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實 EVIDENCE 証

Hospital Authority Head Office
Medical Services Development Division

Clinical Effectiveness Unit
Issue 11. 2001

SCREENING FOR BREAST CANCER:
Breast Self-Examination, Clinical Breast Examination & Mammography

Invited Commentary from Professor A J Hedley, Department of Community Medicine and Unit for Behavourial Sciences, The University of Hong Kong.

"Screening for breast cancer, time to think and stop?" That was the rhetorical question raised by the ***Lancet*** letters column in 1995. This issue of [實EVIDENCE証] should at least prompt us to *stop and think* about breast screening. An evidence-based approach is needed here because on the one hand, breast cancer is a common registered cause of death in younger women, of unknown aetiology and with low survival rates after treatment. On the other hand screening receives a hard sell to women, both in the US and here in Hong Kong e.g. "If you are over 35 and haven't had a mammogram, you need more than your breasts examined." and "You've got time for dim sum but no time to check your breasts?". This implied promise of benefit hangs on a meta-analysis result of eight trials indicating that a 23% reduction in age specific mortality can be achieved. But five of the eight trials were non-significant, baseline imbalances and defects in randomisation affect half or more of them, and the outcome of the meta-analysis critically depends on the relatively large effect found in the oldest trials. The Swedish trial (1985) was one of the earliest but by 1999, following implementation of screening, no decrease in mortality was observed. The recent reports of reduction in mortality in some countries should be interpreted cautiously because this trend antedated screening. Although it may in part be attributed to screening, the admixture of different variants to the notified case mix, improved treatment protocols, surgical management and tamoxifen are all likely to have played an important role, if indeed the trend is real. In general the current emphasis on the delay in deaths identified by the meta-analysis is inappropriate and lacks a balanced public health approach; it ignores the harm and other costs which inevitably accompany a screening strategy of this type. Three quarters of eligible women do not benefit from screening programmes in the West even assuming the best overall effect of the intervention and many of them will predictably experience major disbenefits. The most important reference in this issue of [實 EVIDENCE 証] is by two Canadian surgeons Wright and Mueller: "Screening mammography and public health policy: the need for perspective". If we apply Wright and Mueller's framework to the Hong Kong population of women aged 50-69 (about 500,000) who are eligible for screening according to the results of the Western trials, and assume the prevalence of cancer at screening is the same as in the West, then we find that over 7 years there would be: 77,000 positive tests, of which only 7,000 would be cancers, and 200 deaths avoided with an absolute risk reduction of 0.04%. To achieve one death avoided per year, *if prevalence at screening was the same as in the West*, we would need to screen 17,500 women over the 7 years programme (of these 2275 would have a false positive) at cost of about $7 million each, not including the costs of investigating the false positives. In fact the lifetime risk in Hong Kong is lower than in the US by a large (about 3 times) order of magnitude. As a result false positives are likely to be much higher than estimated here. Furthermore it should be remembered that if any screening programme was as good as the meta-analysis it would only delay 23% of deaths in the 50-69 year olds, which is only 8% of all breast cancer deaths in the SAR. Selectively targeting high-risk women, as opposed to mass screening, may offer relatively greater benefits.

There is as yet no framework for rational policy making on screening in Hong Kong but we are gradually drifting into a situation where opportunistic screening on a non population basis is becoming widespread. There should now be a moratorium on all well-population breast screening until a firm evidence based policy is agreed and universally applied.

This issue of [實 EVIDENCE 証] presents the current best evidence on the effectiveness of different screening modalities in reducing breast cancer death and put them in the local context.

Framing the question

Patient	Asymptomatic women of age ≥50 with no known risk factors for breast cancer other than age
Intervention	Breast Self Examination; Clinical Breast Examination; Screening Mammography
Comparison	No screening
Outcome	Reduction in breast cancer mortality

BREAST SELF-EXAMINATION (BSE): Insufficient evidence at present to recommend, for or against, BSE with confidence

Interim analyses of two large RCTs on BSE were published.

