Workshop: Enhancement of the Scientific Process and Transparency of Observational Epidemiology Studies 24-25 September 2009, London

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Workshop: Enhancement of the Scientific Process and Transparency of Observational Epidemiology Studies

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1. EXECUTIVE SUMMARY

In September 2009, the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) held a workshop at the Royal College of Physicians to discuss how the transparency in the design, conduct and report of observational epidemiology studies can be improved. This report summarises the recommendations of this workshop, how the improvements could be achieved, and the contribution that ECETOC and other groups might make.

Over 30 experts including practitioners, editors of medical journals and scientists from regulatory bodies attended the workshop.

The workshop participants recognised several key points related to enhancing the transparency of observational epidemiology studies. These are:

1.1 Registering observational epidemiology studies

There is evidence that a proportion of observational epidemiology studies are not published, either because they are not submitted for publication or because they were rejected by journals. This results in selective reporting and publication bias, accompanied by a distorted representation of observational study findings in the open scientific literature. One solution to this problem is to create a system for tracking, organising and disseminating information about observational epidemiology studies in a similar way to clinical trials. Currently such trials are recorded in databases such as the WHO International Clinical Trials Registry Platform (ICTRP), the ISRCTN register or the ClinicalTrials.gov register. Possibly, existing registers, such as the ClinicalTrials.gov register, which already contains observational epidemiology studies (approximately 16% of the total number of registrations) could be adapted and expanded with new data elements to accommodate all types of observational epidemiology studies.

The main benefits of registering observational epidemiology studies were considered by the workshop participants to be:

- Increasing the transparency and thus credibility of observational epidemiologic research;
- improving the peer-review process, and ethical aspects of conducted studies;
- having the totality of the evidence available, if such a register were complete.

Increasing the transparency (transparency)

Registering observational studies including pre-specified elements such as their *a priori* hypotheses, the study protocol, any amendments, the study results and information about their publication in a central global register would help identify which studies have been or are being

conducted on a specific topic, to determine which of these studies have been published and whether the totality of the results obtained have been reported. Such a register would help to prevent selective reporting and could reduce if not eliminate publication bias.

Improving the peer-review process and ethical aspects (ethics)

Registering observational studies would enable peer-reviewers to better evaluate submitted manuscripts. Reviewers could compare the reported study results with the registered protocol and differentiate between hypothesis driven results and hypothesis generating activities.

Finally, an OSR has an ethical justification that emerges from the moral obligation of the investigator towards the study subjects, who invested time and effort to participate in the study, and to both society and the scientific community to make the best use of the collected information and make the results available to as large an audience as possible.

Having the universe of the evidence available (universality)

Observational epidemiology results are essential information for society, since they provide valuable evidence on the aetiology of disease and thus form the basis for preventive actions. As noted above, it is an ethical obligation of investigators to make the best use of the scientific information gained by studying humans, to make best use of human and financial resources and to disseminate the results to the best of their capabilities. The confidence that can be ascribed to this body of literature depends, to a great extent, on the confidence that all the available information is available for review.

At the workshop the potential disadvantages of an OSR were also addressed. Registration with an OSR does require an effort on the part of the principal investigator to provide the needed study details. This was the only disadvantage of an OSR that was noted. It was therefore important for the success of this initiative that the registration process be simple, efficient, and easily updated.

1.2 Starting research and collecting empirical evidence for the need of registering observational epidemiology studies

The conceptual arguments for registering observational epidemiology studies (as outlined above) need to be supported by empirical evidence and examples of specific benefits for the stakeholders involved (investigators, policy-makers, regulators, research organisations, journal editors, consumers and society at large). At present, this evidence is largely anecdotal, and only specific

case studies are available. Similar evidence for clinical trials strongly increased support for the now required registration of drug trials.

Some exploratory research has been undertaken that showed an increased risk of false positive outcomes from non hypothesis driven research (Swaen *et al*, 2001) and in many systematic reviews funnel plot analyses indicate the presence of underreporting of smaller negative studies (Duval and Tweedie, 2000; Moreno *et al*, 2009). More research is needed to demonstrate that registration could indeed help to obtain the most un-biased estimates of associations from observational epidemiology studies.

1.3 Convincing stakeholders about the need of registering epidemiology studies

The workshop participants recognised that it may be a protracted process to convince stakeholders about the need for registering observational epidemiology studies. Success is only to be expected if it can be shown that registration will improve our ability to characterise true associations of exposures with disease risks by increasing transparency. To this end, illustrative case studies should be developed and a comprehensive comparison of the outcomes from registered versus non-registered studies would be important (see also above).

