Participating in primary care research

GENERAL practitioners (GPs) should welcome the development of partnership between those who conduct research and those on whom, and on whose behalf, the research is done. The discipline has a long history of recognising people as 'co-producers of health',[1] rather than the passive objects of medical attention.[2] The recasting of people as 'participants in' rather than 'subjects of' research is a natural and welcome progression. Furthermore, GPs know only too well what it feels like to have research done 'on' them by those, often outside primary care, who seem to have missed the point.[3] In addition, practitioners can feel that they are regarded as mere conduits to reservoirs of people on their lists by researchers who have paid scant regard to the practitioners' preferences about study designs or recruitment strategies. Though clearly GPs do not experience the impacts of research felt by patients, they can claim some affinity with those who feel that their priorities are not always reflected in research designs, conduct, or outcomes. In this editorial we explore what it means to participate in primary care research from the perspectives of patients, GPs, and researchers.

The movement to recognise the role of patients or 'consumers' in the identification of research agendas and the commissioning and prosecution of research has been embraced by major funders of health research in the United Kingdom, including the Medical Research Council[4] and the National Health Service,[5] as well as by the Cochrane Collaboration,[6] the Royal Colleges, and other major organisations involved in commissioning research. The benefits of involving research participants are increasingly evident.[7] A recent trial of thrombolysis for acute ischaemic stroke, for example, used a model of mutually educative partnership.[8] The investigators canvassed the opinions of older people (who are the most likely to have strokes), presented the results to a separate research group, and then used the outcomes to inform the content of information leaflets and a strategy for obtaining consent for admission to the trial. These were then reviewed by people who had recently had a stroke, or by their carers. This iterative and incremental approach to collaboration produced workable solutions to the ethical problems inherent in recruiting acutely ill people to important but potentially risky research.

Such partnership yields benefits for participants, lead investigators, and for collaborators who recruit participants and run studies 'on the ground', particularly when this takes the form of collaborative preliminary work to assess the feasibility, relevance, and acceptability of proposed research.[9] The multi-centre national trial of HRT in women with a history of breast cancer diagnosed at an early stage began with a research project and feasibility study, led by the Consumers Advisory Group for Clinical Trials, to identify the outcomes prioritised by both patients and researchers now included in the main trial protocol. This work also identified specific training needs for those who would run the trial and the information needs of participants, patients, and health professionals.[10]

Though much of the research and commentary about consumer involvement has focused on large multi-centre trials rather than the study designs more often found in primary care research, it is clear that consumer involvement in research poses particular challenges for primary care. Disturbing mismatches between the research agendas of researchers and the priorities of patients have been identified.[11] The primary care research community must not delude itself that the special character of the doctor–patient relationship in general practice means it already understands people's priorities. Ways must be found to ensure that the primary care agenda for research closely maps what patients want to have researched.

For studies conducted in primary care, it is particularly important that patients are involved in the choice of research outcomes and how they are measured. For example, although a reduction in the mean duration of otitis media from three to two days by using antibiotic therapy[12] may be seen as clinically insignificant, it might be very important to parents and children. Consumers also consider important a broader range of outcomes than those usually studied. These are often the outcomes that are most difficult to measure (and therefore most vulnerable to being 'designed out' of studies).[13] The optimal choice of outcomes is therefore directly informed by consumer views. In this issue, Salisbury and colleagues describe the impact of a school nurse-led clinic on the care of adolescents with asthma.[14] They report no change in 'disease outcomes' but found a preference by participants for care provided at school to care provided in their general practices. If we knew how participants valued this finding, then we would be much better placed to assign this its proper weighting. Qualitative research could help further explore the findings of this trial,[15] which makes a refreshing contribution to the currently under-researched field of organisation of health services for children.[16]

