Adverse Effects Subgroup of NRSMG
Notes of informal meeting to discuss progress and problems, 22.3.02 10.30-12.15
at UK Cochrane Contributors' meeting, Oxford

Present: Jeff Aronson, Sheena Derry, Yoon Loke, Deirdre Price, Lesley Smith, Phil Wiffen (all Oxford), Paul Garner, Harriet MacLehose, Tony Marson (all Liverpool), Andrew Herxheimer, Mustafa Soomro (both London), Lee Hooper (Manchester), Saad Shakir (Southampton). Apologies from Rune Dahlqvist (Umeå), Ralph Edwards (WHO, Uppsala), Stephen Evans (London),Tom Jefferson (Rome), Lena Westin (Stockholm).

Thanks to all who helped to improve these notes. AH

1. The systematic inclusion of adverse events in systematic reviews requires much extra time and effort from reviewers and CRGs. Funding of CRGs is now based on their productivity in terms of completed protocols and reviews, as shown by the Collaboration's monitoring process. If many reviews were to take longer to complete than they do now, productivity would fall, and consequently funding. Unless the basis of funding is adjusted to take this problem into account, CRGs may be reluctant to include adverse events routinely.

2. Meta-analyses of adverse event reports are rarely possible or justified because of great heterogeneity both between and within different types of study (case-control, cohort, case series, etc). The Brighton Collaboration is reviewing adverse events related to MMR vaccine (partly funded by the EU); Tom Jefferson is reviewing the efficacy & safety of DTP vaccine. Deirdre Price emphasised the importance of analysing the reports in a separate compartment for each type of study.

3. When the number of uncommon serious adverse events in an RCT is greater than expected, the statistics should be reported, but it is usually inappropriate to calculate a p value because most trials have insufficient power to justify this.

4. Adverse events reported in RCTs and discussed in reviews fall into two categories that are best considered separately: those primarily affecting **safety**, which endanger life or health and are labelled 'serious', and those affecting **tolerability**. The LIFE trial illustrates this (Lancet 23.3.2002, p995 & 1004). An event of either kind may cause a patient to drop out; the total number of drop-outs is less informative than the numbers in each category.

5. We are engaged in two kinds of activity that we need to distinguish. One is finding out the frequencies of ADRs, and using various kinds of systematic review is one way of doing that. That is a **retrospective** method involving analysis of trials that have already been done. Another activity is to encourage those who report their RCTs to include information on ADRs in their publications and to get indexers to index trials helpfully; that includes work (e.g. producing CONSORT type statements) which relates **prospectively** to future trials.

6. The infectious Diseases Group is systematically including adverse events in several reviews. The meeting encouraged Harriet MacLehose and colleagues to report their experiences with this, eg in an article for Cochrane News.

7. Severity of reported adverse events was mentioned in only 86 of 185 RCTs examined, and only 42 of those stated how severity was defined (Loke & Derry. BMC Clin Pharmacology 2001, 1:3 or http://www.biomedcentral.com/1472-6904/1/3). Severity as assessed by the patient should be reported separately from severity assed by the clinician/ researcher, both in trials and in reviews.

8. It may be clinically useful to estimate the relative frequencies of adverse effects for drugs in the same therapeutic category and to use these to rank the drugs - as has been done with NSAIDs (see CSM/ MCA. Current Problems 1994; 20:9-11). This would provide useful information in cases in which absolute frequencies cannot be calculated.

9. Searching databases for RCT reports that contain data on adverse events/ effects at best retrieves only 75% of the relevant trials (Loke & Derry). Indexing must be much improved, and a big effort is needed to educate indexers at NLM, ISI, Embase.

10. Regulatory trials contain useful information on AEs, but in most their frequency and severity is not adequately reported, especially in relation to the duration of trials and duration of drug use.

11. The time frame/ time course of AEs needs routine analysis; Aronson & Ferner have prepared a paper on this, still unpublished.

12. Chadwick has used 'time to withdrawal' in the assessment of anti-epilepsy drugs. This combines withdrawal because of an adverse event and withdrawal because there was no therapeutic effect.

Finally, what we need and want:

A. Better access to AE data in the future

- Trialists should plan and execute trials to include the capture of AEs (in most cases this is probably done as a requisite of ethical approval), and report methods used to detect and assess AEs, and unadjusted/raw data for each arm of the trial.
- The CONSORT statement should be amended to include reporting of AEs with as much rigour as beneficial therapeutic effects.
- Statements analogous to CONSORT are needed for non-randomised studies of various types, including anecdotes. As background work for this we need to find out which journals publish what types of report from what sources. Jeff Aronson is preparing a draft statement on anecdotal reports and analysing the SEDA literature for information on sources (for the first tranche see Fundamental & Clinical Pharmacology 2002; 16: 49-56).
- Journal editors should not publish trials/reports that do not address AEs where relevant.
- Indexing on bibliographic databases needs to be made more consistent to allow easy identification of reports that contain information on AEs.

B. Guidance for reviewers in dealing with existing data

- We must be aware of, and make allowances for, the constraints imposed by incomplete reporting and retrieval of data.
- Reviewers need a guide to inform them on how to deal with AEs [the CCSG will shortly consider a request to include our draft recommendations in the Handbook].
- Reviews must highlight harms as well as benefits, as for example in the reviews of rotavirus vaccine.
- We need clear definitions of all the terms.
- Reviewers should deal with AEs from RCTs first, then the NRSs.
- The methods group needs to focus on the nuts and bolts of handling non-randomised studies.
- We must consider the generic and specific issues of how we can incorporate data from NRSs and qualitative data in reviews.
- The Brighton Group's review of AEs with MMR (in progress) will be a useful example of a methodological approach for a safety review.
- The DSRU plans to establish a registry of serious cardiovascular events linked to non-cardiovascular drugs.
- A time/hazard approach is being used in an ongoing review of the safety of atypical antipsychotic drugs, and should be considered in other areas.
- On occasion safety/tolerability reviews can be spin-offs from efficacy reviews, as happened with AEs of non-steroidal anti-inflammatory drugs.
- Population-based studies of AEs, eg. cohort studies of hospital admissions, need systematic reviewing: where would they fit into the Cochrane Collaboration? Would EPOC be an appropriate CRG?