

# Nordic Cochrane News

Newsletter for the Nordic Cochrane Centre (NCC)



Issue 9, December 2004



Front cover illustration by Pernille Götzsche

## Trial registration and access to protocols and full results

The idea of registering trials with a unique identification number is not new, but is finally getting momentum, helped by recent revelations of drug companies withholding important information and publication of several pivotal “trials” that were not trials but disguised lumping of separate, quite different trials, with flawed reporting as well. The International Committee of Medical Journal Editors (the Vancouver group) as well as the BMJ recently declared that, starting from Sept 2005, reports of trials would not be accepted for publication if the trials had not been registered.

At a brainstorming meeting held during the recent Cochrane colloquium in Ottawa, a draft document on trial registration was discussed with methodologists, journal editors, funders, ethics review board

representatives, industry representatives and others. The Ottawa Statement on principles of trial registration was edited by An-Wen Chan, Kay Dickersin and Karmela Krleza-Jeric, and was sent to the WHO, which held two meetings shortly afterwards on trial registration, one with participation of ministers of health. The Ottawa Statement gives a good ethical and scientific argumentation as to why the public should have full access to information from protocols before the first patient is enrolled, and why all final trial results should be made publicly available. Responsibilities of involved parties are proposed, including a suggestion that the research ethics review boards should be responsible for ensuring that the initial registration is a condition for the ethics approval.

*Peter C. Götzsche, NCC*

## Hospital doctors' self-rated skills in and use of evidence-based medicine

Problems in understanding methodological terms and basic aspects of evidence-based medicine (EBM) may form barriers to its implementation in clinical practice. We examined hospital doctors' skills and related these skills to their use of various information sources. We sent a questionnaire to all hospital doctors ( $n = 376$ ) at a university hospital in Denmark that included 12 questions on frequently used methodological terms and a question on a non-existing dummy term (relative odds ratio reduction) (published in: *Ugeskrift for Læger* 2004;166:4040-3). The participants were asked about their use of six information sources, self-rated skills in critical appraisal of the literature, and level of implementation of evidence-based principles.

A representative sample of 60% responded. Ten doctors (5%) could define and explain all 12 methodological terms; most doctors were interested in knowing more about the terms. Ten doctors (5%) knew about the dummy term and could explain it to others and 111 doctors (51%) felt they had an idea about it, but would like to know more.

Doctors most often consulted textbooks and colleagues when searching for clinical evidence. *The Cochrane Library* was the least consulted of six information sources; it was always used by only 17 doctors (9%) but as much as 51% were familiar with it. Compared to seldom or never users of *The Cochrane Library*, frequent users had significantly higher academic degrees, familiarity scores, and use of *PubMed*.

Most doctors seem to lack knowledge of key methodological statistical terms and tend to overestimate their skills. Doctors should consult EBM sources based on updated evidence instead of traditional sources of information.

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**How to become involved in the  
Cochrane Collaboration?  
See [www.cochrane.dk](http://www.cochrane.dk)**

## Cochrane Occupational Health Field

The Cochrane Occupational Health Field was registered in May 2004. It is based at the Finnish Institute of Occupational Health in Kuopio, Finland, with Jos Verbeek as Field Co-ordinator. The Field has been quite active. We have registered three titles for Cochrane Reviews and another three are expected soon. In March 2004, we held our first introductory course for reviewers, and in October there was another two-day course where some of the participants started to prepare protocols for Cochrane Reviews.

We have developed an optimal search strategy to be able to detect relevant studies in MEDLINE (Jos Verbeek et al. A search strategy for occupational health intervention studies, in press) and have started to assemble the studies in a specialised register. Hand-search training material has been prepared and volunteers have been contacted.

The Cochrane Occupational Health Field will assist people who are willing to perform Cochrane Reviews on topics related to occupational health. Currently, we have ongoing review protocols on interventions for hearing protection, lifting advice for back pain, common mental health problems and health surveillance. We have a list of suggested review topics and welcome further suggestions. People willing to do handsearching will get training and advice from the Field on how to get started. The Field web site will be opening soon at [www.cohf.fi](http://www.cohf.fi).

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*Iris Pasternack, Finnish branch*

## Polyclonal immunoglobulin for treatment of sepsis

Polyclonal immunoglobulin is not labelled for treatment of sepsis, but more than half of its use in the USA is off-label, and in 2000, polyclonal immunoglobulin comprised the second largest pharmaceutical expense at our hospital, Rigshospitalet in Copenhagen.

It is therefore important to know whether the trials on immunoglobulin for treatment of sepsis justify off-label use for sepsis. We found many small, low-quality trials that demonstrated a large treatment effect (relative risk 0.61; 95% confidence interval 0.50 to 0.73). However, there were also a few small, high-quality trials and a large high-quality trial. The protocol of the large trial has been published, but its results have only been qualitatively reported in an abstract; we obtained mortality data from the primary author. The high-quality trials showed a relative risk of 1.02 (0.84 to 1.24). This difference in effect is compatible with the expected influence of bias associated with lack of adequate allocation concealment and lack of double blinding in the low-quality trials. We therefore suggest that polyclonal immunoglobulin should not be used for treatment of sepsis except in randomised trials. Our review has had consequences for clinical practice since polyclonal immunoglobulin is now only recommended in exceptional cases of sepsis, like streptococcal toxic shock syndrome, at our hospital.

