NRSMG: AESg
NOTES OF MEETING AT UKCC ON 2 JULY 2002

The AESg agenda was considered in two parts: the AESg first met on its own, and then joined the other members of NRSMG for part 2 of the agenda. The subsequent NRSMG business meeting also included items relevant to the AESg.

PART 1

1. Experience of participants – in applying the AESg draft recommendations, etc

a. Agreed that studies of AEs of an intervention should include all those in which the intervention had been used in similar intensity for a comparable duration, regardless of the indication, even when the review does not cover all the indications.

b. Important to look for particular adverse events, but also to note others that emerge.

c. Quality assessment: Deirdre Price had used the Ottawa scale for case-control and cohort studies, the York CRD checklist for other studies.

d. Saad Shakir: the DSRU review of three or four atypical antipsychotics focused on weight gain, hyperglycaemia, diabetes; examined reports from regulatory agencies; considered the timing of reports in relation to clinicians' awareness of the problem, and the chance background of, eg diabetes; looking at >1 country; at primary and secondary care; also considered Bayesian approach.

2. The selection of adverse effects to review: brief outline by Sheena Derry and Yoon Loke.

Noted that RCTs were potentially a good source for data on common non-serious effects, but that they have to be adequately described; important to ask whether a study provides time points. Reviews of AEs from RCTs should exclude reports that mention no AEs, unless they state how AEs were looked for.

Questions to be decided:

1. What should one do with AEs from RCT reports?
2. How to deal with rare serious effects? and
3. With non-serious rare effects? – which are less urgent but still need work.

3. Work needed on AEs in Cochrane reviews and outside the Collaboration:

a. CRGs should deal with RCTs first. Where existing Cochrane reviews have not dealt with AEs, this could be remedied either in a separate review of AEs, or the material on AEs could be incorporated when the review is updated.

b. Priority drugs for Cochrane groups are those with a narrow benefit/ harm relationship (high ratio of NNT to NNH) or with non-serious which importantly impair quality of life.

The 'Proposed patient-centred measure of the likelihood of being helped and harmed by a treatment' could be used in this context [Straus SE, Moore A, McQuay H, Sackett DL. Proc 5th Cochrane colloquium Amsterdam 1997, abstract 22, p141], and the Glasziou / Irwig net benefit model could also be used.

c. Saad Shakir noted that 140 decisions by national regulators had been inconsistent, and that the evidence on which these decisions had been based had not been disclosed. (CIOMS IV). This evidence should be made accessible. A paper in EJCP had reviewed drug withdrawals for safety reasons:

Arnaiz JA, Carne X, Riba N, Codina C, Ribas J, Trilla A. The use of evidence in pharmacovigilance. Case reports as the reference source for drug withdrawals. *Eur J Clin Pharmacol* 2001; 57(1):89-91.

Arnaiz *et al*. evaluated 22 drugs withdrawn from the Spanish market from January 1990 to December 1999. The scientific evidence supporting the drug withdrawals was critically appraised. In 18 of 22 cases (82%), the evidence supporting the drug withdrawal came from individual case reports, case series or the combination of data provided by RCTs and case reports. Only four withdrawals were based on evidence from observational studies including a comparison group. The authors concluded that it is necessary to improve the quality of evidence supporting the withdrawal process of drugs linked to unexpected and severe ADRs.

Recent examples, still being reconsidered, are sertindole and alosetron (Lotronex).

PART 2
Items discussed by the whole NRSMG [not only the AESg members listed]

4. Getting the recommendations into the Reviewers' handbook and used:

a. We need criteria for evaluating safety in RCTs **[who to work on this?]**

b. 1st step: identify all statements now in the handbook that are relevant to adverse events. Ole Olsen and Yoon Loke agreed to do this.

c. 2nd step: make modest recommendations in Handbook, produce a checklist for editorial groups, starting with 'Are side effects mentioned?'

d. Article in Cochrane News. Yoon Loke is willing to write this.

e. Write to CRGs, asking them to appoint an editor to take care of methods issues who could take part in a workshop.

f. Inclusion of spontaneous reports makes it desirable to work with Bayesian statisticians.

5. Developing a network of people able to comment on protocols and draft reviews, advise reviewers and editors on how to handle adverse effect data and discussions:

This was considered unrealistic. The initiative would best come from individual CRGs. CRGs should have a checklist for editors in which adverse effects are an item. An article on this should be prepared for Cochrane News.

6. Possible workshops, training seminars, etc

a. A one day training course plus a half day practical example using a checklist could be offered at the autumn 2003 workshop for editors at the Nordic CC in Copenhagen. Likewise at other editors' workshops in UK and Australia.

b. Consider writing to CRGs to nominate someone to go to such workshops.

c. Put the checklist on the Nordic CC website.

d. A distance-learning course will be launched at the Stavanger Colloquium. Ask / help its authors to incorporate AE information/ training.

e. Suggest AEs as a topic for a plenary at Barcelona Colloquium. Doubt about running a workshop there, because it's more important to 'train' editors to consider the subject important and to enable them to check their reviews.

f. Start and maintain an e-mail AE discussion list.

7. Lee Harper's review

The protocol is now in the Cochrane Library – do look at it and comment on the decisions that have been taken. More detailed update at next NRSMG meeting.

8. Vaccines – Deirdre Price

a. Need guidelines urgently. Much practical experience exists, but not yet collected together. A workshop may be the best way to do this, meanwhile an e-mail list?

b. Suggestion to set this up as a research question, in a poster or paper, to preserve it. Perhaps need to 'scope' the question first. Suggestion that UK people could meet and report in Barcelona.

9. Feedback to Steering Group about how best to group together expertise for AE reviews.

Ask Lee to set out the problem in her experience.

10. A Research agenda and priorities

a. Decide what is needed now – terminology, separating wheat from chaff – and what's needed for the future – amend CONSORT statement, improve reporting, include AEs in abstracts.

b. How to find trials / other studies – indexing.

c. How to spot false positive AEs?
Repeat the work of GR Venning (BMJ 1984/85) on the provenance / genesis of knowledge about important AEs reports: hypothesis-generating and hypothesis-testing reports.

d. Are there systematic differences between small and large cohorts?

e. How to decide whether to include case-control studies in a sysrev; whether to look only for large, or for all, cohort studies depends on nature of AE/ADR

f. Categorise into:
- papers identifying possible AEs,
- papers that quantify frequency of AEs,
- papers that quantify relative frequency of AEs with a drug v. placebo

g. Yoon Loke agreed to draft a list of research priorities.