5/2012

UNCOVER is an FP7-funded project under Contract N° 282574

AIT
DUK UNC

Kylie Thaler, MD, MPH

DEFINITION AND CONSEQUENCES

UNCOVER project deliverable D1.1

This report should be cited as follows: Thaler, K., Chapman, A., Gartlehner, G., Buchinger, E., Bangdiwala, S. Deliverable D1.1 of the UNCOVER FP7-funded project under contract number 282574: Definition and consequences. Publicly available under http://publicationbias.eu.

.

This deliverable was prepared for the UNCOVER project consortium:

AIT Austrian Institute of Technology
Department for Foresight & Policy Development
Coordinating partner

Vienna, Austria

DUK Danube University Krems
Department for Evidence-based Medicine and Clinical Epidemiology

Krems, Austria

UNC University of North Carolina at Chapel Hill
Gillings School of Global Public Health

Chapel Hill, North Carolina, United States

Contact
Dr. Dirk HOLSTE, MBA
Technology Management
Department for Foresight & Policy Development
AIT Austrian Institute of Technology GmbH
Donau-City-Straße 1
A-1220 Vienna
Austria

T +43(0) 50550-4517
F +43(0) 50550-4599

dirk.holste@ait.ac.at

www.ait.ac.at

DEFINITION AND CONSEQUENCES

.

This deliverable was prepared by:

Kylie Thaler, MD, MPH
Andrea Chapman, MA, BSc
Gerald Gartlehner, MD, MPH

Other contributions to the deliverable by:

Eva Buchinger, MA
Shrikant Bangdiwala, PhD

Content

Table Index

Figure Index

Introduction

1.1 The UNCOVER project

Systematic reviews of medical literature are a central resource for evidence-based decision-making. Randomized controlled trials (RCTs) are the gold standard in evaluating the effects of treatment and as such are an essential source of information for systematic reviews. For systematic reviews to be an accurate reflection of the state of the existing evidence, RCTs must be correctly registered, published, and locatable.

From the Project Proposal – Part B

The UNCOVER project is a direct contribution to overcome non-publication of clinical studies that have been designed and executed as RCTs.

UNCOVER's aim is three-fold:

- to apply established and develop novel, solid, and useful methods for fact-finding and interventions into the socio-economic system defined by causes and sources of the publication bias;
- to engage with stakeholders and identify strategies, barriers, and facilitating factors associated with the publication bias and its consequences; and
- to synthesize lessons learned and recommend feasible measures to deal with the publication bias.

RCTs are currently best practice to avoid or minimize both systematic and random errors in clinical studies. They provide the best utility as input to systematic medicinal reviews, one cornerstone of evidence-based medicine (EbM) for improved safety and efficacy / effectiveness of patient outcomes, and their end-users.

That is provided that, and only then, RCTs are both correctly registered and published at least once. Because non-publication, as well as publication with time delay of RCTs, may

decisively reduce the advantage of such systematic reviews of drugs, medical devices or procedures, it affects the knowledge base, patient value, and level of public health. Therefore, in a perspective way, this project contributes pro better allocation of funds to sponsor studies and patient value, and contra duplication of work and patients risk.

The issues of the publication bias are treated with quantitative, qualitative and participatory means in an interdisciplinary approach in areas with little or no lines of evidence as to how they perform in practice:

1. Framing the publication bias in terms of EbM and system's theory (including stakeholder mapping) to both acknowledge and reduce the complexity of the problem and focus on the main players in publishing studies as well as their strategies.
2. Objective, systematic and balanced identification of key opinion leaders, as well as measures (law, regulations, policies, practices, guidelines, methods, tools) to overcome bias, from documents and sites by bibliometric means and comprehensive site searches on the world-wide web.
3. Systematic review of current measures substantiated by own experience ("inside-out") as well as inclusion of experts and external knowledge of international methods groups ("outside-in") in the field of systematic reviews and meta-analyses.
4. Design of interviews (telephone, face-to-face: privacy, group settings) with editors and other stakeholders based on stakeholder mapping/analysis to reflect measures in terms of experiences, own strategies and existing conflict of interests.
5. Development of needed software solutions for the demonstration and treatment of unpublished studies on statistical meta-analyses.
6. Recommendations for the implementation of feasible measures and milestones, as well as open gaps addressed by new research, to overcome non-publication.