While the benefits of involving patients in the planning, design, and running of research projects are clear, both in principle and, increasingly, in practice, there is also, like any new approach, a need for careful evaluation. The rhetoric of consumer involvement is persuasive but it has dangers. One is the danger of romanticising patients' perspectives and failing to make appropriate judgements about the legitimacy or feasibility of their priorities. GPs are used to dealing with conflict between professional objectives (e.g. tight control over asthma symptoms) and patient autonomy (e.g. a wish to avoid inhaled steroids). It is sometimes impossible to resolve these conflicts in daily practice and similar tensions will arise when the legitimate objectives of research are not precisely the same as they are for those who participate in it. In moving towards partnership with research participants, it is important that we do not see this as implying that all and any patient objectives are substitutable for those originally chosen by the researchers; rather, there should be proper and respectful debates between all concerned. This principle of partnership and joint ownership should also underpin research done in primary care by those outwith it. In many

cases GPs are the 'consumers' of research just as patients are, and should be recognised as partners in the research process too, as well as be involved in the design, planning, choice of outcomes, and running of research projects.

All those who participate in research, be they patients, professionals, or researchers, should be recognised as participants; it will enhance research and its interpretation. Recognising and implementing this principle will be challenging, but lest we grow discouraged we (as patients, professionals, and researchers) should reflect on those well-intentioned studies that asked the wrong question, used the wrong outcomes, involved the wrong people or were performed at the wrong time and how we wished our advice had been asked.

ROBERT K MCKINLEY

Senior Lecturer, Department of General Practice and Primary Health Care, University of Leicester

MARY DIXON-WOODS

Senior Lecturer in Social Science and Health, Department of Epidemiology and Public Health, University of Leicester

HAZEL THORNTON

Independent Advocate for Quality in Healthcare and Research, Colchester

References

1. Tudor Hart J. *Feasible socialism: the National Health Service, past, present and future*. London: Socialist Health Association, 1994.
2. Fugelli P, Heath I. The nature of general practice. *BMJ* 1996; **312:** 456-457.
3. McKinley RK, Khunti K. Management of angina. *Br J Gen Pract* 1995; **45:** 328.
4. Medical Research Council. *Consumer Liaison Group: Terms of Reference*. URL: http://www.mrc.ac.uk/index/public-interest/public-consumer_liaison_group.htm (date accessed: 12 September 2000.)
5. National Cancer Research Network. *Promoting consumer involvement in NHS Research & Development*. URL: http:www.conres.co.uk/aim.htm. (date accessed: 12 September 2002)
6. Cochrane Collaboration Consumer Network. Cochrane Collaboration. URL: http://www.cochraneconsumer.com/welcome (date accessed: 12 September 2002)
7. Hanley B, Truesdale A, King A, *et al*. Involving consumers in designing, conducting, and interpreting randomised controlled trials: questionnaire survey. *BMJ* 2001; **322:** 519-523.
8. Koops L, Lindley RI. Thrombolysis for acute ischaemic stroke: consumer involvement in design of new randomised controlled trial. *BMJ* 2002; **325:** 415.
9. Thornton H, Dixon-Woods M. Recruitment of women into trials. *Lancet* 2002; **359:** 164-165.
10. Thornton H. Patient perspectives on involvement in cancer research in the UK. *Eur J Cancer Care* 2002; **11:** 205-209.
11. Tallon D, Chard J, Dieppe P. Relation between agendas of the research community and the research consumer. *Lancet* 2000; **355:** 2037-2040.
12. Little P, Gould C, Williamson I, *et al*. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. *BMJ* 2001; **322:** 336-342.
13. Chalmers I, Clarke M. Outcomes that matter to patients in tombstone trials. *Lancet* 2001; **358:** 1649.
14. Salisbury S, Francis C, Rogers C, *et al*. A randomised controlled trial of clinics in secondary schools for adolescents with asthma. *Br J Gen Pract* 2002; **52:** 988-996 (this issue).
15. Campbell M, Fitzpatrick R, Haines A, *et al*. Framework for design and evaluation of complex interventions to improve health. *BMJ* 2000; **321:** 694-696.
16. Dixon-Woods M, Young B, Heney D. Partnerships with children. *BMJ* 1999; **319:** 778-780.

