Examples of Systematic Reviews with Qualitative or Quantitative Signals for Updating

I. All 8 Reviews with Signals for "Potentially Invalidating Changes in Evidence" (criteria for signals A1-A3)

1. The Albumin Reviewers (Alderson P, Bunn F, Lefebvre C, Li Wan Po A, Li L, Roberts I, Schierhout G). Human albumin solution for resuscitation and volume expansion in critically ill patients (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2001. Oxford: Update Software.

Question(s) addressed	Does human albumin or plasma protein fraction reduce mortality in patients who are critically ill (hypovolemia, burns, or hypoalbuminemia)?
Findings of Original Review	The original review found that "For each patient category the risk of death in the albumin treated group was higher than in the comparison group… an increase in the risk of death of 6% (3% to 9%). These data suggest that for every 17 critically ill patients treated with albumin there is one additional death."
New Findings	A pivotal trial found no difference in the risk of death between patients who received albumin and those who did not (relative risk of death, 0.99; 95 percent confidence interval, 0.91 to 1.09; P=0.87). It concluded: "In patients in the ICU, use of either 4 percent albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days."
Qualitative signal	**Opposing findings**: The original systematic review reported an increase in mortality; a pivotal trial showed no difference in risk of death
Quantitative signal	**Change in statistical significance**: Relative risk of death became non-significant RR = 1.68 (1.26, 2.23) → 1.04 (0.95, 1.13) **Change in effect magnitude of 50% or more**: Relative risk increase for death of 0.68 → increase of only 0.04
Other signals	Increase in number of patients of at least 50%: N=1419 → N=8352 Trial with sample size at least 3 times the size of previous largest trial: Previous largest trial had 219 patients; new trial had 6933 patients Change in width of 95% confidence interval of at least 50%: as shown above
Source(s) of new evidence	**Pivotal trial:** Finfer S et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350:2247-56.

Time to signal	Qualitative signal: 3.0 years Quantitative signal: same

2. Alejandria MM, Lansang MA, Dans LF, Mantaring JBV. Intravenous immunoglobulin for treating sepsis and septic shock (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2001. Oxford: Update Software.

Question(s) addressed	Does intravenous immunoglobulin (IVIG) reduce mortality, bacteriological failure rates, and duration of stay in hospital in patients with bacterial sepsis septic shock?
Findings of Original Review	Comparing polyclonal IVIG versus control, the original review reported a relative risk of death 0.60 (95% CI: 0.47 to 0.76) among a total of 413 patients. The authors concluded that polyclonal intravenous immunoglobulin "significantly reduces mortality and can be used as an adjuvant treatment for sepsis and septic shock."
New Findings	A subsequent meta-analysis (Pildal 2004) included 763 patients and found that "[h]igh-quality trials …showed a relative risk of 1.02 (95% CI, 0.84-1.24), whereas other trials (involving a total of 948 patients, 292 of whom died) showed a relative risk of 0.61 (95% CI, 0.50-0.73). Because high-quality trials failed to demonstrate a reduction in mortality, polyclonal immunoglobulin should not be used for treatment of sepsis except in randomized clinical trials." The textbook Up-To-Date quotes this subsequent meta-analysis and states intravenous immunoglobulin "is rarely used to treat patients with septic shock in the United States, and this approach is not recommended pending the demonstration of benefit in large, well designed trials."
Qualitative signal	**Opposing findings**: The original systematic review reported a definite reduction in mortality; a subsequent meta-analysis showed no benefit
Quantitative signal	**Change in statistical significance:** among higher quality trials only **Change in effect magnitude of 50% or more**: among higher quality trials only
Other signals:	Increase in number of patients of at least 50%: N=1992 → N=3082 (this increase was for meta-analysis of monoclonal anti-endotoxins; for polyclonal IVIG, increase was not 47%)
Source(s) of new evidence	Pildal J, Gotzsche PC. Polyclonal immunoglobulin for treatment of bacterial sepsis: a systematic review. Clin Infect Dis. 2004;39(1):38-46.
Time to signal	Qualitative signal: 3.0 years Quantitative signal: not applicable

3. Bucher, H. C., Guyatt, G. H., and Cook, R. J., Effect of calcium supplementation on pregnancy-induced hypertension and preeclampsia: A meta-analysis of randomized controlled trials. *JAMA.* 1996. 275: 1113-1117.

Question(s) addressed?	What effects does calcium supplementation during pregnancy have on blood pressure, preeclampsia, and adverse maternal and fetal outcomes
Findings of Original Review	The original review showed a substantial, statistically significant reduction in the occurrence of preeclampsia among women who received calcium supplementation compared with placebo was (OR of 0.38; 95% CI, 0.22 to 0.65), as well as significant improvements in blood pressure. It concluded: "Calcium supplementation during pregnancy leads to an important reduction in systolic and diastolic blood pressure and preeclampsia."
New Findings	A pivotal trial published the following year reported: "Calcium supplementation did not significantly reduce the incidence or severity of preeclampsia or delay its onset… There were no significant differences between the two groups in the prevalence of pregnancy-associated hypertension without preeclampsia (15.3 percent vs. 17.3 percent) or of all hypertensive disorders (22.2 percent vs. 24.6 percent). The mean systolic and diastolic blood pressures during pregnancy were similar in both groups." It concluded that "Calcium supplementation during pregnancy did not prevent preeclampsia, pregnancy-associated hypertension, or adverse perinatal outcomes in healthy nulliparous women."
Qualitative signal	**Opposing findings**: The original systematic review reported a definite reduction in pre-eclampsia and development of hypertension; a pivotal trial showed no impact on either outcome.
Quantitative signal	**Change in effect magnitude of 50% or more**: reduction in odds of pre-eclampsia of 0.62 → reduction of only 0.21; and reduction in odds of developing hypertension of 0.70 → reduction of only 0.25
Other signals:	Increase in number of patients of at least 50%: N=2280→ N=7059 Trial with sample size at least 3 times the size of previous largest trial: previous largest trial included 1167 patients; new trial included 4779 patients
Source(s) of new evidence	**Pivotal trial**: Levine RJ, Hauth JC, Curet LB, et al. Trial of calcium to prevent preeclampsia. N Engl J Med. 1997;337:69-76. **Additional trials**: 1. Cong K et al. Calcium supplementation during pregnancy for reducing pregnancy induced hypertension. Chin Med J (Engl) 1995;108:57-9.