Study	Study period	No. of subjects		Age (yr) at enrolment	Findings on interim analysis
		BSE	Control		
RCT (1)	1985 -	57,712	64,759	40-64	At 9-year follow-up, survival from time of tumour detection was 65% (BSE) vs. 55% (control); $p > 0.05$
RCT (2)	1989 -	133,375	133,665	30-65	At 5-year follow-up, cumulative breast cancer mortality between the BSE and control groups were similar

- The Russian study (1) randomised subjects on health clinic / factory basis, and provided aggressive education and reminders to the BSE group. Subjects were analyzed on an intention-to-treat basis. Survival from time of tumor detection was better in the BSE group but did not reach statistical significance. This finding must be carefully interpreted. First, it was not unexpected that the interim analysis would not achieve statistical significance as the sample size had power of 0.72 - 0.94 to detect a 30% reduction in breast cancer mortality at 15 years if compliance to BSE was 50 - 70%. Evidence indicated that only 18% of the BSE group reported monthly practice at the 4th year (3). Secondly, survival time, rather than breast cancer mortality, was reported and this made one hard to isolate bias due to earlier detection of cancer (i.e. lead time bias).

- The Chinese study (2) randomised subjects by work units, and provided aggressive education, reminders and periodic reinforcement for up to 6 years. Apart from excluding 1.91% and 2.04% of subjects from the BSE and control groups who did not respond after randomisation, analysis was performed on an intention-to-treat basis. Although economic reforms since 1994 had resulted in merging and closure of some factories, close to 90% of BSE subjects attended reinforcement sessions in 1994 and more than 80% had attended all education and reinforcement sessions. Cumulative breast cancer mortality at 5 years were 30.9 and 32.7 per 100,000 for the BSE and control group, respectively. The finding remains inconclusive due to short follow-up and that analysis was based on small

numbers of breast cancer deaths from a subset of subjects recruited in the first year of study.

Public Policy Recommendation

The U.S. Preventive Health Service Task Force recommended in 1996 that "There is insufficient evidence to recommend for or against the teaching of BSE." (4). The (U.K.) Government's Advisory Committee on Breast Cancer Screening agreed in 1998 that "The effectiveness of breast self examination in reducing mortality from breast cancer has never been consistently demonstrated, in the UK or elsewhere. The Advisory Committee recommended that it should not be promoted as a screening procedure

Current Position

The effectiveness of BSE remains unresolved. Hopefully the Chinese study will provide a better answer at completion. An important yet difficult issue is the establishment of an effective programme to ensure high levels of enthusiasm and compliance from participants, without which Type II error could not be avoided.

[Source: (1) Semiglazov VF, Moiseenko VM, Manikhas AG, Protsenko SA, Kharikova RS, Popova RT. et al. Interim results of a prospective randomised study of self-examination for early detection of breast cancer. Vopr Onkol 1999; 45(3):265-71. (2) Thomas DB, Gao DL, Self SG, Allison CJ, Tao Y, Mahloch J. et al. Randomized trial of breast self-examination in Shanghai: methodology and preliminary results. J Natl Cancer Inst 1997; 89(5):355-65. (3) Semiglazov VF, Moiseenko VM, Bavli JR et al. The role of breast self-examination in early breast cancer detection (result of the 5-year USSR/WHO randomized study in Leningrad). Eur J Epidemiol 1992 Jul;8(4):498-502. (4) Eastman P. Task force issues new screening guidelines [news]. J Natl Cancer Inst 1996 Jan;88(2):74-6. (5) Department of Health. Clinical examination of the breast. London: Department of Health, 1998 (Professional Letter: PL/CMO/98/1, PL/CNO/98/1. 2 February 1998)

CLINICAL BREAST EXAMINATION (CBE): Scanty evidence

No RCT directly compared CBE performed by health professionals against no screening. There is no direct level I, II or III evidence that supports CBE is effective in reducing breast cancer mortality over no screening. A systematic review, combining data from six studies, estimated the sensitivity and specificity of CBE as 54% (95% CI 48.3-59.8) and 94% (90.2-96.9), respectively (1).

Public Policy Recommendation

The U.S. Preventive Health Service Task Force recommended in 1996 that "There is insufficient evidence to recommend for or against the use of screening CBE alone." (2) The (UK) Government 's Advisory Committee on Breast Cancer Screening agreed in 1998 that "there was no evidence to support the efficacy of breast examination by health professionals of the well women" and advised "that palpation of the breast by either medical or nursing staff should not be included as part of routine health screening for women. " (3)

[Source: (1) Barton MB, Harris R, Fletcher SW. Does this patient have breast cancer? The screening clinical breast examination: should it be done? How? JAMA 1999 Oct 6; 282(13):1270-80. Available from:URL: http://jama.ama-assn.org/issues/v282n13/rfull/jrc90000.html (2) Eastman P. Task force issues new screening guidelines [news]. J Natl Cancer Inst 1996 Jan;88(2):74-6. (3) Department of Health. Clinical examination of the breast. London: Department of Health, 1998 (Professional Letter: PL/CMO/98/1, PL/CNO/98/1. 2 Feb 1998)

SCREENING MAMMOGRAPHY: Evidence in the West suggests that benefit is age-dependent

Randomised Controlled Trials

- Breast cancer screening has been intensively evaluated. There are eight completed RCTs, in which 456,349 women have participated.