Most support in this process is expected from those who would benefit from registering observational epidemiology studies, such as policy-makers, regulators, institutional review boards (IRBs)/ethics committees, public health practitioners, funding agencies, and journal editors. The position of journal editors and their cooperation in this process is seen as key, as has been shown in the clinical trials area. The workshop participants did not come to a consensus on whether registration would be required or voluntary. If the latter it could be stated that potential authors would be encouraged to register and comply with the STROBE guidelines (von Elm, 2007) as part of a quality standard and quality indicator for journal articles.

1.4 Other approaches to enhance the transparency and credibility of observational epidemiology studies

Registering observational studies is one of several tools to enhance the transparency and credibility of epidemiological research. Data sharing and collaborative efforts such as the Cochrane Collaboration would also contribute to these objectives. In this respect reference was made to an initiative several years ago to develop guidelines for archiving, and documenting epidemiology studies; Good Epidemiological Practice (GEP). It was recognised that increasing awareness and engaging the broader scientific community in these discussions will take time.

1.5 Deciding who will take the lead to bring this project forward

There was agreement that it would be most effective if the next steps would be led by epidemiologic practitioners, their professional associations and journal editors. The first steps needed may begin with discussions within professional groups, at meetings of professional societies, ideally with the type of examples as to why and how an OSR would increase transparency.

1.6 The role of ECETOC in the process

If the idea of registering observational epidemiology studies gathers momentum, ECETOC is happy to organise another workshop in 2 to 3 years to review progress and to facilitate further development of the initiative. However, it is now rather up to the epidemiologic community to bring the matter forward.

2. INTRODUCTION

Observational epidemiology studies have greatly contributed to the identification of causes of disease. There is a general consensus on the research designs and methods applied in observational epidemiology studies which have been extensively described in textbooks and methodological publications. However, the scientific process for conducting observational epidemiology studies itself is not subject to agreed guidelines. An observational epidemiology study, just as any other study, requires the formulation of an *a priori* hypothesis to be tested. There should be a study protocol that describes in detail how the study will be carried out, including population selection, ascertainment of risk factors, other relevant covariates and outcome parameters, and the statistical analysis that will be used to analyse the data.

Currently, there is no guarantee that published results reflect all of the analyses done in a study nor that they were obtained in accordance with the original study protocol. Because of various reasons some study results, either positive or negative, may remain unpublished. There is evidence showing that publication bias can result in a distorted representation of study findings in the open scientific literature. Industry researchers may be accused of only publishing those results that are favourable to industry. On the other hand, non-industry researchers may be accused of only disclosing the most interesting results, i.e. the positive findings.

A similar situation, in which publication bias in the form of non-publication of negative findings in the area of clinical epidemiology occurred, led to great controversy and distrust. Pharmaceutical industry researchers were accused of not publishing or delaying the publication of clinical trials that did not show beneficial effects of their products. These accusations eventually resulted in the creation of Clinical Trials Registers and the requirement by Medical Journal Editors that a clinical trial must be registered before patient recruitment, for a manuscript to be considered for publication. The requirement of prior registration of clinical trials has greatly contributed to the restoration of public trust in clinical trials research.

This workshop was a one and a half day event, convened by ECETOC to discuss the above issues. There were invited experts from academia, medical journals, regulatory authorities, and industry. On the first day, several presentations were given describing the current scientific process in the conduct of observational epidemiology studies and clinical trials and how the results are reflected in the scientific literature. On the second day, participants were requested to join one of three breakout groups to discuss a number of questions. Following these discussions a *rapporteur* from each breakout group reported back to the entire group followed by a plenary discussion. In a final panel discussion, a set of conclusions and recommendations was formulated.