2. Purwar M et al. Calcium supplementation and prevention of pregnancy induced hypertension. J Obstet Gynaecol Res. 1996;22:425-30.

Time to signal Qualitative signal: 1.2 years
Quantitative signal: same

4. Coward LJ et al. Safety and efficacy of endovascular treatment of carotid artery stenosis compared with carotid endarterectomy: a Cochrane systematic review of the randomized evidence. *Stroke*. 2005;36(4):905-11.

Question(s) addressed In patients with carotid stenosis, what are the risks and benefits of endovascular treatment compared with carotid endarterectomy?

Findings of Original Review The original review found no significant difference in the odds of treatment related death or any stroke (odds ratio [OR], endovascular surgery, 1.33; 95% confidence interval [CI], 0.86 to 2.04), death or disabling stroke (OR, 1.22; CI, 0.61 to 2.41), or death, any stroke, or myocardial infarction (OR, 1.04; CI, 0.69 to 1.57). At 1 year after randomization, there was no significant difference between the 2 treatments in the rate of any stroke or death (OR, 1.01; CI, 0.71 to 1.44).

It concluded: "No significant difference in the major risks of treatment was found but the wide confidence intervals indicate that it is not possible to exclude a difference in favor of one treatment. Minor complication rates favor endovascular treatment."

New Findings One pivotal trial (Mas 2006) was stopped early because of significantly inferior outcomes for endovascular treatment. "The 30-day incidence of any stroke or death was 3.9% after endarterectomy (95% CI: 2.0 to 7.2) and 9.6% after stenting (95% CI: 6.4 to 14.0); the relative risk of any stroke or death after stenting as compared with endarterectomy was 2.5 (95% CI: 1.2 to 5.1)." Rates of death and stroke at 6 months were also lower with endarterectomy than with stenting.

Another pivotal trial (Ringleb 2006) found that "The rate of death or ipsilateral ischemic stroke from randomization to 30 days after the procedure was 6.84% with carotid-artery stenting and 6·34% with carotid endarterectomy (absolute difference 0·51%, 90% CI –1·89% to 2·91%). Based on a pre-defined non-inferiority margin of 2.5%, the authors concluded that endovascular treatment "failed to prove non-inferiority of carotid-artery stenting compared with carotid endarterectomy… The results of this trial do not justify the widespread use in the short-term of carotid-artery stenting for treatment of carotid-artery stenoses."

Qualitative signal

Opposing findings: The original review reported no major differences between the two treatments. The review emphasized the uncertainty of the comparison, but did not specifically indicate any possibility that endovascular treat was inferior to endarterectomy. Two pivotal trials indicate inferiority of endovascular treatment (in one case, of sufficient magnitude to result in termination of the trial).

Editorials for both pivotal trials discuss possible explanation for these findings that leave open the possibility of non-inferiority. But the point remains that the publication of these two high profile trials with results substantially different from those of previous trials constitutes an important signal for the need for updating the original systematic review.

Quantitative signal

Change in statistical significance: Relative risk of stroke or death within 30 days became statistically significant, with both limits of 95% confidence interval now lying on side of increased risk with endovascular treatment

RR = 1.33 (0.86, 2.04)→ 1.35 (1.02, 1.80)

Other signals:

Increase in number of trials of at least 50%: 6 trials → 9 trials
Increase in number of patients of at least 50%: N=1269 → 3376

Source(s) of new evidence

Pivotal trials:

1. Mas JL, Chatellier G, Beyssen B, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. N Engl J Med. 2006;355:1660-71.
2. Ringleb PA, Allenberg J, Bruckmann H, et al. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomized non-inferiority trial. Lancet. 2006;368:1239-47

Additional trial:
Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) phase I clinical trial: 1-year results. J Vasc Surg. 2005;42:213-

Time to signal

Qualitative signal: 1.5 years
Quantitative signal: same

5. Hemminki E, McPherson K. Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. *BMJ.* 1997;315:149-53.

Question(s) addressed

Is hormone replacement therapy (HRT) associated with cardiovascular events or cancer in postmenopausal women?