UNCOVER will thus both provide viable solutions for the publication bias, for better allocation efficiency of medicinal and health related research funds, and develop methodologies for future bias research efforts.

1.2 Description of the Work-package WP1

Work package 1 consists of two tasks:

- Definition of the conceptual base of publication bias to establish a common understanding of its scope and consequences in clinical trials and to provide a frame of reference for the project-inherent multidisciplinary research approach involving systems analyses, evidence-based medicine, and evaluation research (Task 1.1)
- Identification of stakeholders and grouping of them according to their specific roles and rationalities (mapping) (Task 1.2).

1.3 Aim of the Task 1.1

The aim of task 1.1 is to establish the definitions of all relevant terms in the research field of publication bias. The terms will be used by all project partners and will enable accurate communication.

2 Methods

Task 1.1 was conducted in two parts: 1) identification of relevant terms and 2) definition of these terms. This involved reviewing the existing research on publication bias, specifically with respect to the partial publication or non-publication of the results of RCTs.

2.1 Inclusion criteria

Publications that provide an analytical frame and/or definitions of publication bias and/or related terms were considered for inclusion.

A preliminary definition of publication bias was used as an orientation point:

Publication bias "occurs when the publication of research results depends on the nature and direction of the result".[1 p.3] *Examples of publication bias include the non-publication of statistically insignificant results by editors of journals or the non-publication of negative results of studies funded by pharmaceutical companies.*

2.2 Data sources and access to data

We drew our data from several sources:

1) As a starting point, we identified relevant terms and their definitions from the publication *Dissemination and publication of research findings: an updated review of related biases*.[1] These terms formed the basis of our *Data extraction form Task 1.1* found in **Fehler! Verweisquelle konnte nicht gefunden werden.**

2) We conducted an abstract review for publications obtained from
   - a literature search, as described below,
   - references noted by the Cochrane Bias Methods Group[2],
   - publications from our internal *Methods Library*[1]
3) We scanned the following publications for relevant terms and their definitions:
   - the "Cochrane Handbook" of the Cochrane Collaboration[3], and

[1] The publications in our internal Methods Library have been categorized according to subject matter. The Methods Library consists of references and the corresponding publication in electronic form. References have been amassed over the course of 6 years. A list of new publications pertinent to the field of evidence-based medicine is generated biweekly by an information specialist of the Evidence-based Practice Center of the Oregon Health and Science University, USA. These lists are periodically reviewed by staff of the Department for Evidence-based Medicine and Clinical Epidemiology of the Danube University, Krems for publications dealing with methods in evidence-based medicine. References identified as potentially relevant then undergo a full text review.

- the "Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews" of the Agency for Healthcare Research and Quality
- "The guidelines manual" from the National Institute for Health and Clinical Excellence[5]
- Centre for Reviews and Dissemination "Systematic Review Guidance"[6]
- European network for Health Technology Assessment (EUNetHTA) [7]
- HuGENet (Human Genome Epidemiology Network)[8]
- The German Network of Evidence-based Medicine *(Deutsches Netzwerk Evidenzbasierte Medizin)*[9]
- The Epidemiological Glossary of the University of Halle *(Universität Halle, Epidemiologisches Glossar)*[10]
- The Epidemiological Glossary of the University of Basel *(Universität Basel, Epidemiologisches Glossar)*[11]
- Glossary of the Institute for Quality and Efficiency in Healthcare, Germany *(Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), Glossar)*[12]

* Publications of high quality are then imported into the EndNote-based Methods Library and assigned a method-category to be searchable.

2.3 Literature search

A specific literature search, documented in **Fehler! Verweisquelle konnte nicht gefunden werden.** was conducted for Task 1.1 in two electronic databases: Cochrane Methodology Register Database (CMRD) via the Cochrane Library and PubMed.