Study	Start day	Screening interval (months)	No. of mammographic views	Annual CBE	Number randomised	
					Screening	Control
New York (1)	1963	12	2	no	30,131	30,565
Malmo (2)	1976	21	2	no	21,088	21,195
Kopparberg (3)	1977	24	1	no	38,589	18,582
Ostergotland (3)	1977	24	1	no	38,491	37,403
Edinburgh (4)	1979	24	2 (1st round), then 1	yes	22,926	21,342
Canadian (5,6)	1980	12	2	yes	44,925	44,910
Stockholm (7)	1981	24-28	1	no	40,318	19,943
Gotenburg (8)	1982	18	2	no	11,724	14,217
All studies					248,192	208,157

[Source: (1) Chu KC, Smart CR, Tarone RE. Analysis of breast cancer mortality and stage distribution by age for the Health Insurance Plan clinical trial. J Natl Cancer Inst 1988 Sep 21; 80(14):1125-32 (2) Andersson I, Aspergren K, Janzon L, Landberg T, Lindholm K, Linell F et al. Mammographic screening and mortality from breast cancer: the Malmo mammographic screening trial. BMJ 1988 Oct 15; 297(6654):943-8 (3) Tabar L, Fagerberg G, Chen HH, Duffy SW, Smart CR, Gad A et al. Efficacy of breast cancer screening by age: new results from the Swedish Two-County Trial. Cancer 1995 May 15; 75(10):2507-17 (4) Alexander FE, Anderson TJ, Brown HK, Forrest AP, Hepburn W, Kirkpatrick AE et al. 14 years follow-up from the Edinburgh randomised trial of breast-cancer screening. Lancet 1999 Jun 5; 353(9168):1903-8 (5) Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 1-breast cancer detection and death rates among women aged 40-49 years. CMAJ 1992 Nov 15; 147(10):1459-76 (6) Miller AB, To T, Baines CJ, Wall C. The Canadian National Breast Screening Study: update on breast cancer mortality. J Natl Cancer Inst Monogr 1997; (22):37-41 (7) Frisell J, Lidbrink E, Hellstrom L, Rutqvist LE. Follow-up after 11 years: update of mortality results in the Stockholm mammographic screening trial. Breast Cancer Res Treat 1997 Sep; 45(3):263-70 (8) Bjurstam N, Bjorneld L, Duffy SW, Smith TC, Cahlin E, Erikson O et al. The Gothenburg breast screening trial: first results on mortality, incidence, and mode of detection for women ages 39-49 years at randomisation. Cancer 1997 Dec 1; 80(11):2091-9]

- Systematic reviews were published by several health agencies on these RCTs including:

  (1) National Cancer Institute. Screening for breast cancer. Sep 2000. Available from: URL: http://www.graylab.ac.uk/cancernet/304723.html

  (2) Hider P, Nicholas B. The early detection and diagnosis of breast cancer: a literature review - an update. NZHTA Report 1999;22

  (3) Hatstall, C. Mammography screening: mortality rate reduction and screening interval. Alberta, Canada: Alberta Heritage Foundation for Medical Research: June 2000. (HTA-21).

  A series of meta-analysis were also published. The latest one being published in 2000.