3. PRESENTATIONS

3.1 The current epidemiologic enterprise and its conflict with the scientific ethos

Dr J McLaughlin (International Epidemiology Institute, Rockville, USA) advocated organised scepticism, a cornerstone of science and the scientific ethos, which is largely neglected in the field of epidemiology as it is practised today. It has been replaced instead by a multitude of non-scientific and anti-scientific tendencies. Further, the necessary methodological vigilance so important in non-experimental epidemiology has been largely replaced by a mania for publications, a focus on high impact factor journals, and eager collaboration by investigators in media hype, contributing to the proliferation of false positive reports and bad science. Science is not a democracy. A consensus vote does not confirm a hypothesis or theory. Scientists must always be open to considering data that challenge their most cherished beliefs and hypotheses. Otherwise, one is practising a belief system based on faith not science. A scientist cannot function simultaneously as a researcher on a topic and an advocate or activist on that same issue. The scientific process demands uncertainty, activism demands certainty. It is an irresolvable contradiction, and the quintessential conflict of interest, too often ignored in epidemiology. A true research scientist, especially in a non-experimental field such as epidemiology, does not have the luxury of certainty. This epistemological fact of life is ignored on a daily basis as epidemiologists lecture the world on aspects such as how to eat, work, organise the 'healthy lifestyle' and prepare for the long-term effects of climate change.

3.2 Sources and consequences of publication bias and related biases

Dr J Kleijnen (Kleijnen Systematic Reviews Ltd., NL) explained that publication bias occurs if the results from studies which have not been published are different from the published ones. Publication bias complicates the interpretation of research findings and the conduct of systematic reviews and meta-analyses. If favourable results are published more often, there will be an overestimation of the effects of a treatment, but the bias can actually go in any direction.

There have been several attempts to assess the magnitude of publication bias. Unpublished studies could be identified by means of a survey among researchers, and the results could subsequently be compared with the outcomes of published studies. The results from published studies could also be compared with studies from a registry or abstracts in conference proceedings. Furthermore, the results from registered but unpublished studies could be compared with those of registered and subsequently published studies. Studies addressing publication bias have shown that it is a serious problem, which complicates the interpretation of findings and the conduct of systematic reviews.

In assessments of publication bias several factors must be taken into account. These include the mode of publication: peer-reviewed journals, other journals, books, etc. Differences could be related to the quality of studies as well. Furthermore, the source of funding may influence both the results and subsequent publication. Publication bias can only be avoided by registration of all studies before data collection is started; several of such registries already exist. Also reporting bias (selectively reporting certain outcomes and/or subgroup analyses) might become a smaller problem if study registers have been put in place.

There is a range of related biases and when addressing these in systematic reviews it would be better to use the more general term 'small study bias' instead of publication bias. Perhaps, if more of such registries exist, reviewers could only use registered studies for their main conclusions. All other information could then be considered liable to bias. There may also be wider implications of having registries of studies, which would allow major revision of current guidance about how to deal with multiple outcomes and multiple subgroups.

3.3 A history of the rationale for and path to implementation of clinical trials registration

Dr K Dickersin (John Hopkins Bloomberg School of Public Health, USA) explained that, for decades, there had been international concern about 'hidden' clinical trials and selective outcome reporting in clinical trials. One result of hidden research would be that systematic reviews of the evidence could be biased, if investigators tend to selectively publish their positive finding over their negative findings ('reporting bias'). For many years, a dedicated group of researchers advocated registration of all initiated trials, with each trial assigned a unique identifier, to alert those performing reviews (and others) about the full scope of work undertaken, not just published research.

The advocacy for trial registration was ultimately successful for a number of reasons. First, the public and the scientific community at large understand that it is unethical not to report a study's existence and results, especially because study participants who consent to be studied do so in the belief that they are contributing to knowledge. Second, the progress of science depends on full disclosure of all (not a selection) research findings. Third, the conduct of research involves a public investment and a public trust, with investigators, research organisations and institutions, journal editors, taxpayers, patients and others believing that the system of study initiation and results dissemination is performed honestly and transparently.

For clinical trials registration is a reality although, for the moment, it is not yet universally applied. Study registration should not be limited to clinical trials. Observational studies, and the variables examined in those studies, should be registered as well.

3.4 Medical journal guidelines for publication of clinical trials research

Dr D MacAuley (British Medical Journal, London/UK) explained that trial registration is essential to ensure that, when research is undertaken and completed, the results are available in the public domain. It is an ethical imperative for the integrity of the evidence base used in clinical decision-making. There are theoretical benefits to researchers in that it allows mapping of future research and may avoid duplication of studies while enhancing the protection of patients, and proper use of resources. For editors and readers, it encourages transparency in primary and secondary outcomes. Mandatory clinical trials registration has been formally included in the International Committee of Medical Journal Editors (ICMJE) requirements, the FDA Amendment Act and EU requirements for paediatric trials. For ICMJE, clinical trials started after 1 July 2005 must be registered before participants are recruited. This applies to trials "where human participants are prospectively assigned to one or more health related interventions [including health services and behavioural interventions] to evaluate the effects on health outcomes". FDA requires that any ongoing clinical trial of a drug, biological product or device regulated by FDA must be registered at ClinicalTrials.gov and from September 2008 the results of such trials must also be posted there. This applies to all trials except phase I drug trials and small feasibility studies of devices. These policies are implemented in the British Medical Journal and it is ensured that all papers have been registered. The trial protocol is requested before a paper is sent for external review.

