group was 0.5% in the HERA trial, 4.1% in the B-31 trial, and 2.9% in the N9831 trial.

On the basis of these results, the standard of care in North America has already seen a paradigm shift. But what are the implications for women with breast cancer worldwide? Trastuzumab is currently licensed in Britain for advanced breast cancer but has not been approved for early stage disease. One of the barriers to licensing is undoubtedly cost. In Canada the cost of the drug alone is almost \$C50 000 (£25 000, US\$43 000, €36 000) for one year of treatment. Although rapidly adopted as standard of care in the United States, trastuzumab was not approved for funding in Ontario, Canada, until after a substantial media frenzy.

Trastuzumab is the first (though certainly not the last) monoclonal antibody to show a survival benefit as an adjuvant treatment. The implications of these novel treatments in oncology are important not only for patients but also for healthcare costs. The costs incurred are not just the price of the drug but also the resources related to giving the drug (such as nursing, pharmacy, physician time, serial cardiac multiple gated acquisition scans). Another barrier is the cost of testing for HER2 expression. Many centres offer HER2 testing to women with early disease, but this is by no means standard. A recent survey in England and Wales found that more than a quarter of women are never tested for HER2 overexpression, and only half are currently tested at the time of initial diagnosis.⁸

Novel targeted treatments for other cancer types are continually being tested and developed, and treatments have advanced rapidly advanced in other common malignancies besides breast cancer. If we are to ensure equity of access to such highly effective but

expensive targeted treatments we need transparent, timely, and appropriately funded processes in place to prepare healthcare systems for these important advances. It is no longer appropriate for healthcare systems to be continuously "trying to drink water from the proverbial fire hose."

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Including older people in clinical research

Benefits shown in trials in younger people may not apply to older people

There are more old people alive today than at any time in history. Older people are, quite rightly, "the core business of the NHS."¹ The need to be able to draw on the results of good quality research to inform best practice in the specific management of older people is compelling. So we might expect that researchers would have eagerly embraced the participation of older people in clinical trials. Yet this is not the case. What do clinicians and researchers have to do to redress the serious bias against older people in clinical research?

The evidence that older people are being excluded from clinical research is widespread. Although the world is facing a global increase in the prevalence of diabetes mellitus, and by 2030 it is estimated that over 48 million older people in developed countries will have diabetes, the mean age of participants in the United Kingdom Progression of Diabetes Study was only 53 years. Guidelines on older people with diabetes have acknowledged the dearth of evidence, basing recommendations on expert opinion and extrapolation from research in younger populations.² A systematic review of cancer clinical trials reported that patients aged over 65 were under-represented, with only a quarter to a third of

potentially eligible older patients enrolled.³ Research on cardiovascular disease tells a similarly depressing story as 40% of the 593 randomised trials of coronary artery disease published between 1991 and 2000 had explicit exclusions on the basis of age.⁴ Analysis of a national cohort of 20 388 older Medicare beneficiaries with heart failure showed that only 18%, 13%, and 25% met the enrollment criteria for the SOLVD, MERIT-HF, and RALES trials respectively.⁵

In 1997 it was reported in the *BMJ* that one third of research papers published in four major medical journals excluded older people without justification.⁶ We repeated this analysis for papers published in the same journals in 2004, and found that although matters have improved a little, almost 15% of papers still unjustifiably excluded older people, and that fewer than 5% of the papers published were specific to older people (see table on bmj.com).

The under-representation of older people in clinical research is clear, but what might the explanation be? The first possibility is that investigators

Table appears on bmj.com

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seeking clean science and low drop out rates are deterred by the prospect of enrolling participants with comorbidities and multiple medicines, which are common features of late old age. Such individuals clearly have many risk factors for drug interactions, side effects, death, and admission, all of which may fail to flatter trial findings. Age, protocol restrictions on comorbidities, and physicians' perceptions have been identified as important contributors to the exclusion of older patients from cancer trials.³ The narrow eligibility and exclusion criteria used in many clinical trials achieve a homogeneity of study population, and so reduce unexpected variations in drug efficacy and adverse events.⁷ Clearly a tension exists between the validity and the generalisability of trial findings, but this practice leaves a yawning chasm between patients in the real world and patients who participate in clinical studies. This greatly disadvantages older people, to whom the evidence does not apply.

The second possibility is that investigators view the older population as vulnerable and so in need of protection from researchers. This, of course, undermines autonomy. Sadly, the growing regulatory burden on researchers has provided a further disincentive to research in under-studied groups.⁸ Yet, when approached, older people report a high rate of willingness to consider participation in clinical trials.⁹

The final possibility is that investigators are daunted by the hard work involved in enrolling and maintaining older, frail people in clinical trials. Screening may be a prolonged process, and many older patients wish to discuss the trial with relatives, carers, and other health professionals before enrolling. Transport and mobility problems present another set of barriers to participation, especially among poorer, socially isolated patients—who ironically are most likely to suffer from ill health. Obtaining informed consent can be more challenging, as cognitive, hearing, and visual impairments may need to be surmounted.

It cannot be assumed that the benefits to younger patients enrolled in trials can be extrapolated to frail older people.¹⁰ Several strategies could potentially improve the current situation. Firstly, regulatory authorities should ensure that the population likely to be prescribed a particular drug once licensed actually participates in its evaluation.¹¹ Secondly, those funding and commissioning research should favour proposals in

typical populations which incorporate end points that are meaningful and relevant to older people. Both ethics committees and funders should recognise as unethical applications proposing to apply arbitrary and unjustified age restrictions.¹² Funders could ensure that grant funding includes resources to address issues like access, transport, social networks, and the management of treatment-related events. Thirdly, protocols should be specifically designed to stratify by age or use modified exclusion criteria to allow the inclusion of patients with comorbid disease and multiple medication.³

Promotion of the benefits of research in older people is required by engaging with the public as a whole, older people, funding bodies, researchers, and clinicians. The greatest burden of disease in the developed world falls on older people. It is time that research activity reflected this.

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Human resources for health in Africa

Better training and firm national policies might manage the brain drain

African countries have a very low density health workforce, compounded by poor skill mix and inadequate investment.¹ Yet trained healthcare staff continue to migrate from Africa to more developed countries. The World Health Organization has estimated that, to meet the ambitious targets of the millennium development goals, African health services will need to train and retain an extra one million health workers by 2010.²

It is too simplistic and misleading to define or try to resolve the crisis in human resources for health in Africa

by looking only at overall numbers and density of workers, not least because these vary from country to country.^{3,4} Furthermore, the poor performance of health services in African countries is often compounded by shortages of drugs and other essential supplies, broken equipment, and poor logistical support. Africa needs balanced investment in human resources, infrastructure, drugs, logistics and other supportive services that will enhance the capacity to deliver health care.

Seven main principles should guide the debate on developing and refining African health services (box).