Women aged ≥ 50: Current best evidence shows a trend toward reducing breast cancer mortality after 7-9 years of screening by mammography

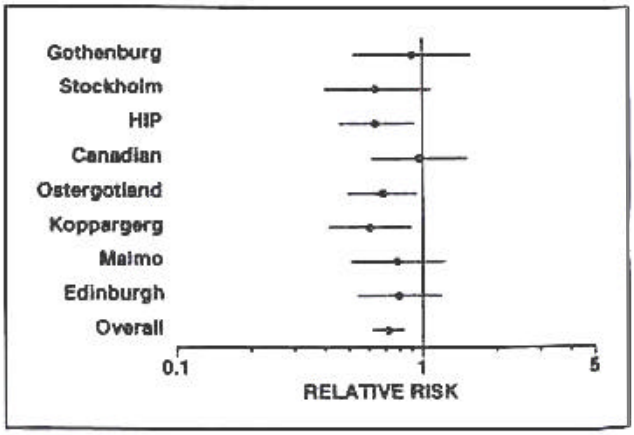
- Seven out of the eight RCTs favoured screening by mammography though not all of them achieved statistical significance. Combining their data using a fixed-effect statistical method, Kerlikowske et al yielded a summary relative risk of 0.77 with 95% CI 0.69 - 0.87 (1).

- To demonstrate the effect of follow-up duration and to avoid excessive influence from trials with longer follow-up (which had more breast cancer events), Kerlikowske et al performed sub-group analysis and showed that reduction in mortality reached statistical significance after 7 to 9 years (1).

Follow-up (yrs)	Relative Risk	95% CI
7 – 9	0.73	0.63 – 0.84
10 – 12	0.76	0.67 – 0.87

[Source: Kerlikowske K. Efficacy of screening mammography among women aged 40 to 49 years and 50 to 59 years: comparsion of relative and absolute benefit. J Nat Can Inst Monographs 1997;(22):79-86.]

Reduction in breast cancer mortality in women aged 50 to 74 years after seven to nine years of follow-up from the initiation of screening mammography among randomised controlled trials.



- Controversy exists as to the suitability to include all studies for meta-analysis and the appropriateness to combine their data, due to variations in randomisation (cluster vs. individual), intervention (one-view vs. two-view mammography, screening intervals from 12 to 33 months, mammography with or without clinical breast examination) and study population. Gotzsche and Olsen doubted adequacy of randomisation in some studies and claimed that six of the eight RCTs had baseline imbalance and / or inconsistencies in the number of women randomised. Sensitivity analysis showed that the combined relative risk was significantly different between the two adequately randomised RCTs (1.04 with 95%CI 0.84-1.27) and the remaining RCTs (0.75 with 95%CI 0.67-0.83). (3)

- The Canadian National Breast Screening Study-2 compared breast cancer mortality following annual screening (total for 4-5 years) by consisting of two-view mammography and CBE with mortality following annual screening by CBE only (4). BSE was taught to all participants and reinforced on each screening visit. 39,459 women were randomly assigned to the two arms, 99.86% of them were successfully followed up at 13 years. Analysis showed no clinically important outcome difference, the cumulative rate ratio to be 1.02 (95%CI 0.78 – 1.33).

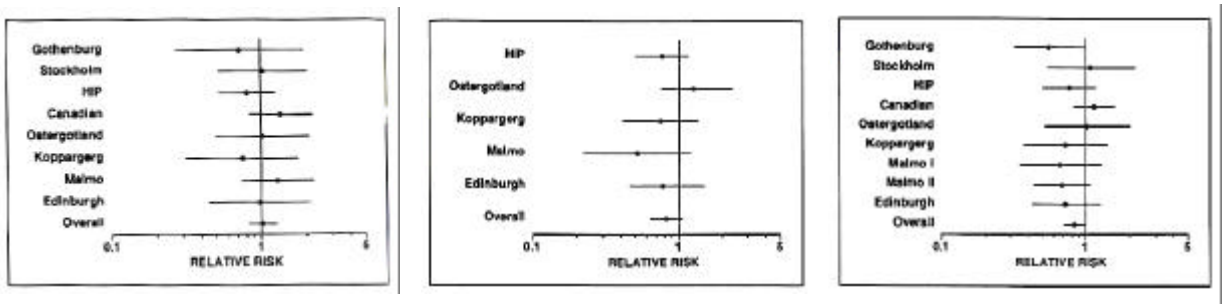
	Mammography plus CBE (and BSE)	CBE (and BSE)
No. of participants	19,711	19,694
Invasive breast cancer	622	610
In situ breast cancer	71	16
Breast cancer mortality	107	105

[Source: (1) Kerlikowske K, Grady D, Rubin SM, Sandrock C, Ernster VL. Efficacy of screening mammography. A meta-analysis. JAMA 1995 Jan11;273(2):149-54. (2) Kerlikowske K. Efficacy of screening mammography among women aged 40 to 49 years and 50 to 59 years: comparsion of relative and absolute benefit. J Nat Can Inst Monographs 1997;(22):79-86. (3) Gotzsche PC and Olsen O. Is screening for breast cancer with mammography justifiable? Lancet 2000 Jan 8; 355(9198):129-34. (4) Miller AB, To T, Baines CJ, Wall C. Canadian National Breast Screening Study-2: 13-year results of a randomised trial in women aged 50-59 years. J Natl Cancer Inst 2000; 92(18):14990-1499.]