Findings of Original Review	The original review concluded that was no clear evidence of an association between cardiovascular outcomes and HRT, but noted that "Data on cardiovascular events and cancer were usually given incidentally, either as a reason for dropping out of a study or in a list of adverse effects." We therefore characterized the original systematic review as having concluded that effectiveness was 'uncertain'.
New Findings	A pivotal trial (Hulley 1998) found no difference between HRT and placebo in terms of the primary or secondary cardiovascular endpoints. (RR=0.99; 95% CI: 0.80 to 1.22). The trial also showed an increase in thromboembolic events. It concluded: "Based on the finding of no overall cardiovascular benefit and a pattern of early increase in risk of CHD events, we do not recommend starting this treatment for the purpose of secondary prevention of CHD." A second, larger pivotal trial (Rossouw 2002) was stopped early "because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits." Based on a mean follow-up of 5.2 years, "[a]bsolute excess risks per 10 000 person-years attributable to estrogen plus progestin [HRT] were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10 000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10 000 person-years. "Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD."
Qualitative signal	**Opposing findings:** The original systematic review found no clear relationship between HRT and cardiovascular outcomes. Two pivotal trials clearly demonstrated a lack of benefit and evidence of some harm.
Quantitative signal	**Change in statistical significance**: odds of *increased* cardiovascular and thromboembolic events became statistically significant. Odds ratio of 1.64 (0.65, 4.18) → 1.70 (1.18, 2.43)

Other signals: Increase in number of patients of at least 50%: N=4124 → 25140

Trial with sample size at least 3 times the size of previous largest trial: previous largest trial had N=1265; new trial had N=16608
Change in width of 95% confidence interval of at least 50%: as shown above

Source(s) of new evidence

Pivotal trials:

1. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998;280(7):605-13.
2. Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. N Engl J Med. 2000;343(8):522-9.
3. Waters DD, Alderman EL, Hsia J, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. JAMA. 2002;288(19):2432-40.
4. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA.2002;288(3):321-33.

Time to signal Qualitative signal: 1.1 years
Quantitative signal: same

6. Kjaergard LL, Krogsgaard K, Gluud C. Interferon alfa with or without ribavirin for chronic hepatitis C: systematic review of randomized trials. *BMJ*. 2001;323:1151-5.

Question(s) addressed How efficacious and safe is interferon alfa with or without ribavirin in the treatment of chronic hepatitis C?

Findings of Original Review The original review found that, compared with interferon alone, "combination therapy reduced the risk of not having a sustained virological for 6 months by 26% in naïve patients (relative risk 0.74, 95% confidence interval 0.70 to 0.78), 33% in relapsers (0.67, 0.57 to 0.78), and 11% in non-responders (0.89, 0.83 to 0.96). Morbidity and mortality showed a non-significant trend in favour of combination therapy (Peto odds ratio 0.45, 0.19 to 1.06). Combination therapy significantly reduced the risk of not having improvement in results of histology by 17% in naive patients (0.83, 0.74 to 0.93) and by 27% in relapsers and non-responders (0.73, 0.66 to 0.82). The authors concluded that "treatment with interferon alfa plus ribavirin has a significant beneficial effect on the virological and histological responses of patients with chronic hepatitis C…"

New Findings

Two pivotal trials compared the combination evaluated in the original systematic review with an alternative treatment, peginterferon alfa combined with ribavirin.

The first trial included three treatment arms, standard interferon alfa-2b plus ribavirin (as evaluated in the original review), pegylated interferon alfa-2b (1.5 µg/kg per week for four weeks followed by 0.5 µg/kg per week) plus ribavirin, and pegylated interferon alfa-2b (1.5 µg/kg per week) plus ribavirin. The primary endpoint of sustained virologic response "was significantly higher (p=0.01 for both comparisons) in the higher-dose peginterferon group (274/511 [54%]) than in the lower-dose peginterferon (244/514 [47%]) or interferon (235/505 [47%]) groups."

They concluded "In patients with chronic hepatitis C, the most effective therapy is the combination of peginterferon alfa-2b 1.5 microg/kg per week plus ribavirin," though they noted that "The benefit is mostly achieved in patients with HCV genotype 1 infections."

The second pivotal trial (Fried 2002) found that "a significantly higher proportion of patients who received peginterferon alfa-2a plus ribavirin had a sustained virologic response (defined as the absence of detectable HCV RNA 24 weeks after cessation of therapy) than of patients who received interferon alfa-2b plus ribavirin (56 percent vs. 44 percent, P<0.001) or peginterferon alfa-2a alone (56 percent vs. 29 percent, P<0.001)." They concluded: "In patients with chronic hepatitis C, once-weekly peginterferon alfa-2a plus ribavirin was tolerated as well as interferon alfa-2b plus ribavirin and produced significant improvements in the rate of sustained virologic response, as compared with interferon alfa-2b plus ribavirin or peginterferon alfa-2a alone."

The textbook Up-To-Date cites these two trials (and a subsequent trial that evaluated the optimal doe of ribavarin) in making the statement that "combination therapy with pegylated interferon plus ribavirin is generally associated with a higher sustained virologic response rate compared to combination therapy with standard interferon plus ribavirin or pegylated interferon monotherapy. As a result, this is usually the preferred approach in patients with hepatitis C who have not previously received treatment." The chapter in Up-To-Date noted the influence of genotype on response, which was seen in both trials. Because the benefit in the first trial was largely confined to patients with a particular genotype, we did not take that trial by itself as the basis for the signal of a superior alternate treatment. We regarded the signal as triggered by the second trial (Fried 2002).

Qualitative signal

Superior new treatment: Head to head comparisons in two pivotal trials showed that an alternative treatment is superior to the therapy evaluated in the original systematic review.