2.4 Review of the literature

A review of the literature yielded from the sources described in point **Fehler! Verweisquelle konnte nicht gefunden werden.** above was conducted as follows:

- During the abstract review, two reviewers identified possible publications for Task 1.1. It was sufficient for inclusion when one reviewer identified an abstract as potentially relevant.
- All publications selected via the abstract review for Task 1.1, were examined for relevant terms and their corresponding definitions.

2.5 Extraction of data

The extraction of data was conducted as follows:

1) Identification of relevant terms: All terms from the Song et al.[1] publication were compiled in the *Data Extraction Form for Task 1.1*. (see **Fehler! Verweisquelle konnte nicht gefunden werden.**) Additional terms identified from publications selected during the full text review were then added to the extraction form.
2) Extraction of the definitions: One person extracted the definitions of the identified terms into the *Data extraction form for Task 1.1*. Data extractions were then checked for accuracy by a second person.

2.6 Data management

All terms and definitions were extracted into one master document.

The results of the literature search and additional references were saved in EndNote (EndNote X4.0.2, Thomson Reuters). References were coded using the Custom 1 field in EndNote as “I” (include) or “E” (exclude) with the reason for exclusion (e.g. “not obtainable”, “meeting abstract”, or “no definitions”).

2.7 Selection of results

The results are comprised of relevant terms and a corresponding definition. Rather than a synthesis of all definitions extracted for each term, the definition most suitable to the objectives of this project was selected. If suitable, these definitions were cited word for word, and if this was not possible the definition was developed based on the context of the corresponding publication. Where no definition was available, we defined the terms in a group process amongst the UNCOVER WP 1 team. These definitions have no reference.

3 Results

3.1 Literature search results

During the process of identifying terms related to publications bias we located 466 references after excluding duplicates. We identified 79 potentially relevant citations. We were unable to locate one reference. We scanned full-texts for definitions and abstracted definitions for relevant terms from 64 full-text publications.

We classified the terms important for this project into four categories:

- Publication bias and related biases
- Evidence-based medicine
- Statistical terms
- Stakeholder roles

We used a consensus approach within our team to decide on the relevant terms for inclusion in the glossary and to decide on the correct definition for our purposes. In addition, we consulted colleagues from the German Cochrane Centre in Freiburg,

Germany, who are currently working on another project on publication bias (OPEN) to ensure the key terms were agreed upon between the two projects.

We obtained multiple definitions for many terms. The synthesized definitions obtained for each term are presented in tables (Table 1, Table 2, Table 3 and Table 4). Additionally, the publications from which the definitions were extracted are cited. Where no citation is given the definition was agreed upon by consensus and not taken directly from another publication.

Many of the terms were eloquently defined in the pivotal publication on publication bias by Song et al. in 2010.[1] In general, we chose to remain consistent with the definitions provided by Song et al. of many terms and have added information from other publications only where it helps to clarify the use of the term. Some additional terms not defined in Song et al. have been included in this summary because of the broader scope of the UNCOVER project. Where no citation is provided the definition was posed and agreed upon by the work package 1 team.

3.2 Definitions: Publication bias and related biases

The definitions of terms in the category “publication bias” are presented in Table 1. In this sections we attempt to summarize the various terms for biases in the medical literature to ensure that the UNCOVER partners use these terms consistently throughout the project and to ease communication within the teams and between project partners. In addition we want to ensure that the results of UNCOVER are explicitly and easily understandable to other stakeholders.