Women aged 40-49: Current best evidence shows inconsistent effect on breast cancer mortality after 7-9 years of screening by mammography

- None of the RCTs had sufficient sample size to detect meaningful mortality reduction for women aged 40 to 49 years with confidence (1). Individual RCTs yielded heterogeneous results after 7-9 years. Meta-analyses by fixed- and random-effects statistical methods showed similar outcomes between the study and control groups (2, 3). Reduction in breast cancer mortality only became apparent at much longer follow-up (10-14 years). Part of the benefits was probably due to detection of cancer at or after the age of 50. Although individual RCT lacks power, meta-analysis should have been able to identify a trend earlier if screening was, indeed, beneficial for women aged 40-49 years. This was, however, not detected.

[Source: (1) Hatstall, C. Mammography screening: mortality rate reduction and screening interval. Alberta, Canada: Alberta Heritage Foundation for Medical Research: June 2000. (HTA-21) (2) Kerlikowske K. Efficacy of screening mammography among women aged 40 to 49 years and 50 to 59 years: comparsion of relative and absolute benefit. J Nat Can Inst Monographs 1997;22:79-86. (3) Glasziou PP, Woodward AJ, Mahon CM. Mammographic screening trials for women aged under 50. A quality assessment and meta-analysis. Med J Aust 1995 Jun 19; 162(12):625-9.]



Follow-up (years)	7 – 9	10 – 12	10-14
Summary RR (95% CI)	1.02 (0.82 – 1.27)*	0.83 (0.65 – 1.06)	0.84 (0.71 – 0.99)

* Calculated based on a 'fixed-effects' statistical method. Glasziou et al (1995), however, derived a RR of 0.95 (0.77 – 1.18) using a 'random-effects' statistical method (3).

[Source: Kerlikowske K. Efficacy of screening mammography among women aged 40 to 49 years and 50 to 59 years: comparison of relative and absolute benefit. J Nat Can Inst Monographs 1997;22:79-86.]

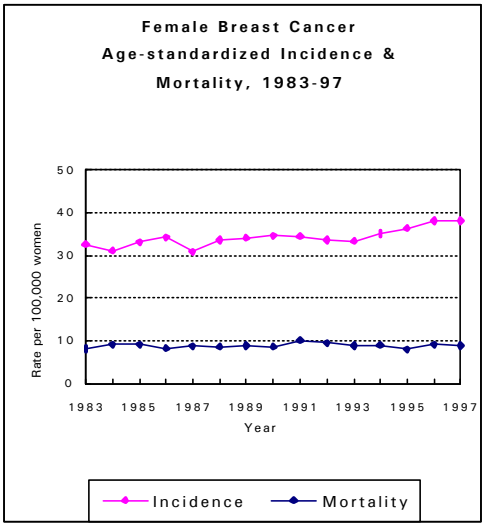
Current Position in the Western Countries

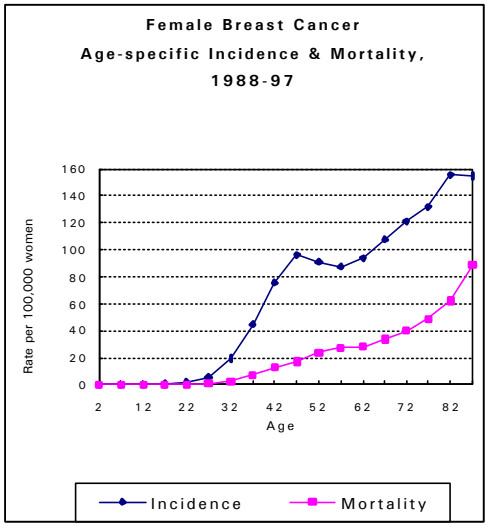
Current best evidence derived from the Western population generally supports that screening mammography can reduce breast cancer mortality in women aged ≥ 50 but not below.