Quantitative signal	Not applicable – comparisons in new trials differ from those in the original systematic review
Other signals:	None
Source(s) of new evidence	**Pivotal trials**: 1. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. Lancet. 2001;358:958-65. 2. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002;347(13):975-82.
Time to signal	Qualitative signal: 0.9 years Quantitative signal: Not applicable

7. Lefering R, Neugebauer EA. Steroid controversy in sepsis and septic shock: a meta-analysis. *Crit Care Med*. 1995;23(7):1294-303.

Question(s) addressed	Does the use of corticosteroids in patients with sepsis or septic shock lower the risk of death?
Findings of Original Review	The original review found that "Corticosteroids did not change 28 day mortality (15 trials, n = 2022; relative risk 0.92, 95% confidence interval 0.75 to 1.14) or hospital mortality (13 trials, n = 1418; 0.89, 0.71 to 1.11)." The authors concluded that "No overall beneficial effect of corticosteroids in patients with septic shock was observed…"
New Findings	A randomized, double-blind, multi-center trial evaluated the impact of a 7-day course of low-dose hydrocortisone versus placebo in patients who showed signs of relative adrenal insufficiency. It found a significantly lower risk of death in the corticosteroid group (hazard ratio, 0.67; 95% confidence interval, 0.47-0.95; P=.02). It concluded that "a 7-day treatment with low doses of hydrocortisone and fludrocortisone significantly reduced the risk of death in patients with septic shock and relative adrenal insufficiency without increasing adverse events." A subsequent meta-analysis showed that, among five trials (n = 465) involving long courses (> or = 5 days) with low dose (< or = 300 mg hydrocortisone or equivalent), the relative risk for mortality at 28 days was 0.80 (95% CI: 0.67 to 0.95).

Qualitative signal

Opposing findings: The original systematic review found no mortality benefit regardless of dose. A pivotal trial and subsequent meta-analysis showed define reductions in mortality with low dose regimens given for at least 5 days.

Quantitative signal

Change in effect magnitude of 50% or more: the absolute risk reduction for mortality increased from 0.2% to 4.3% (the criterion was first met at after Slusher 1996, when updated risk reduction increased to 1.1%)

Other signals

Increase in number of patients of at least 50%: N=530 → N=1067

Increase in number of trials of at least 50%: 10 trials → 16 trials

Change in width of 95% confidence interval of at least 50%: The original 95% CI for mortality with low-dose steroids extended from a 20% absolute reduction to a 16.2% increase in mortality. The 95% CI for the updated result extended from a 13.6% reduction to a 0.5% increase.

Source(s) of new evidence

Pivotal trial:
Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002;288:862-71.

Additional trials and meta-analysis:

1. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med. 1998;26(4):645-50.
2. Briegel J, Forst H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. Crit Care Med. 1999;27(4):723-32.
3. Slusher T, Gbadero D, Howard C, et al. Randomized, placebo-controlled, double blinded trial of dexamethasone in African children with sepsis. Pediatr Infect Dis J. 1996;15(7):579-83.
4. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. BMJ. 2004;329(7464):480.

Time to signal

Qualitative signal: 7.1 years
Quantitative signal: 1 year

8. Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ*. 2003;327:951-953.

Question(s) addressed

Does metformin improve pregnancy and ovulation rates in women with polycystic ovary syndrome?

Findings of Original Review	The original review found that "metformin is effective in achieving ovulation in women with polycystic ovary syndrome, with odds ratios of 3.88 (95% confidence interval 2.25 to 6.69) for metformin compared with placebo and 4.41 (2.37 to 8.22) for metformin and clomifene compared with clomifene alone. An analysis of pregnancy rates shows a significant treatment effect for metformin and clomifene (odds ratio 4.40, 1.96 to 9.85)." Referring to the use of metformin, the authors concluded that "its choice as a first line agent seems justified."
New Findings	A pivotal trial compared clomifene citrate plus metformin with clomifene plus placebo and found a lower ovulation rate in the metformin group "(64% compared with 72% in the placebo group, a non-significant difference (risk difference − 8%, 95% confidence interval − 20% to 4%). There were no significant differences in either rate of ongoing pregnancy (40% v 46%; − 6%, − 20% to 7%) or rate of spontaneous abortion (12% v 11%; 1%, − 7% to 10%). A significantly larger proportion of women in the metformin group discontinued treatment because of side effects (16% v 5%; 11%, 5% to 16%)." The authors concluded that "metformin is not an effective addition to clomifene citrate as the primary method of inducing ovulation in women with polycystic ovary syndrome." The accompanying editorial also concluded that "metformin should not be used routinely as part of first line treatment for inducing ovulation."
Qualitative signal	**Opposing findings**: The original systematic review concluded that metformin is definitely effective, recommending it as a first line agent. A pivotal trial showed no benefit and concluded that metformin should not be considered a first line treatment.
Quantitative signal	**Change in statistical significance**: increase in ovulation rate in patients treated with metformin and clomifene vs. clomifene alone lost statistical significance Odds ratio of 4.41 (2.37, 8.22) → 1.42 (0.98, 2.05) **Change in effect magnitude of 50% or more**: Relative increase in ovulation rate in patients treated with metformin and clomifene vs. clomifene alone decreased by over 50% (OR of 4.41→ 1.42), as did the relative increase in clinical pregnancy rate among patients who received metformin and clomifene vs. clomifene alone (OR of 4.40→ 2.07)
Other signals:	Increase in number of patients of at least 50%: for the outcome of clinical pregnancy rate, the number of patients increased from 173 to 537 Increase in number of trials of at least 50%: for the outcome of clinical pregnancy rate, the number of trials increased from 3 to 8