Table 1: **PUBLICATION BIAS AND RELATED BIAS TERMS**

Term	Definition
Bias	Bias refers to types of systematic errors in the collection, analysis, or interpretation of research data that distort the outcomes; bias at times may be either unrecognized or intentional, but both negate the validity of the study.[13] In statistics, the bias of an estimator is the difference between this estimator's expected value and the true value of the parameter being estimated.
Citation bias	Occurs when the chance of a study being cited by others is associated with its result. For example, authors of published articles may tend to cite studies that support their position. Thus, retrieving literature by scanning reference lists may produce a biased sample of articles and reference bias may also render the conclusions of an article less reliable.[1]
Database bias (indexing bias)	Occurs when there is biased indexing of published studies in literature databases. A literature database, such as MEDLINE or EMBASE, may not include and index all published studies on a topic. The literature search will be biased when it is based on a database in which the results of indexed studies are systematically different from those of non-indexed studies.[1]
Dissemination bias	Occurs when the dissemination profile of a study's results depends on the direction or strength of its findings. The dissemination profile is defined as the accessibility of research results or the possibility of research findings being identified by potential users. The spectrum of the dissemination profile ranges from completely inaccessible to easily accessible, according to whether, when, where and how research is published.[1]
Full publication bias	Occurs when the full publication of studies that have been initially presented at conferences or in other informal formats is dependent on the direction and/or strength of their findings.[1]
Grey literature bias	Occurs when the results reported in journal articles are systematically different from those presented in reports, working papers, dissertations or conference abstracts.[1]
Language bias	Occurs when languages of publication depend on the direction and strength of the study results.[1] Rationale: Authors having completed a clinical trial yielding negative results might be less confident about having it published in a large

Term	Definition
	diffusion international journal written in English and would then submit it to a local journal. If these investigators work in a non-English speaking country the paper will be published in their own language in a local journal. Positive results by authors from non-English speaking countries are thus more likely to be published in English, and negative results in the investigators language.[14]
Media attention bias	Occurs when studies with striking results are more likely to be covered by the media (newspapers, radio and television news).[1]
Multiple publication bias (duplicate publication bias)	Occurs when studies with significant or supportive results are more likely to generate multiple publications than studies with non-significant or unsupportive results. Duplicate publication can be classified as 'overt' or 'covert'. Multiple publication bias is particularly difficult to detect if it is covert, when the same data are published in different places or at different times without providing sufficient information about previous or simultaneous publication.[1]
Non-publication	See "publication bias" the term we use for non-publication of the results of clinical trials.
Outcome reporting bias	Occurs when a study in which multiple outcomes were measured reports only those that were significant.[1] Selective [outcome] reporting bias in a study is defined as the selection, on the basis of the results, of a subset of analyses to be reported. Selective reporting may occur in relation to outcome analyses, subgroup analyses, and per protocol analyses, rather than in intention to treat analyses, as well as with other analyses. Three types of selective reporting of outcomes exist: the selective reporting of some of the set of study outcomes, when not all analyzed outcomes are reported; the selective reporting of a specific outcome—for example, when an outcome is measured and analyzed at several time points but not all results are reported; and incomplete reporting of a specific outcome—for example, when the difference in means between treatments is reported for an outcome but no standard error is given. A specific form of bias arising from the selective reporting of the set of study outcomes is outcome reporting bias, which is defined as the selection for publication of a subset of the original recorded outcome variables on the basis of the results.[15]
Place of publication bias	Place of publication bias is defined as occurring when the place of publication is associated with the direction or strength of the study findings. For example, studies with positive results may be more likely to

Term	Definition
	be published in widely circulated journals than studies with negative results. The term was originally used to describe the tendency for a journal to be more enthusiastic towards publishing articles about a given hypothesis than other journals, for reasons of editorial policy or readers' preference.[1] Furthermore, clinical trial results may be publically available (for example as PDFs via company or public webpages); however they may not be indexed in any databases and therefore practically difficult to locate.
Positive-outcome bias	Preference (of journals) for (publishing) trials showing significant results.[16]
Publication bias	Occurs when the publication of research results depends on the nature and direction of the results. Because of publication bias, the results of published studies may be systematically different from those of unpublished studies.[1] The non-publication of clinical trials might mean that the results are entirely unavailable/inaccessible, that the results are submitted to a regulatory agency but are unavailable to other researchers, systematic reviewers, or other stakeholders, or that some of the results remain unavailable (see selective outcome reporting bias).
Time lag bias	Occurs when the speed of publication depends on the direction and strength of the trial results. For example, studies with significant results may be published earlier than those with non-significant results.[1]

