



<b>Title</b>	<b>Screening and mortality from cervical cancer. Study shows importance of centralised organisation in screening.</b>
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<b>Citation</b>	<b>Bmj (Clinical Research Ed.), 1999, v. 319 n. 7210, p. 642-643</b>
<b>Issued Date</b>	<b>1999</b>
<b>URL</b>	<b><a href="http://hdl.handle.net/10722/43569">http://hdl.handle.net/10722/43569</a></b>
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47247

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**Guidelines do not ignore clinically relevant end points**

EDITOR—In his commentary on the European rivastigmine study<sup>1</sup> Bayer states that the absence of measures of neuropsychiatric outcome and the burden on carers is unfortunate but that the choice of these end points was governed by requirements of regulatory authorities rather than the aim of measuring the real impact of the illness on the lives of patients and their families. He says that the need for clinically relevant outcome measures should now be better appreciated.

However, the European guideline on medicinal products in the treatment of Alzheimer's disease recommends that improvement of symptoms should be assessed in the following three domains: cognition, as measured by objective tests (cognitive end point); activities of daily living (functional end point); and overall clinical response, as reflected by global assessment (global end point).<sup>2</sup> Efficacy variables should be specified for each of the three domains. Two primary variables should be stipulated, one evaluating the cognitive end point and the other the clinical relevance of the improvement in cognition. The protocol should specify this second primary variable and to which domain (global, or preferably functional) it is related. Moreover, the instruments which measure burden on carers and activities of daily living should have been validated for Alzheimer's disease. The study should be designed to show significant differences in at least two of the primary variables. If this is achieved, then the overall benefit (response) should be assessed in individual patients, and the effect of treatment should be illustrated in terms of the proportion of patients who achieve a meaningful benefit (responders).

In our view these recommendations show that the emphasis of regulatory authorities is on clinically relevant end points, and the Committee for Proprietary Medicinal Products guideline stresses the need to develop these. Therefore, the statement that the choice of the outcomes in clinical drug trials in dementia was governed by the requirements of regulatory authorities is not justified.

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- 1 Rösler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, et al on behalf of the B303 Exelon study group. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial (commentary by Bayer T). *BMJ* 1999;318:633-9. (6 March)
- 2 Committee for Proprietary Medicinal Products. *Note for guidance on medicinal products in the treatment of Alzheimer's disease (CPMP/EWP/553/95)*. London: European Agency for Evaluation of Medicinal Products, 1995. ([www.eudra.org/emea.html](http://www.eudra.org/emea.html))

**Screening and mortality from cervical cancer**

**Does screening really reduce mortality?**

EDITOR—We were rather non-plussed to read that the conclusion of the paper by Quinn et al on screening for cervical cancer<sup>1</sup> is not supported by their data, and we wonder whether so called political correctness had anything to do with it. The statement "800 deaths might have been prevented in 1997" is based on a projected mortality of a completely arbitrarily (alas, not randomly) selected part of a subset of graphs showing trends in mortality. The opposite conclusion may be reached using the same graphs. For example, in women aged 35-44 mortality fell from 10 per 100 000 to 5 per 100 000 in the period 1960 to 1975, and it should have approached zero by 1997 assuming that the trend had continued. Similarly, with the same age groups as in the original paper, in women aged 25-34 mortality fell from 2.5 per 100 000 to 1.1 per 100 000 in the period 1955 to 1965, so by 1997 it should have again approached zero. Since the only new intervention has been screening, and the mortality is excessive at 5 per 100 000, screening may have caused up to 2900 extra deaths in 1997—by the same logic.