3.5 The US Government Clinical Trials Registry

Dr D Zarin (US Government Clinical Trials Registry, USA) reported on ClinicalTrials.gov[1], the registry established and maintained by the National Library of Medicine (NLM) on behalf of the National Institutes of Health (NIH). ClinicalTrials.gov contains nearly 76,000 clinical studies. From its inception in 2000, the registry has accommodated the registration of observational studies. As of September 2009, approximately 16% (12,956) of all studies registered in ClinicalTrials.gov are observational studies. ClinicalTrial.gov has an established set of mandatory and voluntary structured data elements[2] intended to ensure the public availability of key study attributes including descriptive information about the purpose, principal focus, and study design, recruitment information, such as eligibility criteria and recruitment status; geographic location and contact information; and administrative information, including study sponsor and a unique study identifier. While the data elements for interventional and observational studies overlap considerably, certain data elements specific to observational studies

[1] http://ClinicalTrials.gov

[2] http://prsinfo.clinicaltrials.gov/definitions.html

were updated in October 2007[2]. These updates were influenced by the STROBE statement[3,4] and the data elements cover many of the protocol-related requirements of the guidelines. The availability of the 'basic results' database in September 2008 allows for reporting of results of observational studies, including statistical methods. Since the launch of the 'basic results' database, 41 observational studies with results have been posted on ClinicalTrials.gov.

[3] Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M, for the STROBE Initiative. 2007. Strengthening the reporting of observational studies in epidemiology (STROBE): Explanation and elaboration. *Ann Intern Med* 147(8):163-194.

[4] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, for the STROBE Initiative. 2007. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Ann Intern Med* 147(8):573-577.

4. PROPOSAL FOR ENHANCING THE SCIENTIFIC PROCESS OF OBSERVATIONAL EPIDEMIOLOGY STUDIES: RATIONALE FOR AN OBSERVATIONAL STUDIES REGISTER (OSR)

Dr G. Swaen
The Dow Chemical Company, NL

4.1 The ideal scientific process

Among epidemiologists there is general agreement that any scientific investigation must be based on:

- A well-defined *a priori* hypothesis that can be tested;
- a project description (study protocol);
- an *a priori* defined approach to the statistical analysis.

There is also general agreement that the findings of any epidemiological investigation should be published and disclosed, regardless of its results. Since the open scientific literature is the best available database on study results, it is of eminent importance to guarantee that this database is as unbiased and transparent as possible, and to guarantee its scientific integrity.

4.2 The current practice in epidemiology

The scientific environment in which observational epidemiology studies are conducted has considerably changed over the last decades and current practice in observational epidemiology is different from the ideal scientific process.

- There is concern that not all study results make it to the open literature, and publications frequently are difficult to interpret because the original protocol is not available. Hypothesis driven analyses are difficult to distinguish from more exploratory type of analyses.
- Publication bias is difficult if not impossible to assess because at present there is no central place where all observational studies are registered prior to their conduct.

4.3 How can the scientific process for observational epidemiology studies be improved?

An Observational Study Register (OSR) would make it possible to identify studies that have been conducted but have not been published in the open literature. Also, there is currently no guarantee that published results reflect all of the data generated in an observational study. Industry researchers may be accused of only publishing those results that are favourable to

industry. On the other hand, non-industry researchers may be accused of only disclosing the most interesting results, i.e. the positive or 'statistically significant' findings.

An OSR would make it possible to identify where studies have deviated from their original project proposal. Journal readers would be in a position to distinguish study results based on exploratory analyses from hypothesis-driven ones. Several occupational epidemiology examples were presented to demonstrate the importance of an *a priori* project description (study protocol) and an *a priori* defined approach to the statistical analysis. A comparison of 75 false positive outcomes with 150 true positive outcomes revealed that there was a five-fold higher opportunity of a false positive outcome if an *a priori* hypothesis was not available (Swaen *et al*, 2001).

An OSR is proposed as an important tool to assess publication bias, as the list of studies in the register could easily be compared to the list of published studies.