3.3 Definitions: Evidence-based medicine terms

In this sections we present the definitions of commonly used terms in the field of evidence-based medicine (EbM) not specifically related to publication bias (Table 2). EbM, or evidence-based practice, is an approach to the practice of medicine that involves integrating individual clinical expertise with the best available external clinical evidence from systematic research.[6]

When possible we chose to remain consistent with the international Cochrane Collaboration definitions of EbM terms. The Cochrane collaboration has been a pioneer in

the field of EbM and is currently the largest and most well-established entity in the field. The use of Cochrane definitions for the EbM terms will ensure clear and consistent communication both within the UNCOVER project and to any external stakeholders in the EbM field.

Table 2: **EVIDENCE-BASED MEDICINE TERMS**

Term	Definition
Citation	Citation, the act of connecting text statements through reference to the broader literature is not simply an impartial scholarly method for joining related published knowledge. Citation may be used for self-serving purposes or as a tool for persuasion. These aspects of citation might be called social citation.[17]
Clinical Trial	An experiment to compare the effects of two or more healthcare interventions. Clinical trial is an umbrella term for a variety of designs of healthcare trials, including uncontrolled trials, controlled trials, and randomized controlled trials.[18]
Cochrane Collaboration	An international organisation that aims to help people make well informed decisions about health by preparing, maintaining and ensuring the accessibility of systematic reviews of the benefits and risks of healthcare interventions.[3]
Cochrane Controlled Trials Register (CCTR)	A database of references to controlled trials in health care. Cochrane groups and other organisations have been invited to contribute their specialised registers, and these registers, together with references to clinical trials identified on MEDLINE and other sources, form the CENTRAL register of studies. Records from CENTRAL, following quality control to try to ensure that only reports of definite randomised controlled trials or controlled clinical trials are included, make up The Cochrane Controlled Trials Register (CCTR).[3]
Cochrane Database of Systematic Reviews (CDSR)	The major product of the Cochrane Collaboration. It brings together all the currently available Cochrane Reviews and is updated quarterly. Collaborative Review Groups submit modules of edited reviews to the Parent Database for inclusion in the CDSR. See also Cochrane Library.[3]
Cochrane Library (CLIB)	A collection of databases, published on CD-ROM and the Internet and updated quarterly, containing the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Register, the Database of Abstracts of Reviews of Effectiveness, the Cochrane Review

Term	Definition
	Methodology Database, and information about the Cochrane Collaboration.[3]
Cochrane Review	A Cochrane Review is a systematic, up-to-date summary of reliable evidence of the benefits and risks of healthcare. Cochrane Reviews are intended to help people make practical decisions. For a review to be called a "Cochrane Review" it must be in the Parent Database maintained by the Cochrane Collaboration. The Parent Database is composed of modules of reviews submitted by Collaborative Review Groups (CRGs) registered with the Cochrane Collaboration. The reviews contributed to one of the modules making up the Parent Database are refereed by the editorial team of the CRG, as described in the CRG module. Reviewers adhere to guidelines published in the Cochrane Reviewers' Handbook. The specific methods used in a Cochrane Review are described in the text of the Review. Cochrane Reviews are prepared using Review Manager software, also known as RevMan, provided by the Collaboration and adhere to a structured format that is described in the Handbook.[3]
Equivalence trial (see also non-inferiority)	A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.[3]
Grey literature	Grey literature is the kind of material that is not published in easily accessible journals or databases. It includes things like conference proceedings that include the abstracts of the research presented at conferences, unpublished theses (dissertations), working papers, and so on.[3]
Handsearch	Handsearching refers to the planned searching of a journal page by page (i.e. by hand), including editorials, letters, etc., to identify all reports of randomized controlled trials and controlled clinical trials. All the identified trials, regardless of the topic, are sent to the United States Cochrane Center, for inclusion in CENTRAL, and forwarding to the US National Library of Medicine (NLM) for re-tagging in MEDLINE. Trials that are within the scope of a Collaborative Review Group or Field go into their specialized register of trials.[3] "Manual searching" can also be used to refer to this process, as well as searching references lists or key articles or searching the grey literature.
Health	A multidisciplinary process that summarizes information about the