Address for correspondence

Dr Robert K McKinley, Department of General Practice and Primary Health Care, University of Leicester, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW.

Breast cancer prevention

DESPITE advances in therapeutic strategies over the past three decades, breast cancer remains the leading cause of cancer deaths among women in most developed countries. The lifetime risk of developing the disease among women in Western Europe and North America is approximately 10% and therefore it is important to identify effective prevention strategies.

A recent review of the literature[1] has concluded that postmenopausal obesity and a sedentary lifestyle are important risk factors for breast cancer and modification of such factors can reduce the risk of developing the disease. It is thought that decreased serum concentrations of oestrogens, insulin and insulin-like growth factor 1 (IGF-1) mediate breast cancer risk reduction associated with postmenopausal weight reduction and regular physical activity. However, no conclusive evidence has been found regarding the role of dietary fat, phytoestrogens, and protein in relation to breast cancer risk.

Furthermore, it has been concluded that excessive alcohol consumption is associated with an approximately 15% increase in the risk of developing breast cancer.[1]

The Collaborative Group on Hormonal Factors in Breast Cancer reviewed the worldwide literature and concluded that the oral contraceptive pill (OCP) was associated with a small increase in breast cancer among current users and those who had stopped use in the past 10 years. However, the cancers diagnosed in women who had used the pill were less advanced than women who had not used them.[2] The group reported that the use of hormone replacement therapy (HRT) for five years or longer significantly increased the risk of breast cancer by 35% ($P<0.001$). The risk seems to revert to normal five years after HRT cessation.[3] However, there is no evidence so far that HRT increases breast cancer mortality, as the cancers diagnosed in HRT users tend to have favourable tumour characteristics. Nevertheless, the risks of breast cancer should be taken into account when considering treatment with HRT and OCP.

The most promising research into breast cancer prevention is provided by four randomised placebo-controlled studies using the selective oestrogen receptor modulator (SERM), tamoxifen.[4-7] Although the results of these trials have been inconsistent, a combined analysis[4] of the findings seems to favour the use of tamoxifen in reducing the risk of breast cancer by approximately 38%. Risk reduction is

greatest for oestrogen receptor-positive tumours. The incidence of endometrial malignancy and thromboembolism is significantly increased (odds ratios of 2.41 and 1.94 respectively), but no significant increase is noted in the incidence of other secondary cancers or all-cause mortality.[7] Although tamoxifen seems to be ineffective in BRCA1 carriers who are known to have an increased frequency of oestrogen receptor-negative tumours, there is evidence that bilateral oophorectomy significantly reduces the breast cancer risk in this subgroup of women.[8] The overall risk-to-benefit ratio for the use of tamoxifen in prevention remains unclear and longer follow-up of the current trials is required.

Raloxifene is another SERM which has been shown clinically and experimentally to be antiestrogenic on the breast and uterus. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial showed a reduction in breast cancer incidence of 76% in women treated for osteoporosis.[9] Raloxifene seems to have a more favourable adverse effect profile than tamoxifen, especially regarding the uterus. These two SERMs are currently undergoing direct comparison in the Study of Tamoxifen and Raloxifene (STAR), which started in 1999 and continues to recruit women.

The preliminary results of the Arimidex, Tamoxifen Alone or in Combination (ATAC) Trial have been reported recently.[10] The study showed that adjuvant anastrozole (a third-generation aromatase inhibitor) was superior to tamoxifen in reducing the incidence of contralateral breast cancer (HR = 0.42, $P<0.007$). This is likely to be a consequence of the difference in mechanism of action between the two drugs. The investigators observed that anastrozole was superior to tamoxifen in terms of disease-free survival (HR = 0.83, $P<0.013$), and non-musculoskeletal adverse effects, including endometrial cancer ($P<0.03$). However, tamoxifen was superior to anastrozole in terms of musculoskeletal adverse effects ($P<0.03$). It is clear, however, that intermediate to long-term follow-up is required to assess the effects of anastrozole on bone mineral density and cognitive function. The two drugs will be compared directly as chemopreventative agents within the IBIS II study.