Of course, acceptance and support of such an OSR by epidemiology professional societies and associations would be essential. It must be publicly available and maintenance be assured to supply the necessary infrastructure, quality assurance and guidance.

Registering a study in an OSR should be a future requirement for publication in a peer-reviewed journal; the study protocols should be made available to the reviewers.

It was noted that the registry should not be seen as a 'straight jacket'. Since insight may change during the conduct of a study it must be possible to deviate from the original protocol as long as this is documented and the rationale presented. The possibility of future exploratory analyses is also recognised as important.

4.4 What types of studies should be registered and whose responsibility is it?

Ideally, an OSR would include all types of studies on risk factors for specific diseases; secondary analyses should also be included. Each new analysis done on the basis of a large data set should have a protocol, an *a priori* hypothesis and should be registered, or the original registration be updated. It is suggested that meta-analyses be registered as well.

It should be the responsibility of the principal investigator to submit a complete and transparent registration.

4.5 Issues that need further consideration

- Should the full protocol be registered, or a set of structured data elements?
- Should the raw data set (together with a description of the data) be stored in the registry or in a publicly available on-line archive?

4.6 Other ways to enhance the scientific process of observational epidemiology studies

The current peer-review process would be enhanced by requesting that the study protocol be submitted before an article is accepted for peer-review. The original protocol should be made available to the peer-reviewer.

In parallel, a Cochrane-like collaboration for aetiology studies would result in an increase in quality of the conducted systematic reviews and meta-analyses, just as it has done in the clinical trials area.

As a more long-term goal, data repositories should be created that will allow recording of key epidemiological datasets and preserve these for future needs.

5. REPORTS FROM BREAKOUT GROUPS

5.1 Breakout Group I

Chair: Doug Weed
Rapporteur: Neil Carmichael

Pietro Alberto Bertazzi
Paul Brandt-Rauf
Katja Bromen
David Coggon
Davina Ghersi
Jeffrey Lewis
Bill Summerskill

Should there be a registry?

Though there were some reservations with regard to whether the quality pay-off would be as high as some expect, there was general support of the idea of having a registry of observational epidemiology studies.

1. Transparency would be improved by such a process and it would become obvious which studies are available.
2. Repetition or unnecessary duplication of studies would be avoided.
3. It would become obvious for which studies no or only incomplete publication is available.

The highest consensus in the group was with regard to the improvement of the peer-review process due to the possibility of comparing reported data with the original study design.

Registering observational epidemiology studies was seen as an incremental and evolutionary but not as a revolutionary step in promoting the scientific process. Together with other tools to improve the scientific reporting of observational epidemiology, this is regarded as worthwhile to undertake.

What type of registry should it be? How should it be structured?

There was general consensus that there was no need to invent something new, but that existing registers such as the ClinicalTrials.gov register could be used, which can already accommodate observational studies after implementing minor changes.

There was also agreement not to start with 'everything at once', but to use a pilot project or a type of study or subset/category that was the most amenable to this sort of process. If the pilot study was successful there would be a natural pressure on other groups to take up the process.

What would it take to make it happen?

Further to asking professional societies to back the process, it would be most important to seek the support of those who have the greatest benefit from registering, such as regulators, funding agencies, investors. Journal editors will have a critical role in promoting the process by 'selling' this to potential authors or readers as part of a quality standard or quality indicator for journal articles. Editors should encourage potential authors to use the STROBE guidelines.

5.2 Breakout Group II

Chair: Jos Kleijnen
Rapporteur: Gerard Swaen

Patricia Buffler
Aaron Cohen
John Doe
Claudia Fruijtier-Pölloth
Carlo LaVecchia
Jørgen Olsen
Miquel Porta
Lesley Rushton
Deborah Zarin

This group reported back similar outcomes as group 1. More emphasis was given, however, to ethical considerations and the role of institutional review boards (IRBs)/ethics committees.

Should observational studies be registered?

There was consensus that an observational study registry might be a useful tool to enhance transparency; however, problems of confidentiality would still need to be addressed. Registering observational studies was in particular seen as a moral obligation to make the best use of the information collected on human subjects and to maximise transparency. A registry would allow identifying other studies being conducted on the topic, and thus avoid unnecessary duplication of work. IRBs and ethics committees could more easily make a decision on whether a new study is

actually needed. Registering was considered as a small additional bureaucratic step in the process of obtaining study authorisation.