實EVIDENCE 証in CONTEXT

Putting evidence into local context

- Most Asian women, including the Chinese population in Hong Kong, has lower incidence of breast cancer compared to the West (1). The trends in age-standardized and age-specific incidence and mortality of breast cancer in Hong Kong are shown below (2).





[Source : Hong Kong Cancer Registry, Hospital Authority]

- Justification for mass, population screening should take into consideration of benefits, harm and cost from a public health perspective. To evaluate screening mammography in terms of population benefit, one should use practical yardsticks such as the "Number Needed to Screen (NNS)" i.e. the number of participants needed to screen regularly to prevent one breast cancer death, or added years of life, rather than lives at risk after diagnosis. Such an assessment was published by Wright and Mueller (3).

Table: Screening mammography: randomised prospective controlled clinical trials (2)

	HIP 1982	SNBH 1985	Malmo 1988	Edln 1990	Stockholm 1991	CNBSS 1992
No of women screened	31,888	78,085	21,088	23,226	40,318	44,854
Deaths from breast cancer:						
Screened	147	87	63	68	39	76⁺
Control	192	127*	66	76	58*	67
Reduction in mortality (relative %)	23 (p<0.05)	31 (p<0.02)	5 (NS)	11 (NS)	33 (NS)	.. (NS)
No of women screened for 1 less death/year	7086	13 665	63 264	20 322	15 703	..

Dates = dates of trial publication. HIP = Health Insurance Plan of New York; SNBH = Swedish National Board of Health; Edln = Edinburgh; CNBSS = Canadian National Breath Screening Study; NS = not significant. * Adjusted for the different numbers in study and control groups. ⁺ Increased mortality occurred in those aged 40-49 years.

- Given the Chinese women in HK have a lower incidence of breast cancer than the Caucasians (3), the NNS in HK would be higher than those reported in the West. This also means that the "Number Needed to Harm (NNH)" will be less. False positive rate of mammographies will cause anxiety, unnecessary invasive procedures, and interruption of routines in a significant number of participants.

- For a screening mammography programme to be effective, it requires a high level of uptake and compliance from participants together with a quality screening service. An infrastructure to ensure these factors is yet to be developed in Hong Kong in large-scale. Despite evidence support population-based screening mammography for women aged 50 and above in the West, it is doubtful whether similar benefit could be achieved locally. Given our lower breast cancer incidence, rather unenthusiastic attitude towards regular screening, high mobility and dropout rate, and the lack of an effective infrastructure mentioned above.

- The benefit of screening mammography programme will be greater in selected groups of women who have high risk factors associated with breast cancer. For example, women with a history of breast cancer are at increased risk for a second primary breast cancer with incidence varying from 0.6% to 1% per year. The NNS to prevent one breast cancer death should, in theory, be much lower than that of the general population. Under resources and system constraints, healthcare providers are in better position to target smaller numbers of high-risk participants to ensure compliance for regular screening.

[Source: (1) Leung GM, Lam TH, Hedley AJ. Screening mammography re-evaluated. Lancet 2000 Feb 26; 355(9205):750-51 (2) Hong Kong Cancer Registry, Hospital Authority (3) Wright CJ, Mueller CB. Screening mammography and public health policy: the need for perspective. Lancet 1995 Jul1;346(8966):29-32.]

Please also see comments from review panel members in 實 EVIDENCE 証 論 FORUMS 壇 **available from HALIS.**

Review Panel: Dr Dickson Chang, Dr Lorraine Ho, Dr W H Kwan, Dr Gabriel Leung, Dr S P Lim, Dr H W Liu, Dr T K Yau.

Time taken to prepare and produce this issue of [實 EVIDENCE 証] :

	Man-hour		
Type of involvement	**Medical**	**Technical/ Scientific**	**Administrative & clerical**
Brainstorming (identify area of interest, agree on priority and approach, etc.)	2	2	
Convene review panel			1
Review panel discussion (consolidate ideas and formulate the review question)	15	5	
Search current best evidence and filter out the obviously unsuitable ones		4	
Assess quality of evidence for inclusion in the review exercise	2	3	
Perform critical appraisal, record findings	10	5	
Synthesis findings and draft [實 EVIDENCE 証]	10	5	
Review and revise draft [實 EVIDENCE 証]	6	3	
Invite comments from experts			2
Total	**45**	**27**	**3**

20 Jan 2001