	Change in width of 95% confidence interval of at least 50%: as shown above
Source(s) of new evidence	**Pivotal trial**: Moll E et al. Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomized double blind clinical trial. BMJ 2006;332:1485. Four additional trials contained in meta-analysis: Kashyap S, Wells GA, Rosenwaks Z. Insulin-sensitizing agents as primary therapy for patients with polycystic ovarian syndrome. Hum Reprod. 2004;19:2474-83.
Time to signal	Qualitative signal: 2.6 years Quantitative signal: same

II. Examples of Reviews with Signals for "Major Changes in Evidence" (criteria A4-A7)

Examples of criterion A4: Pivotal trial, new meta-analysis, more recent practice guideline, or recent textbook does not contradict the previous review, but characterizes benefit in substantially different terms (e.g., therapy previously characterized as "promising", "likely beneficial" or similar description and now characterized as definitely beneficial.)

Original Review	Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324(7329):71-86.
Question(s) addressed	Covered a variety of questions related to the effects of antiplatelet therapy among patients at high risk of occlusive vascular events, including: Is aspirin plus dipyridamole was more effective than aspirin alone for the secondary prevention of vascular events after ischemic stroke of presumed arterial origin?
Findings of Original Review	The original review stated that "the addition of dipyridamole to aspirin was associated with only a non-significant further 6% (6%) reduction in serious vascular events…The apparent reduction in non-fatal stroke was derived mainly from one large study… but this result was not supported by the findings for non-fatal stroke in the other studies." It concluded: "Addition of dipyridamole to aspirin produced no significant further reduction in vascular events compared with aspirin alone."

New Findings	A pivotal trial found that patients who received aspirin and dipyridamole had a significantly lower risk of the primary outcome (a composite of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication, whichever happened first), with a hazard ratio 0.80, 95% CI 0.66-0.98; absolute risk reduction 1.0% per year, 95% CI 0.1-1.8). Combining these data with previous trials resulted in an overall risk ratio for the composite of vascular death, stroke, or myocardial infarction of 0.82 (95% CI 0.74-0.91). The authors concluded: "The ESPRIT results, combined with the results of previous trials, provide sufficient evidence to prefer the combination regimen of aspirin plus dipyridamole over aspirin alone as antithrombotic therapy after cerebral ischaemia of arterial origin."
Qualitative signal	**Major change**: possibly superior → definitely superior
Quantitative signal	**Change in statistical significance**: The lower risk of serious vascular events (vascular death or death from unknown cause, MI or stroke) became statistically significant. Odds ratio of 0.94 (0.84, 1.06) → 0.90 (0.81, 0.99) As noted above, the random effects meta-analytic result for relative risk is 0.82 (0.74-0.91), which more clearly shows the change in statistical significance. Odds ratios were used in our analysis because the original review used odds ratios.
Other signals	Because the original review covered a number of distinct questions related to antiplatelet therapy for the prevention of vascular events, other qualitative and quantitative and signals may have been met. For example, a pivotal trial found that adding aspirin to clopidogrel increased bleeding without reducing recurrent ischemic vascular events in high-risk patients.[2] Another pivotal trial found that clopidogrel plus aspirin did not differ from aspirin alone for reducing MI, stroke, and cardiovascular death in patients with clinically evident cardiovascular disease or multiple risk factors.[3] Both of these qualitative signals occurred prior to the signal involving the comparison of aspirin plus dipyridamole with aspirin alone, but the latter more clearly fit one of our qualitative criteria and involved a quantitative signal as well.
Source(s) of evidence	**Pivotal trial:** Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet. 2006;367(9523):1665-73.

	Additional pivotal trials addressing other questions in the original review: 1. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet. 2004;364(9431):331-7. 2. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006;354(16):1706-17.
Time to signal	Qualitative signal: 4.4 years Quantitative signal: same
Original Review	Avezum A, Tsuyuki RT, Pogue J, Yusuf S. Beta-blocker therapy for congestive heart failure: a systemic overview and critical appraisal of the published trials. Can J Cardiol. 1998;14(8):1045-53.
Question(s) addressed	Do beta-blockers reduce mortality and morbidity in the treatment of heart f failure?
Findings of Original Review	The original review reported a lower odds of death with beta-blockers that had borderline statistical significance (OR = 72; 99% CI 0.51 to 1.00). The authors were concerned about the sparseness of the data on mortality compared with evaluations of beta-blockers of patients with myocardial infarction. They concluded: "Although the effects on mortality were nominally statistically significant, the use of formal methods of interim monitoring adapted for meta-analyses suggests that substantially more patients still need to be studied in large scales trials to provide reliable and conclusive evidence."
New Findings	A pivotal trial (MERIT-HF 1999) was stopped early because of the magnitude of reduction in the beta-blocker group, with a relative risk 0.66 (95% CI 0.53-0.81; p=0.00009 or adjusted for interim analyses p=0.0062). The authors concluded: "Metoprolol CR/XL once daily in addition to optimum standard therapy improved survival." A second pivotal trial (CIBIS-II 1999) published the same year was also stopped early because of the survival benefit evident in the beta-blocker group. A third pivotal trial (Packer 2001) demonstrated a significant reduction in mortality for patients with more severe heart failure.
Qualitative signal	**Major change**: possible mortality benefit → definite benefit
Quantitative signal	**Change in statistical significance: borderline** reduction in mortality became statistically significant