Pildal J, Gøtzsche PC. Polyclonal immunoglobulin for treatment of bacterial sepsis: a systematic review. *Clin Infect Dis* 2004; 39(1):38-46.

*Julie Pildal, NCC*

## Course on systematic reviews 8-11 November 2004

In my capacity as Review Group Co-ordinator of The Cochrane Hepato-Biliary Group, I participated in a four-day intensive course with 24 participants on systematic reviews and meta-analyses, sponsored by The Danish Clinical Intervention Research Academy and arranged by the Nordic Cochrane Centre. These four days at 'Rolighed' conference centre in the outskirts of Great Copenhagen, overlooking the sea, immersed in tranquillity and taught by extremely well-trained and -known lecturers - Peter Gøtzsche, Asbjørn Hróbjartsson, and Bodil Als-Nielsen from the Nordic Cochrane Centre and the statisticians Doug Altman, UK, and David Moher, Canada - are to be remembered.

The course added to my knowledge on how to critically read and use results from medical publications, how to balance benefits and harms, how important the statistical choice is in making correct conclusions, what the limitations of systematic reviews are, and how biased the reporting of trial results from the industry may be. Other interesting topics were reviews on diagnostic tests and how to search PubMed. Although the presentations and group sessions were tight, the course was very focused and met its goals.

We were taught how important it was to have a reliable summary of medical evidence ensuing from a well-formulated scientific question, and how methodological issues should be addressed when evaluating studies for possible inclusion.

*Dimitrinka Nikolova, Cochrane Hepato-Biliary Group*

## Influenza vaccine for healthy adults

On 19<sup>th</sup> October 2004, the major Danish newspaper Politiken had a front-page story on the effect of influenza vaccine on healthy individuals below 65 years. The story was based on a Cochrane review that reported that out of 100 vaccinated healthy individuals, 75 would get influenza anyway during outbreaks if the disease was diagnosed clinically, and 30 if the diagnosis was confirmed in a laboratory. In Denmark about 720,000 individuals out of a population of five million are vaccinated every year. The topic was widely discussed in national newspapers and TV. It resulted in a debate between a representative for a private influenza vaccine firm and Margrethe Nielsen from the Danish Consumer Council who questioned the relevance of the information provided by the vaccine firm that emphasised the many deaths during the influenza pandemic in 1918, the so-called Spanish Flu. The National Board of Health does not recommend vaccination of healthy adults, and as a result of all the publicity, many people cancelled their planned vaccinations. Unfortunately, this also applied to older individuals and other people at special risk where the vaccine is recommended, although the Cochrane review did not address these risk groups.

*Asbjørn Hróbjartsson, NCC*

## Antioxidant supplements for prevention of gastrointestinal cancers

The role of antioxidant supplements in cancer prevention is controversial, and when we published a review in issue 4, 2004 in the Cochrane Library, it provoked world-wide interest. We combined the results of 14 randomised trials that compared betacarotene, vitamins A, C, and E, and selenium, alone or in combinations, with placebo. The trials ranged from small (N = 226) to large (N = 39,876) and were mostly of high quality. In total, more than 170,000 participants were included; daily antioxidant supplements had been given orally for 1 to 12 years. Overall, there was no significant difference between the placebo and supplements groups in the incidence of esophageal, gastric, colorectal, pancreatic or liver cancers. A possible exception was selenium, which was associated with a lower incidence of hepatocellular carcinoma, but most of these trials were of low quality.

We concluded that antioxidant supplements do not offer protection against gastrointestinal cancer and might, in fact, increase overall mortality. In a fixed effect model analysis, as well as in a random effects model analysis, a small, but statistically significant increase in mortality was shown based on six high-quality trials, after exclusion of trials involving selenium. Betacarotene in particular, in combination with vitamin A or vitamin E, was linked with increased mortality risk. The potential preventive effect of selenium should be studied in randomised trials that follow the CONSORT statement ([www.consort-statement.org](http://www.consort-statement.org)).

The review was made possible by a grant given to the first author by The Danish Cancer Society, obtained through the Danish Knowledge and Research Centre for Alternative Medicine (ViFAB).

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## New staff at the NCC



### Karsten Juhl Jørgensen

Research fellow, joined the Nordic Cochrane Centre on 1 August 2004.

## Workshops hosted by the NCC in 2005

Date	Event
11 April	Protocol workshop
3 October	Protocol workshop

*Details on [www.cochrane.dk](http://www.cochrane.dk)*

## New web site for the Nordic Cochrane Centre

In September 2004, the Nordic Cochrane Centre launched a new web site refining the content, appearance and functionality. We hope you will find the new site more user-friendly, easy-to-read and accessible. Please visit the site at [www.cochrane.dk](http://www.cochrane.dk) and feed back any suggestions you might have for improvements.

*Jannie Hedegaard, NCC*

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