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- 1 Quinn M, Babb P, Jones J, Allen E, on behalf of the United Kingdom Association of Cancer Registrars. Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. *BMJ* 1999;318:901-8. (3 April)

**Authors' reply**

EDITOR—The conclusions in our paper are not based solely on the analysis of mortality. We presented strong evidence that the introduction of national call and recall and of incentive payments to general practitioners led to a dramatic fall in the incidence of cervical cancer in women in all age groups from 30 to 74 and in all regions of England. Other evidence confirms the expected shift towards detection of earlier stages of disease. There is no other plausible explanation for these patterns. If women do not get cervical cancer, they will not die from it. In addition, it has been recognised for over 30 years that mortality from cervical cancer shows very strong cohort trends (reflecting those in incidence)<sup>1</sup> and so Vaidya and Baum's simple extrapolation of age specific trends is totally inappropriate. We extrapolated the cohort rates for the relevant age groups. Our analysis and conclusions are supported by a similar study in Scotland<sup>2</sup> and by the results from formal age period cohort models.<sup>1</sup>

We remain deeply concerned about the many well known problems with cervical screening which we mentioned in our paper: cervical cancer is a comparatively rare disease and its natural course is not well

understood; the smear test has both low sensitivity and low specificity; many tests are technically unsatisfactory and the proportion of such tests varies widely across the country; the mix of three and five year screening intervals is inequitable; too many smear tests are opportunistic; and the programme costs four times as much as breast screening. Nevertheless, there is now conclusive evidence that cervical screening has markedly reduced both incidence and mortality.

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- 1 Hill GB, Adelstein AM. Cohort mortality from carcinoma of the cervix. *Lancet* 1967;ii:605-6.
- 2 Walker JJ, Brewster D, Gould A, Raab GM. Trends in incidence of and mortality from invasive cancer of the uterine cervix in Scotland (1975-1994). *Public Health* 1998;112:373-8.
- 3 Sasieni P, Adams J. Effect of screening on cervical cancer mortality in England and Wales: analysis of trends with an age period cohort model. *BMJ* 1999;318:1244-5. (8 May)

**Study shows importance of centralised organisation in screening**

EDITOR—The paper by Quinn et al reporting the effects of screening on incidence of and mortality from cervical cancer in England<sup>1</sup> highlighted the characteristics of successful programmes elsewhere<sup>2,3</sup> and showed that the national screening programme had been effective.

The situation in Hong Kong, where there is no systematic population based cervical screening programme, shows the importance of central organisation. Hong Kong is a generally affluent community with a better health profile than most developed countries. Infant mortality is low (4.6 per 1000 live births in 1995, compared with 6.2 in the United Kingdom), and life expectancy is high (81.5 years at birth for women, compared with 79.4 years in the United Kingdom). Women in Hong Kong are at lower risk of developing many common cancers, such as those of the breast and lung, than are their counterparts in most Western countries yet the reverse is true for cervical cancer.

The figure shows the trend in the incidence of and mortality from cervical cancer standardised to the European standard population (for age bands of five years). Although incidence has reduced gradually over time, it has not fallen dramatically as in the United Kingdom after organised screening achieved a coverage greater than 70%, and the death rate has changed little. The standardised incidence of 16.9 per 100 000 for invasive cancer in 1994 was higher than the baseline rates of disease before organised screening started in the United Kingdom. Cervical cancer is the fourth most common newly diagnosed cancer and accounts for 4% of deaths from cancer in local women, compared with 2% in the United Kingdom.

One of us (PA) recently found that 56% of nearly 1800 women aged between 20 and 75 in Hong Kong had never had a cervical screening test.<sup>4</sup> Coverage was lowest among



Age standardised incidence of invasive cervical cancer and mortality from cervical cancer, Hong Kong, 1982-7

older women (72% of women over 50 had never been screened) and those in the lower socioeconomic groups. Less than a quarter of all women were screened regularly, and these were generally screened yearly or more often.

The current screening system in Hong Kong is therefore inequitable, wastes resources, and results in avoidable cases of cervical cancer. It may also cause unnecessary harm by overscreening women at lower risk. The study by Quinn et al provides further support for centralised organisation in any screening system and is a message that should not be ignored by any country with a developed health care system.

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## Use of guidelines should be evaluated in randomised controlled trials

**EDITOR**—It remains to be proved whether implementing guidelines for the prevention of corticosteroid induced osteoporosis will be of benefit overall. The editorial by Lips<sup>1</sup> encouraging the adoption of the UK Consensus Group's guidelines<sup>2</sup> is based on the assumptions that following these guidelines will have no adverse effects, will achieve the benefits the group envisaged mostly by extrapolation of the results from limited studies, and will be worth the costs entailed.