Term	Definition
Technology Assessment (HTA)	medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe effective, health policies that are patient focused and seek to achieve best value healthcare.[7]
Keywords	A string of words attached to an article to be used to index or code the article in a database. See also MeSH and MEDLINE.[3]
MEDLINE	An electronic database produced by the United States National Library of Medicine (NLM). It indexes millions of articles in selected journals, available through most medical libraries, and can be accessed on the Internet.[3]
MeSH	Terms used by the United States National Library of Medicine to index articles in **Index Medicus** and **MEDLINE**. The MeSH system has a tree structure in which broad subject terms branch into a series of progressively narrower subject terms.[3]
Meta-analysis	The use of statistical techniques in a systematic review to integrate the results of included studies. Sometimes misused as a synonym for systematic reviews, where the review includes a meta-analysis.[3]
Non-inferiority trial	A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a pre-specified amount. A one-sided version of an equivalence trial.[3]
PubMed	A free access Internet version of MEDLINE also including records from before 1966 (old MEDLINE), some very recent records and some other life science journals.[3]
Randomized controlled trial (RCT)	An experiment in which two or more interventions, possibly including a control intervention or no intervention, are compared by being randomly allocated to participants. In most trials one intervention is assigned to each individual but sometimes assignment is to defined groups of individuals (for example, in a household) or interventions are assigned within individuals (for example, in different orders or to different parts of the body).[3]
Search strategy	The combination of terms used to identify studies in an electronic database such as MEDLINE.[3]
Systematic literature search	An essential step in the systematic review process in which multiple sources, such as numerous bibliographic databases, are searched to locate published literature and grey literature.[19]
Systematic review	A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant

Term	Definition
	research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.[3]

3.4 Definitions: Statistical terms

The following definitions should serve as an anchor for this project (Table 3). They are not, however, final and unchangeable. If project members feel that changes or additions need to be made these should be discussed and clarified with other project team members who will be affected.

These definitions were provided and approved by Shrikant Bangdiwala, UNCOVER work package 4 leader. In general, our use of these terms is consistent with the definitions in the Cochrane Glossary.

Table 3**: STATISTICAL TERMS**

Term	Definition
Effect size of published studies	A generic term for the estimate of effect of treatment for a study. A dimensionless measure of effect that is typically used for continuous data when different scales (e.g. for measuring pain) are used to measure an outcome and is usually defined as the difference in means between the intervention and control groups divided by the standard deviation of the control or both groups.[18] For binary data, the effect is usually quantified by the risk ratio, defined as: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of one indicates no difference between comparison groups. For undesirable outcomes, a

Term	Definition
	risk ratio that is less than one indicates that the intervention was effective in reducing the risk of that outcome.[18] Also called: Relative risk, RR
Statistical significance	A result that is unlikely to have happened by chance. The usual threshold for this judgment is that the results, or more extreme results, would occur by chance with a probability of less than 0.05 if the null hypothesis was true. Statistical tests produce a p-value used to assess this.[18]
Clinical relevance	A result (e.g. a treatment effect) that is large enough to be of practical importance to patients and healthcare providers. This is not the same thing as statistically significant. Assessing clinical relevance takes into account factors such as the size of a treatment effect, the severity of the condition being treated, the side effects of the treatment, and the cost. For instance, if the estimated effect of a treatment for acne was small but statistically significant, but the treatment was very expensive, and caused many of the treated patients to feel nauseous, this would not be a clinically relevant result. Showing that a drug lowered the heart rate by an average of 1 beat per minute would also not be clinically relevant.[18]
Heterogeneity among studies	Used in a general sense to describe the variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies, or the variation in internal validity of those studies. Used specifically, as statistical heterogeneity, to describe the degree of variation in the effect estimates from a set of studies. Also used to indicate the presence of variability among studies beyond the amount expected due solely to the play of chance.[18]
Fixed effects model	In meta-analysis: A model that calculates a pooled effect estimate using the assumption that all observed variation between studies is caused by the play of chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.[18]
Mixed effects model	In meta-analysis: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. See also fixed-effect model. When there is heterogeneity among

Term	Definition
	the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.[18]
Likely effect from unpublished studies	The nature and direction of the results of a study may impact whether it is published or not. In order to include unpublished studies in a sensitivity meta analysis, one must provide an estimate (guess) of the effects in each unpublished study.

