found negative effects in a double blind crossover trial in 123 patients.[3] A meta-analysis of nine trials (five crossover trials) including the trial of Wright and Burton but excluding that of Bamford *et al* reported positive results, and, more recently, negative results were reported from a parallel trial in 123 patients.[4,5]

For rheumatoid arthritis Joe and Hart discussed three randomised trials with parallel groups and Leventhal *et al* reported another one.[6,7] These trials were small—the largest group was of 19 patients, and the results were mixed. The investigators concluded that further trials were warranted.

For the premenstrual syndrome four trials (three crossover trials) have reported positive results,[8] but more recently Khoo *et al* found no differences between evening primrose oil and placebo in a crossover trial in 38 women.[9] The effects of evening primrose oil on mastalgia, one of the symptoms of the premenstrual syndrome, have been investigated in three small randomised trials, with favourable results.[10]

After a preliminary trial in 22 diabetic patients reported favourable results the Gamma Linolenic Acid Multicenter Trial Group reported positive effects on many neurological and neurophysiological end points in a well performed parallel double blind trial in 111 patients with mild diabetic neuropathy.[11] These encouraging findings indicate that further investigations of evening primrose oil in diabetic neuropathy should be given priority.

Evening primrose oil seems to be safe. Its reported side effects include nausea, softening of the stools, and headache. One recent comment warned of a potential risk of inflammation, thrombosis, and immunosuppression due to slow accumulation of tissue arachidonate after prolonged use of γ linolenic acid for more than one year.[12]

The optimal dose and duration of treatment with evening primrose oil seem not to be known. Trials that

have tried to establish a dose-response effect have shown varying results. In trials the daily dose has ranged from two to 16 capsules of 500 mg. One capsule contains about 320 mg linoleic acid, 40 mg γ linolenic acid, and 10 IU of vitamin E. In the prescribing information a dose of three to six capsules twice daily is recommended. The clinical response is said to occur after three to four months and to last for several months.

Most trials have used placebo capsules containing paraffin and matching the capsules of evening primrose oil by colour and shape.[13] The taste is different, but the capsules should be swallowed unbroken. In doses of 12 capsules daily the amount of vitamin E is a megadose (10 times the recommended daily allowance). Although there are valid arguments for using an inert placebo, one containing linoleic acid and vitamin E would make it possible to isolate the effect of linolenic acid.

The conclusion that I draw from the published research is that evening primrose oil has not been proved to be efficacious in rigorous clinical trials. Many of the trials to date have been crossover studies in small numbers of patients. Publication bias cannot be ruled out (practically all trials have been sponsored by the same company), and for most conditions for which evidence exists from several trials both positive and negative outcomes have been reported. Questions remain about the dose and duration of the treatment, and evening primrose oil should be compared with and shown to be more effective than linoleic acid and vitamin E. Nevertheless, evening primrose oil is an interesting substance, and for some indications it is a promising treatment—especially for diabetic neuropathy and atopic dermatitis, but also for rheumatoid arthritis and the premenstrual syndrome. Further rigorous trials of both evening primrose oil and γ linolenic acid are warranted.

JOS KLEIJNEN
Clinical epidemiologist

Academic Medical Center,
University of Amsterdam,
Department of Clinical Epidemiology and Biostatistics,
PO Box 22700,
NL-1100 DE Amsterdam,
Netherlands