	0.72 (0.51, 1.00) → 0.67 (0.49, 0.91) This change reflects the first shift to statistical significance (after Herlitz 1997); after additional trials, the updated result was 0.78 (0.70, 0.88)
Other signals:	Increase in number of trials of at least 50%: 10 trials → 15 trials Increase in number of patients of at least 50%: N= 2841 → N=14738 Trial with sample size at least 3 times the size of previous largest trial: previous largest trial included 1094 patients; a new trial included 3991 patients
Source(s) of evidence	**Pivotal trial:** Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353(9169):2001-7. **Additional trials (including two pivotal trials):** 1. Herlitz J, Waagstein F, Lindqvist J, Swedberg K, Hjalmarson A. Effect of metoprolol on the prognosis for patients with suspected acute myocardial infarction and indirect signs of congestive heart failure (a subgroup analysis of the Goteborg Metoprolol Trial). *Am J Cardiol*. 1997;80(9B):40J-44J. 2. 2The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999;353(9146):9-13. 3. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344(22):1651-8.
Time to signal	Qualitative signal: 1 year Quantitative signal: -0.6 years
Original Review	Birck R, Krzossok S, Markowetz F, Schnulle P, van der Woude FJ, Braun C. Acetylcysteine for prevention of contrast nephropathy: meta-analysis. *Lancet* 2003;362:598-603.
Question(s) addressed	Does prophylactic acetylcysteine reduces contrast nephropathy in patients with chronic renal insufficiency?
Findings of Original Review	The original review included 7 trials and found that "compared with periprocedural hydration alone, administration of acetylcysteine and hydration significantly reduced the relative risk of contrast nephropathy by 56% (0.435 [95% CI 0.215-0.879], p=0.02) in patients with chronic renal insufficiency. Meta- regression revealed no significant relation between the relative risk of contrast nephropathy and the volume of radiocontrast media

administered or the degree of chronic renal insufficiency before the procedure." The authors acknowledged that it remained unclear to what extent acetylcysteine improved harder clinical endpoints, but the impact on measures of renal function was regarded as robust. They concluded "acetylcysteine with hydration significantly reduces the risk of contrast nephropathy in patients with chronic renal insufficiency."

New Findings

A subsequent meta-analysis (published 1.4 years after the first) included 20 trials and found that the impact on contrast nephropathy was smaller in magnitude and of borderline statistical significance. The authors also emphasized that the trials showed significant heterogeneity that remained unexplained despite exploration of various possible clinical and methodological differences across the studies.

They concluded: "Acetylcysteine may reduce the incidence of contrast-related nephropathy, but this finding is reported inconsistently across currently available trials. High-quality, large clinical trials are needed before acetylcysteine use in this indication can be recommended universally."

Qualitative signal

Major change: Definite benefit → possible benefit

Quantitative signal

Change in statistical significance: the relative risk of contrast nephropathy with acetylcysteine versus hydration alone lost its statistical significance

RR of 0.44 (0.22, 0.88) → 0.81 (0.58, 1.13)

The loss of statistical significance first occurred with Gomes 2003, at which time the updated result was 0.61 (0.37, 1.00)

Change in effect magnitude of 50% or more: The relative risk reduction (RRR) decreased from 0.66 to 0.19

Other signals:

Increase in number of trials of at least 50%: 7 trials → 17 trials (20 trials included in newer meta-analysis, but not all provided data on the primary outcome)

Increase in number of patients of at least 50%: N=805 → N=1964

Source(s) of evidence

Newer meta-analysis:
Nallamothu BK, Shojania KG, Saint S, et al. Is acetylcysteine effective in preventing contrast-related nephropathy? A meta-analysis. *Am J Med* 2004;117:938-947.

	This meta-analysis included 20 trials. The quantitative signal for change in statistical significance occurred with Gomes V, et al. Prevention of contrast-induced nephropathy with N-acetylcysteine in patients undergoing coronary angiography a randomized multicenter trial. Circulation 2003:108:IV–460.
Time to signal	Qualitative signal: 1.4 years Quantitative signal: -0.2 years
Original Review	Ducharme FM, Hicks GC. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma (Cochrane Review). In: The Cochrane Library, Issue 1, 2001. Oxford: Update Software.
Question(s) addressed	How do anti-leukotriene agents compare with inhaled glucocorticoids in terms of efficacy and safety in the management of chronic asthma?
Findings of Original Review	The original review showed non significant trends towards superiority of inhaled corticosteroids, but found the evidence insufficient to permit reliable conclusions regarding relative efficacy of the two treatments. The reviewers concluded: "Anti-leukotriene agents had a similar rate of exacerbations compared to inhaled corticosteroids, but inhaled steroids produced better lung function and quality of life as well as reduced symptoms, night awakenings and need for rescue beta2-agonist. Reliable conclusions cannot yet be drawn regarding the efficacy of this treatment due to the paucity of trials published in full text."
New Findings	A subsequent update of the original review reported: "Patients treated with anti-leukotrienes were 60% more likely to suffer an exacerbation requiring systemic steroids…Significant differences favouring ICS were noted in most secondary outcomes, eg improvement in FEV1…symptom scores… Other significant benefits of ICS were seen for nocturnal awakenings, rescue medication use, and quality of life. Risk of side effects was not different between groups, but anti-leukotriene therapy was associated with 30% increased risk of "withdrawals for any cause" or "withdrawals due to poor asthma control". The updated review concluded "For most asthma outcomes, ICS at 400 mcg/day of beclomethasone-equivalent are more effective than anti-leukotriene agents given in the usual licensed doses... Inhaled glucocorticoids should remain the first line monotherapy for persistent asthma."
Qualitative signal	**Major change:** possibly inferior → definitely inferior