3.5 Definitions: Stakeholder role descriptions

We developed this list of relevant stakeholders in the clinical trial process and a working definition of their role in several workshops conducted between the Danube University work package 1 team and Eva Buchinger of the Austrian Institute of Technology. These meetings also served to clarify the roles and relationships between stakeholders for the stakeholder mapping in task 1.2. Terms are presented in Table 4. Terms related to the process of stakeholder mapping are defined in the report of task 1.2.

The following definitions should serve as an anchor for this project. They are not, however, final and unchangeable. If project members feel that changes or additions need to be made these should be discussed and clarified with other project team members who will be affected.

Table 4**: STAKEHOLDER TERMS**

Term	Definition
Authors	Persons who write manuscripts describing clinical trials for publication. These people may be employed by a private pharmaceutical company (“company”) or members of staff at university hospitals or other public institutions without direct financial interest in the drug being tested (“university hospitals, research institutes”).

Term	Definition
Conductors	Persons who are responsible for the organization and practical supervision of clinical trials. They may be employees of pharmaceutical companies ("companies") or of university hospitals or other public institutions without direct financial interest in the drug being tested ("university hospitals, research institutes").
Consumer advocates	Persons who serve to advocate on behalf of and in the best interests of patients in general or a specific group of patients with a particular illness.
Ethics committees	For a clinical trial to be allowed it must first be approved by an ethics committee. These committees consist of a group of persons with differing clinical, philosophical or ethical backgrounds who protect the rights of clinical trials participants by ensuring that medical research is conducted in accordance with the appropriate ethical standards of the locality.
Financiers (companies, private funds)	Persons or organizations that provide funding for conducting clinical trials. "Companies" who have a direct financial interest in the drug being tested, or public organizations with an interest in the promotion of science, the curing of disease, or other charitable rationalities.
Ghostwriter Gift authorship, honorary authorship	Ghost authorship exists when someone has made substantial contributions to writing a manuscript and this role is not mentioned in the manuscript itself. It often occurs simultaneously with its opposite, guest authorship (sometimes called honorary or gift authorship), where the contributions of the named authors are so small, or nonexistent, that they do not merit authorship.[20]
Insurers and assessment agencies	Organizations with the task of deciding which drugs to allow and/or reimburse in their locality.
Medical doctors	Persons practicing clinical medicine (i.e., making decisions or recommendations to patients about the best medical / pharmaceutical management of medical problems).
Patient organization	A non-profit, non-governmental organization that represents a group of patients in a specific geographical or disease area.
Peer Review	A refereeing process for checking the quality and importance of reports of research. An article submitted for publication in a peer-reviewed journal is reviewed by other experts in the

Term	Definition
	area.[18]
Pharmaceutical company / Pharmaceutical Industry	A pharmaceutical company is a private institution that develops, produces, and markets medications or drugs.
Political decision maker	A person who is a political representative and who is responsible for making decisions regarding health care.
Publishers (scientific journals, databases, mass media)	Organizations who publish manuscripts describing clinical trials ("scientific journals"); who manage searchable databases listing the contents of scientific journals ("Databases"); or who inform the general public about new/interesting results from clinical trials ("mass media").
Registration agency	i.e., European Medicines Agency (EMA): an agency of the European Union responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union.
Regulator	An agency that approves / licenses a drug for use in their administrative locality i.e., EMA (European Medicines Agency)
Stakeholder	Those persons/entities who influence, or are affected by, non-publication actions.
User (patients, trial participants)	Persons who consume health care: "consumers" as per the Cochrane Collaboration terminology. These persons may be unwell with a medical condition, they may be participants in clinical trials, or they may be well and seeking to prevent future illness.