In future (but already requested by some funding agencies) data sharing would enable other investigators to reproduce and/or re-use data stored in a register or data repository.

It was recognised, however, that whether registering observational studies would indeed improve the ability to adequately assess the validity of associations would require further research.

Where should we start?

The group discussed how to define an observational epidemiology study. It was suggested to follow the definition for a study eligible for registration at the US government clinical trials register. In principle, any observational study on human subjects that requires ethical review should be registered. The feasibility and practicalities of registering such studies should however first be tested by starting with registering studies conducted in a specific field, e.g. air pollution, chemicals. Prospective studies were considered the most suitable to start with. The focus should be on studies with regulatory impact (e.g. for safety standards setting, quantitative risk assessment etc).

What would it take to make it happen? What alternatives are there?

It was suggested to start with a small professional group and then inspire or influence other groups to become interested in the topic. To that end a symposium or sub-symposiums could be organised within the frame of professional meetings, i.e. congresses, professional organisation meetings etc.

An editorial and/or journal article could be written on the topic, e.g. in the Occupational and Environmental Medicine Journal or the British Medical Journal or in both.

Ethics committees/IRBs could be asked to request registration of observational studies.

In addition, journal editors should be asked to request the original study protocol and to require registration before publishing observational studies; this would make it possible to identify deviations from the protocol, selective reporting and whether the outcomes of a study were based on multiple explorative analyses rather than being hypothesis-driven and thus improve the quality of peer-review process.

5.3 Breakout Group III

Chair: Jonathan Samet
Rapporteur: J. Morel Symons

Mark Cullen
Elizabeth Delzell
Kay Dickersin
Eduardo Franco
Julian Little
Domhnall MacAuley
Geert Jan Van der Heijden
Paolo Vineis
Mei Yong

Again, this group reported back very similar answers to the questions, but with a stronger focus on building on existing efforts to improve the transparency of observational epidemiology research.

In addition to the outcomes already reported above, the group noted the need for better information management in observational studies and the need of better access to information. Data-sharing is a coming reality, but issues such as individual confidentiality, data protection, and commercial and legal barriers have still to be addressed.

Registering observational studies would require the involvement of various stakeholders, and a coalition of the willing to leverage the implementation. The need to engage the entire scientific community in the concept was recognised. The group suggested starting with a pilot project, e.g. with a limited fixed category of studies, such as occupational exposure studies with chemicals as sub-category. As in the other breakout groups, journal editors and ethics committees/IRBs were seen as key players in the process of promoting registration. Consideration should also be given to a Cochrane-like collaboration and to the collaboration with the WHO. Registration should be global, in particular also help researchers in developing countries and leverage their efforts.

As an alternative to registering observational studies, one should build on existing efforts, such as enhancing transparency by making the protocols better, implementing better education programmes in epidemiology, and better networking with other research groups and existing consortia in research fields (an example is the genetics research organisations).

6. SUMMARY AND RECOMMENDATIONS

Among the workshop participants there was general consensus that current practice in observational epidemiology research is often far from the ideal and that improvements need to be made in particular with regard to enhancing transparency and credibility of observational epidemiological research. The issues of publication and other biases along with undocumented deviation from original study designs were highlighted. The workshop recognised several key points on how to enhance the transparency and credibility of observational epidemiology studies. These are:

6.1 Registering observational epidemiology studies

It was proposed that existing registers, such as the ClinicalTrials.gov register, which already includes observational studies, could be adapted and expanded with new data elements to accommodate new observational study types.

It was stressed that the registry must have the capability to accommodate studies worldwide and must be publicly available. It should be maintained by an independent organisation.

In order to try out the practicality of such a registry, it should be tested with a pilot project. It might be useful, for instance, to start with prospective studies, using an agent-based approach (e.g. benzene) or around a common theme, such as air pollution or occupational cohort studies. This would be a good starting point to create a minimum data elements template. However, to make the idea of registering observational epidemiological studies appealing and convincing to the entire epidemiology community, the pilot project must not be too narrow in scope.

It was noted that the bureaucratic hurdle of registering an observational study is probably very minor in comparison to getting ethical approval.

In summary, the main benefits of registering observational epidemiology studies were considered as:

- Increasing the transparency and thus credibility of observational epidemiology research (transparency);
- strengthening the peer-review process based on the moral obligation to those subjects who participated in the study, and ethical review (ethics);
- having the totality of the evidence available, once the registry is complete (universality).