Quantitative signal	**Change in statistical significance**: The risk of asthma exacerbations with anti-leukotrienes vs inhaled steroids (in adults and children) became statistically significant Relative risk of 1.34 (0.93, 1.91) → 1.45 (1.07, 1.97)
Other signals:	Increase in number of patients of at least 50%: N=1050 → N=1938 Increase in number of trials of at least 50%: 4 trials → 6 trials (for the above outcome)
Source(s) of Evidence	**Subsequent meta-analysis (explicit update):** Ducharme FM, Hicks GC. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database Syst Rev*. 2002(3):CD002314. **New trials included in the meta-analysis** 1. Bleecker ER, Welch MJ, Weinstein SF, et al. Low-dose inhaled fluticasone propionate versus oral zafirlukast in the treatment of persistent asthma. *J Allergy Clin Immunol*. 2000;105(6 Pt 1):1123-9. 2. Busse W, Raphael GD, Galant S, et al. Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: a randomized clinical trial. *J Allergy Clin Immunol*. 2001;107(3):461-8. 3. Kim KT, Ginchansky EJ, Friedman BF, et al. Fluticasone propionate versus zafirlukast: effect in patients previously receiving inhaled corticosteroid therapy. *Ann Allergy Asthma Immunol*. 2000;85(5):398-406.
Time to signal	Qualitative signal: 2 years Quantitative signal: 0.4 years (became positive with Bleecker 2000)

Example of criterion A5 **for 'Expansion of treatment':** Pivotal trial, new or discordant meta-analysis, trial indexed in *ACP J Club*, more recent practice guideline, or recent textbook has expanded of the role of the treatment (e.g., the treatment has now been shown to be of benefit in children or the elderly; or benefit now shown to apply to primary prevention of disease, not just secondary prevention).

Original Review	McIntyre PB, Berkey CS, King SM, et al. Dexamethasone as adjunctive therapy in bacterial meningitis. A meta-analysis of randomized clinical trials since 1988. JAMA 1997;278:925-931.
Question(s) addressed	Does dexamethasone administered as an adjunct to antibiotic therapy improve outcomes for patients with bacterial meningitis, and does effectiveness vary by subcategories of causative organisms and timing or nature of antibiotic therapy?

Findings of Original Review	The original review found that "in Haemophilus influenzae type b meningitis, dexamethasone reduced severe hearing loss overall (combined odds ratio [OR], 0.31; 95% confidence interval [CI], 0.14-0.69)" and "in pneumococcal meningitis, only studies in which dexamethasone was given early suggested protection, which was significant for severe hearing loss (combined OR, 0.09; 95% CI, 0.0-0.71) and approached significance for any neurological or hearing deficit (combined OR, 0.23; 95% CI, 0.04-1.05)." The authors concluded that "The available evidence on adjunctive dexamethasone therapy confirms benefit for H influenzae type b meningitis and, if commenced with or before parenteral antibiotics, suggests benefit for pneumococcal meningitis in childhood." The review contained only one study that included some adults (up to age 25 years of age).
New Findings	A pivotal trial that focused on adults patients and administered dexamethasone before or with the first dose of antibiotic and was given every 6 hours for four days showed: "treatment with dexamethasone was associated with a reduction in the risk of an unfavorable outcome (relative risk, 0.59; 95 percent confidence interval, 0.37 to 0.94; P=0.03). Treatment with dexamethasone was also associated with a reduction in mortality (relative risk of death, 0.48; 95 percent confidence interval, 0.24 to 0.96; P=0.04). Among the patients with pneumococcal meningitis, there were unfavorable outcomes in 26 percent of the dexamethasone group, as compared with 52 percent of the placebo group (relative risk, 0.50; 95 percent confidence interval, 0.30 to 0.83; P=0.006)." The authors concluded that "early treatment with dexamethasone improves the outcome in adults with acute bacterial meningitis and does not increase the risk of gastrointestinal bleeding."
Qualitative signal	**Major change**: **benefit reported in original review expanded to a new patient population** The original review concluded adjunctive dexamethasone conferred benefit only in children with acute bacterial meningitis due to Haemophilus influenzae type b and possibly pneumococcal meningitis. A pivotal trial showed definite benefit for adjunctive dexamethasone in adults with acute bacterial meningitis**.**
Quantitative signal	Not applicable
Other signals:	None
Source(s) of new evidence	**Pivotal trial:** de Gans J, van de Beek D; European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis. N Engl J Med. 2002;347(20):1549-56.

Time to signal	Qualitative signal: 5.2 years Quantitative signal: Not applicable

Example of criterion A6 for **Important caveat**: Pivotal trial, new meta-analysis, more recent practice guideline, or recent textbook adds an important caveat, about the patient populations who benefit, way in which treatment has to be delivered in order to derive benefit, sustainability of benefit (e.g., benefits on short term outcomes, but not long-term ones), or increases in harm that are not sufficient to undermine use altogether, but would clearly affect the decision to recommend treatment for at least some patient populations.