On the contrary, it is easy to imagine that advice to take regular calcium and vita-

min D, to review lifestyle, and to take bisphosphonates (or hormone replacement therapy or calcitriol) will add important problems of adherence to an otherwise simple regimen of glucocorticoid treatment for example, 10 mg once a day for the early management of polymyalgia rheumatica.

Assertions that guidelines (even those which are well thought out) can be implemented without the potential for adverse outcomes and additional economic costs should not be accepted. The introduction of guidelines is seldom tested in randomised controlled trials,<sup>3</sup> yet this is what is required if they are to be evaluated adequately.

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- Lips P. Prevention of corticosteroid induced osteoporosis. *BMJ* 1999;318:1366-7. (22 May.)
- Eastell R, Reid DM, Compston J, Cooper C, Fogelman I, Francis RM, et al. UK Consensus Group on management of glucocorticosteroid induced osteoporosis: an update. *J Intern Med* 2001;251:92.
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## Cognitive therapy is no better than supportive counselling in schizophrenia

**EDITOR**—Minerva is wrong to state that cognitive behaviour therapy can improve symptoms in people with schizophrenia,<sup>1</sup> based on the findings of the latest study by Tarrier and colleagues.<sup>2</sup> In fact, the results they present are similar to those that they published recently in the *BMJ*.<sup>3</sup> They found that although cognitive behaviour therapy was significantly superior to "routine care," there was no significant difference between cognitive therapy and non-specific "supportive counselling." (In fact, some of my patients receive such supportive counselling as part of their routine care.)

As I pointed out in a letter regarding the earlier study,<sup>4</sup> cognitive behaviour therapy is more expensive than supportive counselling. There seems to be a growing assumption that cognitive behaviour therapy is beneficial for patients with schizophrenia. The assumption is based on very little evidence, and it is unhelpful for Minerva to contribute to this trend. Larger studies need to be done to determine whether cognitive behaviour therapy actually has any specific effect other than the effects due to an increased quantity of therapeutic contact.

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## Door to needle times of 12 minutes are possible in one emergency department

**EDITOR**—Several correspondents have discussed call to needle times after acute myocardial infarction.<sup>1</sup> Rapid door to needle times are possible in accident and emergency departments with the use of appropriate protocols and the availability of cover by senior medical staff on the floor 24 hours a day.

In the emergency department of this hospital all adult patients with chest pain are taken immediately to a cubicle by nursing staff; before they see a doctor oxygen treatment and electrocardiographic monitoring are started and an intravenous line is inserted. A 12 lead electrocardiogram is taken to the attending emergency doctor even before it is labelled. When an acute myocardial infarction is diagnosable from this first electrocardiogram the door to needle times are around 12 minutes. Thus thrombolysis is routinely administered in this emergency department.

The key points are that the nurses do not require medical authorisation to instigate their protocol and that the first doctor to read the electrocardiogram has the competence to interpret it correctly and the authority to instigate thrombolysis.

This hospital has a tertiary cardiac surgical service, and its cardiologists envisaged from the outset that the emergency department would function in this way.

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- Correspondence. Call to needle times after acute myocardial infarction. *BMJ* 1999;318:1553-4. (5 June.)

## Early trials of angiogenic factors have not targeted patients most at risk of ocular disease

**EDITOR**—In his clinical review on therapeutic angiogenesis Henry discusses the potential benefits of this treatment in relation to myocardial and limb ischaemia.<sup>1</sup> Vascular endothelial growth factor, fibroblast growth factor, and the angiopoietin receptors have already been evaluated in disease models and small clinical trials and shown to be beneficial. The use of these agents highlights a paradox of subspecialty medicine.

Henry briefly mentions the danger of pathological angiogenesis in other tissues, and this is of particular relevance to ocular disease. Vascular endothelial growth factor, fibroblast growth factor, and angiopoietin have been implicated in the pathogenesis of proliferative diabetic retinopathy, ischaemic central retinal vein occlusion, retinopathy of prematurity, and exudative age related macular degeneration.<sup>2,3</sup> Ocular neovascularisation is common to all these conditions, and visual loss results from vitreous or subretinal haemorrhage, retinal detach-