This, together with other tools (such as Good Epidemiology Practice, better education and teaching, better guidelines and documentation) would improve the quality of observational epidemiology research.

6.2 Encouraging research and collecting empirical evidence for the need of registering observational epidemiological studies

The conceptual argument for registering observational epidemiology studies needs to be supported by empirical evidence and examples of specific benefits for the stakeholders involved (investigators, policy-makers, regulators, research organisations, journal editors, consumers etc). This evidence is at present largely anecdotal, and specific case studies are not available.

At present, there is no quantitative estimate on the number of studies to be covered, or whether this would be feasible and effective. Nor have the consequences of less than complete registration been addressed.

Some exploratory research has been undertaken that showed an increased risk of false positive outcomes from exploratory type of analyses compared to hypothesis driven research; however, more research is needed to demonstrate that registration can indeed help to obtain the most un-biased estimate of an association from observational epidemiologic studies. Specific case studies need to be elaborated.

6.3 Convincing stakeholders about the need of registering epidemiology studies

The workshop recognised that convincing stakeholders, and in particular professional colleagues, about the need of registering observational epidemiology studies is a long process and beyond the conceptual argument for registering, empirical (not anecdotal), evidence has to be provided. Success is only to be expected if it can be shown that registration will improve our ability to characterise associations from observational epidemiologic studies. To this end, illustrative case studies should be developed and a comprehensive comparison of the outcomes of registered versus non-registered studies is necessary. There was general agreement that journals would welcome studies of this type of empirical analysis; this could also be an effective way to start the process on increasing awareness in the scientific and professional communities.

Most support in this process is expected from those that have a benefit from registering observational epidemiology studies, such as regulators, policy-makers, ethics committees/IRBs, practitioners, funding agencies, investors and journal editors. The role of journal editors was seen as critical. Though registering would not be an obligation, it could nevertheless be stated that

potential authors would be encouraged to register and comply with the STROBE guidelines as part of a quality standard and quality indicator for journal articles.

6.4 Promote the use of already existing tools/methods/approaches to enhance the transparency and credibility of observational epidemiology studies

Registering observational studies is one (of many) tool(s) for enhancing the transparency and credibility of epidemiological research. At present, there are systems in place to improve the quality of epidemiology studies, but these systems, such as, for instance, Good Epidemiological Practice (GEP) guidelines, need to be strengthened and disseminated. It is therefore important to work closely with epidemiologic and other professional societies and groups to promote the importance of scientific integrity and transparency in observational epidemiology.

Participants of the workshop offered to bring the issue of registering observational epidemiology studies to the attention of editors, to write editorials on the topic and to write accompanying articles on how to improve the quality of observational epidemiology research, including topics like Good Epidemiological Practice (GEP) guidelines, improvement of the peer-review process etc. They also offered to stimulate discussion in their own professional societies as a nucleus to take this project forward. The European Epidemiology Federation and the International Epidemiological Association (IEA) were specifically mentioned, as well as the opportunity to put the theme on the agenda of the next 'International Congress on Peer Review and Biomedical Publication' in four years' time.

Epidemiology is becoming increasingly inter-disciplinary; it is therefore essential to build on, and link with other initiatives and other professional societies to ascertain that multiple sources of information are used. For instance, the SPIRIT (Standardized Protocol Items for Randomized Trials) initiative was mentioned. This new reporting checklist comprises essential items to ensure that researchers write and register their trial protocols with scientific, ethical, professional integrity and transparency; this could possibly be also a model for observational epidemiology study protocols.

The importance of inter-disciplinary networking was also stressed. As an example, the Human Genome Epidemiology Network (HuGENET) initiative was mentioned.

In addition, other initiatives, such as the further expansion of the Cochrane Collaboration to include etiologic studies could enhance the reliability and transparency of observational epidemiology studies.

In order to make data available for future analyses and use, the possibilities of web-based data archives should be explored for archiving all data from all studies, whether published or not.

6.5 Deciding who will take the lead to bring this project forward

An important issue is who is going to take the lead in this project. There was agreement that it would be most effective if the next steps would be led by epidemiologic practitioners and journal editors working together.