Original Review	Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. *Am J Respir Crit Care Med* 1995;151:969-974.
Question(s) addressed	How efficacious is allergen immunotherapy in controlling the symptoms, improving lung function, or decreasing the requirements for medication use in patients with asthma?
Findings of Original Review	The original review included 20 randomized placebo controlled double-blind trials and reported that "combined odds of symptomatic improvement from immunotherapy with any allergen were 3.2 (95% CI 2.2 to 4.9). The odds for reduction in medication after mite immunotherapy were 4.2 (95% CI 2.2 to 7.9). The combined odds for reduction in BHR [bronchial hyperreactivity] were 6.8 (95% CI 3.8 to 12.0). The mean effect size for any allergen immunotherapy on all continuous outcomes was 0.71 (95% CI 0.43 to 1.00), which would correspond to a mean 7.1% predicted improvement in FEV1 from immunotherapy." The authors also pointed out that "Although the benefits of allergen immunotherapy could be overestimated because of unpublished negative studies, an additional 33 such studies would be necessary to overturn these results." They thus concluded that "allergen immunotherapy is a treatment option in highly selected patients with extrinsic ("allergic") asthma."
New Findings	A pivotal trial reported that: "During the two treatment years, the mean peak expiratory flow rate was higher in the immunotherapy group (489 +/- 16 liters per minute, vs. 453 +/- 17 in the placebo group [P = 0.06] during the first year, and 480 +/- 12 liters per minute, vs. 461 +/- 13 in the placebo group [P = 0.03] during the second). Medication use was higher in the immunotherapy group than in the placebo group during observation and lower during the first treatment year (P = 0.01) but did not differ in the two groups during the second year (P = 0.7). Asthma-symptom scores were similar in the two groups (P = 0.08 in year 1 and P = 0.3 in year 2). The immunotherapy group had reduced hay-fever symptoms, skin-test sensitivity to ragweed, and sensitivity to bronchial

	challenges and increased IgG antibodies to ragweed as compared with the placebo group; there was no longer a seasonal increase in IgE antibodies to ragweed allergen in the immunotherapy group after two years of treatment. Reduced medication costs were counterbalanced by the costs of immunotherapy." The authors concluded that "Although immunotherapy for adults with asthma exacerbated by seasonal ragweed exposure had positive effects on objective measures of asthma and allergy, the clinical effects were limited and many were not sustained for two years."
Qualitative signal	**Major change**: **important caveat** In this case, the caveat concerns the sustainability of benefit.
Quantitative signal	None met
Other signals:	None
Source(s) of new evidence	Pivotal trial: Creticos PS, Reed CE, et al. Ragweed immunotherapy in adult asthma. N Engl J Med. 1996;334(8):501-6.
Time to signal	Qualitative signal: 327 days Quantitative signal: Not applicable

Example of criterion A7 for Opposing findings from discordant meta-analysis or non-pivotal trial: The treatment has been characterized in sufficiently different terms to the cohort review that disagreement would have met criteria for 'potentially invalidating change' (A1) except the source was not a pivotal trial, new-meta-analysis, or more recent practice guideline, or recent textbook—rather, it was a discordant meta-analysis or trial indexed in *ACP J Club*.

Original Review	Hood SC, Moher D, Barber GG. Management of intermittent claudication with pentoxifylline: meta-analysis of randomized controlled trials. *CMAJ*. 1996;155(8):1053-9.
Question(s) addressed	Does pentoxifylline improve the walking capacity of patients with moderate intermittent claudication?
Findings of Original Review	The original meta-analysis found " a statistically significant improvement in the pain-free walking distance after pentoxifylline therapy (weighted mean difference 29.4 m [95% confidence interval (CI) 13.0 to 45.9 m])… A significant improvement was also noted in the absolute claudication distance (weighted mean difference 48.4 m [95% CI 18.3 to 78.6 m])". The authors concluded that "pentoxifylline therapy may be efficacious in improving the walking capacity of patients with moderate intermittent claudication."

New Findings	A randomized trial with a commentary in *ACP Journal Club* (Dawson 2002) compared pentoxifylline with an alternative medication, cilostazol, and placebo. The authors reported: "Mean maximal walking distance of cilostazol-treated patients (n = 227) was significantly greater at every postbaseline visit compared with patients who received pentoxifylline (n = 232) or placebo (n = 239). After 24 weeks of treatment, mean maximal walking distance increased by a mean of 107 m (a mean percent increase of 54% from baseline) in the cilostazol group, significantly more than the 64-m improvement (a 30% mean percent increase) with pentoxifylline (P <0.001). The improvement with pentoxifylline was similar (P = 0.82) to that in the placebo group (65 m, a 34% mean percent increase)." The authors concluded that "Cilostazol was significantly better than pentoxifylline or placebo for increasing walking distances in patients with intermittent claudication… Pentoxifylline and placebo had similar effects." The seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy (Clagett 2004) and UpToDate characterize pentoxifylline as no better than exercise and quote the above trial as the basis for this assessment..
Qualitative signal	**Major change**: possibly beneficial → definitely not beneficial The original review concluded that pentoxifylline was likely efficacious in the treatment of intermittent claudication. A major practice guideline and chapter in recent textbook characterize pentoxifylline as no better than placebo based on the results of a trial that did not meet criteria for pivotal but was indexed in *ACP Journal Club.*
Quantitative signal	None met
Other signals:	None
Source(s) of new evidence	**Trial indexed in ACP J Club:** Dawson DL, Cutler BS, Hiatt WR, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. Am J Med. 2000;109(7):523-30. **Practice guideline:** Clagett GP, Sobel M, Jackson MR, Lip GY, Tangelder M, Verhaeghe R. Antithrombotic therapy in peripheral arterial occlusive disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(3 Suppl):609S-626S.
Time to signal	Qualitative signal: 4.1 years Quantitative signal: not applicable