It has been reported recently that COX-2 expression is upregulated in epithelial cancers, including breast cancer, and that COX-2 plays an important role in angiogenesis. A recent meta-analysis of 14 studies has demonstrated that the use of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with a relative risk of 0.82 of developing the disease (95% confidence interval [CI] = 0.75 to 0.89).[11] Such findings support the notion of randomised controlled trials using selective COX-2 inhibitors as potential chemopreventative agents with good tolerability and a favourable adverse effects profile.

Furthermore, a pilot study using goserelin (Zoladex) as a preventive agent in high-risk premenopausal women has already commenced. Other promising molecular target agents for chemoprevention include vitamin D analogues and inhibitors of lipo-oxgenase, angiogenesis, and tyrosine kinases. Another exciting possibility is gene therapy, which will be applicable to BRCA 1 and 2 carriers.

In addition to chemoprevention, the options for women at high risk for breast cancer include bilateral prophylactic mastectomy and/or oophorectomy. Retrospective studies[12] have shown that prophylactic mastectomy in high-risk patients can reduce breast cancer risk by between 87% and 90%. A recent prospective follow-up study has demonstrated that salpingo-oophorectomy in carriers of BRCA mutations can decrease the risk of breast cancer and BRCA-related gynaecological cancer.[13]

It appears from the above discussion that there is a need to individualise chemoprevention strategies in order to improve effectiveness. For example, tamoxifen is only effective in reducing the risk of developing ER-positive breast cancer and its use in subjects who are at risk of developing oestrogen receptor-negative breast cancer can be harmful. Identifying those at risk of developing oestrogen receptor-positive breast cancer is likely to enhance the effectiveness of this prevention strategy. Research must also be initiated to identify other agents that may be effective for patients at risk of developing oestrogen receptor-negative breast cancer.

KEFAH MOKBEL

Consultant Breast and Endocrine Surgeon and Professor, Brunel Institute of Cancer Genetics (UK), St George's Hospital, London.

References

1. Mokbel K, Leris C. The prevention of breast cancer: an overview. *Curr Med Res Opin* 2001; **16:** 252-257.
2. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: further results. *Contraception* 1996; **54:** 1S-106S.
3. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative re-analysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. *Lancet* 1997; **350:** 1047-1059.
4. Fisher B, Costantino JP, Wickerham DL, *et al*. Tamoxifen for the prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998; **90:** 1371-1388.
5. Powles T, Eeles R, Ashley S, *et al*. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. *Lancet* 1998; **352:** 98-101.
6. Veronesi U, Maisonneuve P, Costa A, *et al*. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. Italian Tamoxifen Prevention Study. *Lancet* 1998; **352:** 93-97.
7. Cuzick J. Update on new studies in Europe. *Eur J Cancer* 2002; **38:** 544 (Abstract 20).
8. Rebbeck TR, Levin AM, Eisen A, *et al*. Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. *J Natl Cancer Inst* 1999; **91:** 1475-1479.
9. Cummings SR, Eckert S, Krueger, *et al*. The effect of raloxifene on the risk of breast cancer in postmenopausal women: results from the MORE randomized trial. *JAMA* 1999; **281:** 2189-2197.
10. Arimidex, Tamoxifen Alone or in Combination Trial. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002; **359:** 2131-2139.
11. Khuder SA, Mutgi AB. Breast cancer and NSAID use: a meta-analysis. *Br J Cancer* 2001; **84:** 1188-1192.
12. Hartmann LC, Schaid DJ, Woods JE, *et al*. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N Engl J Med* 1999; **340:** 77-84.
13. Kauff ND, Satagopan JM, Robson MF, *et al*. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med* 2002; **346:** 1609-1615.

Address for correspondence

Professor Kefah Mokbel, Brunel Institute of Cancer Genetics (UK), St George's Hospital, London SW17 0QT.