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APPENDIX 1: WORKSHOP PROGRAMME

Thursday 24 September 2009

10.45 - 11.15	Registration and coffee	
11.15 - 11.30	**Introduction, reasons and goals for this workshop**	Dr. P. Buffler University of California (Berkeley), USA
11.30 - 12.15	**The current epidemiologic enterprise and its conflict with the scientific ethos**	Dr. J. McLaughlin IEI, USA
12.15 - 13.00	**Sources and consequences of publication bias and related biases**	Dr. J. Kleijnen Kleijnen Systematic Reviews Ltd, NL
13.00 - 14.00	Lunch	
14.00 - 14.45	**A history of the rationale for and path to implementation of clinical trials registration**	Dr. K. Dickersin Johns Hopkins Bloomberg School of Public Health, USA
14.45 - 15.30	**Medical journal guidelines for publication of clinical trials research**	Dr. D. MacAuley British Medical Journal, UK
15.30 - 15.45	Coffee break	
15.45 - 16.30	**The US Government Clinical Trials Registry**	Dr. D. Zarin US Government Clinical Trials Registry, USA
16.30 - 17.00	**Panel discussion**	Dr. P. Buffler/Dr. J. Doe/Dr. J. Samet/Dr. G. Swaen/Dr. J. M. Symons
	Conclusions from day 1 presentations: Learning from clinical trials experience and applicability to environmental epidemiology	
19.00	Dinner	

Friday 25 September 2009

09.00 - 09.15	**Summary of day 1 and objectives of day 2**	Dr. P. Buffler
09.15 - 10.00	**Proposal for enhancing the scientific process of observational epidemiology studies: A plea for an observational studies register (OSR)**	Dr. G. Swaen The Dow Chemical Company, NL
10.00 - 12.00	**Breakout groups** **Chairs:** Dr. J. Kleijnen/Dr. D. Weed/Dr. J. Samet ***Rapporteurs*:** Dr. N. Carmichael/Dr. G. Swaen/Dr. J.M. Symons	
12.00 - 13.00	Lunch	
13.00 - 15.00	**Presentations by *Rapporteurs***	
15.00 - 16.00	**Plenary discussion, consensus statements and final conclusion**	Chairman: Dr. P. Buffler

Close of Workshop

APPENDIX 2: LIST OF PARTICIPANTS

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APPENDIX 3: ORGANISING COMMITTEE

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ECETOC WORKSHOP REPORTS

No. Title

No. 1 Workshop on Availability, Interpretation and Use of Environmental Monitoring Data. 20-21 March 2003, Brussels

No. 2 Strategy Report on Challenges, Opportunities and Research Needs Arising from the Definition, Assessment and Management of Ecological Quality Status as Required by the EU Water Framework Directive Based on the Workshop EQS and WFD versus PNEC and REACh - Are They Doing the Job? 27-28 November 2003, Budapest

No. 3 Workshop on Use of Human Data in Risk Assessment. 23-24 February 2004, Cardiff

No. 4 Influence of Maternal Toxicity in Studies on Developmental Toxicity. 2 March 2004, Berlin

No. 5 Workshop on Alternative Testing Approaches in Environmental Risk Assessment. 7-9 July 2004, Crécy-la-Chapelle

No. 6 Workshop on Chemical Pollution, Respiratory Allergy and Asthma. 16-17 June 2005, Leuven

No. 7 Workshop on Testing Strategies to Establish the Safety of Nanomaterials. 7-8 November 2005, Barcelona

No. 8 Workshop on Societal Aspects of Nanotechnology. 9 November 2005, Barcelona

No. 9 Workshop on the Refinement of Mutagenicity / Genotoxicity Testing. 23-24 April 2007, Malta

No. 10 Workshop on Biodegradation and Persistence. 26-27 June 2007, Holmes Chapel

No. 11 Workshop on the Application of 'Omics in Toxicology and Ecotoxicology: Case Studies and Risk Assessment. 6-7 December 2007, Malaga

No. 12 Workshop on Triggering and Waiving Criteria for the Extended One-Generation Reproduction Toxicity Study. 14-15 April 2008, Barza d'Ispra

No. 13 Counting the Costs and Benefits of Chemical Controls: Role of Environmental Risk Assessment in Socio-Economic Analysis. 4 June 2008, Brussels

No. 14 Use of Markers for Improved Retrospective Exposure Assessment in Epidemiology Studies. 24-25 June 2008, Brussels

No. 15 Workshop on the Probabilistic Approaches for Marine Hazard Assessment. 18-19 June 2008, Oslo

No. 16 Workshop: Guidance on Interpreting Endocrine Disrupting Effects. 29-30 June 2009, Barcelona

No. 17 Workshop: Significance of Bound Residues in Environmental Risk Assessment

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