1 Kleijnen J, Riet ter G, Knipschild P. Teunisbloemolie. Een overzicht van gecontroleerd onderzoek. [Evening primrose oil. Review of controlled trials.] *Pharm Weekbl* 1989;124:418-23. (English translation available from first author.)
2 Wright S, Burton JL. Oral evening-primrose-seed oil improves atopic eczema. *Lancet* 1982;ii:120-2.
3 Bamford JT, Gibson RW, Renier CM. Atopic eczema unresponsive to evening primrose oil (linoleic and γ-linolenic acids). *J Am Acad Dermatol* 1985;13:959-65.
4 Morse PF, Horrobin DF, Manku MS, Stewart JCM, Allen R, Littlewood S, *et al.* Meta-analysis of placebo-controlled studies of the efficacy of Epogam in the treatment of atopic eczema. Relationship between plasma essential fatty acid changes and clinical response. *Br J Dermatol* 1989;121:75-90.
5 Berth-Jones J, Graham-Brown RAC. Placebo-controlled trial of essential fatty acid supplementation in atopic dermatitis [correction appears in *Lancet* 1993;342:564] *Lancet* 1993;341:1557-60.
6 Joe LA, Hart LL. Evening primrose oil in rheumatoid arthritis. *Annals of Pharmacotherapy* 1993;27:1475-7.
7 Leventhal LJ, Boyce EG, Zurier RB. Treatment of rheumatoid arthritis with gammalinolenic acid. *Ann Intern Med* 1993;119:867-73.
8 O'Brien PMS, Massil H. Premenstrual syndrome: clinical studies on essential fatty acids. In: Horrobin DF, ed. *Omega-6 essential fatty acids. Pathophysiology and roles in clinical medicine.* New York: Wiley-Liss, 1990:523-45.
9 Khoo SK, Munro C, Battistutta D. Evening primrose oil and treatment of premenstrual syndrome. *Med J Austr* 1990;153:189-92.
10 Mansel RE, Pye JK, Hughes LE. Effects of essential fatty acids on cyclical mastalgia and non-cyclical breast disorders. In: Horrobin DF, ed. *Omega-6 essential fatty acids. Pathophysiology and roles in clinical medicine.* New York: Wiley-Liss, 1990:557-66.
11 Gamma-Linolenic Acid Multicenter Trial Group. Treatment of diabetic neuropathy with gamma-linolenic acid. *Diabetes Care* 1993;16:8-15.
12 Phinney S. Potential risk of prolonged gamma-linolenic acid use. *Ann Intern Med* 1994;120:692.
13 Horrobin DF, Ells KM, Morse-Fisher N, Manku MS. The effects of evening primrose oil, safflower oil and paraffin on plasma fatty acid levels in humans: choice of an appropriate placebo for clinical studies on primrose oil. *Prostaglandins Leukotr Essent Fatty Acids* 1991;42:245-9.

Trial design in developing countries

The results of studies must be relevant to the populations in which they are carried out

Picture an impoverished region in sub-Saharan Africa where health services are virtually non-existent. A donor funds a group of scientists to test whether regular administration of a prophylactic drug or a micronutrient improves child health. The researchers build a research station, and staff deliver the intervention and record illness and death in the study population. After three years the results are published, the intervention is declared effective, and the scientists move on.

Yet back at the study site there are still no health services and micronutrients are still not being delivered. Has the research benefited the participants of the study? Should researchers be allowed to spend money and intervene in people's lives without helping to develop services to deliver the intervention being tested? Should intervention trials always be directly relevant to the needs and services of the area where the work is conducted? The European Commission is encouraging researchers to consider methods that ensure trials are useful to health managers' decision making as well as being scientifically valid (P Garner *et al*, European Commission meeting on methodology and relevance of field based intervention trials, Barcelona, June 1994).

Researchers face a dilemma. Reliable evidence for the effectiveness of interventions helps to ensure the wise use of scarce resources. Populations chosen for a randomised controlled trial of an intervention in primary care are often poor, with high morbidity and mortality. Usually the health services in such areas are patchy and of poor quality and cannot be relied on either to deliver the intervention or to monitor the effect. In the pursuit of a scientifically valid study the researcher sets up an independent delivery system or adds to existing services in a way that distorts them. For similar reasons morbidity or mortality will be measured in systems separate from existing services.

Though all these aspects of the research design will maximise the chance of detecting a positive effect, it is unclear whether the results are useful to regional or national health managers. To begin with a large research project is likely to have a profound effect on a community, especially in deprived areas with few services. The effect of an intervention, therefore, may never be replicable in practice because the compliance of providers will not be the same. In addition the area being studied may simply not have the resources, skill, or organisational capacity to provide the intervention under test.

Problems in generalising research results are not unique to developing countries.[1] But by using resources that are not locally available research teams lose the opportunity to invest in existing health services. Could the money and skills devoted to these parallel systems be a stimulus to