4 Discussion and conclusions

In this task we have established working definitions of the terms and concepts related to publication bias. These definitions should be used consistently by the UNCOVER project partners in all future work packages to ensure efficient and accurate communication within the project and to stakeholders outside the project. If, during the course of the UNCOVER project (in particular in the process of refining the stakeholder mapping in work package 5), the definitions presented here need to be modified this is to be encouraged, however it should be done with consultation between all project partners.

Since the concept of publication bias first appeared in the scientific literature many conflicting and/or overlapping terms for similar ideas have been used. We abstracted definitions from 64 full-text publications on the topic of publication bias, many of which used unique definitions of key terms and concepts. Although the rationale behind the concerns regarding varying biases was similar, the use of differing terms serves only to confuse and unnecessarily complicate communications between researchers in this area. In 2010, Song and colleagues published a landmark health technology assessment on publication bias which included a comprehensive glossary of relevant terms, in particular for different types of bias. We have chosen, to a great extent, to agree with these definitions as we believe that they are comprehensive, sensible, and usable, and that they will, in time, establish themselves as the "correct" definitions in this field. We have added information of citations from other publications where terms in the Song et al. glossary were absent, where additional information clarifies how terms have been used in the past, or slightly expands ideas of the definitions included.

For similar reasons, in most cases we chose to adopt the Cochrane Collaboration definitions for terms related to EbM. The Cochrane Collaboration is a network of over 30,000 active researchers, medical personnel, and consumer advocates who have pioneered the methodology of systematic reviews and championed EbM principles in over 30 countries worldwide. Using the Cochrane Collaboration terminology accurately allows the results of UNCOVER to be easily understood by all stakeholders, in particular by speakers of languages other than English who are already familiar with their use through Cochrane Reviews and Cochrane Collaboration. We differed from the Cochrane definitions only where we believed that additional information was needed to specify the exact meaning of terms in the context of this specific project on publication bias.

The stakeholder terms we have presented here were agreed upon in a workshop-type process of discussion between the project partners Austria Institute of technology (AIT) and the Danube University Krems (DUK). These terms are considerably more likely than the

publication bias related terms and the EbM terms to require some specification or modification in the course of this project.

The aim of task 1.1 was to establish the definitions of all relevant terms in the research field of publication bias. The terms will be used by all project partners and will enable accurate communication. In order to establish these definitions we performed a scoping search of the scientific literature on the subject of publication bias, specifically with respect to clinical trials. In addition, we obtained key publications and manuals from the Cochrane Collaboration Bias Methods group. After extracting definitions for hundreds of terms it became clear that that the consistent use of terms amongst researchers in this area is essential and that the landmark work by Song and colleagues and the definitions of the Cochrane Collaboration should serve as the basis for our definitions in UNCOVER. We were not able to identify any major gaps in regard to the establishment of definitions and clarification of the problem of publication bias. In particular, we located much empirical research describing and clarifying the existence of publication bias and related biases. Further work packages in this project, in particular the systematic review of the effectiveness of measures to counter publication bias in work package 3, will surely add to this knowledge base.

5 References

1. Song F, Parekh S, Hooper L, et al. Dissemination and publication of research findings: an updated review of related biases. *Health Technol Assess.* Feb 2010;14(8):iii, ix-xi, 1-193.

2. Cochrane Bias Methods Group. References & Resources. 2011; http://bmg.cochrane.org/references-resources. Accessed October 11, 2011.

3. The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. In: Higgins JPT, Green S, eds: The Cochrane Collaboration; 2011: http://www.cochrane-handbook.org/.

4. Agency for Healthcare Research and Quality. Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews. 2007; Websource:

http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf. Accessed Accessed: August 31, 2010

5. National Institute for Health and Clinical Excellence. The guidelines manual. 2007. www.nice.org.uk.

6. Centre for Reviews and Dissemination. CRD's guidance for undertaking reviews in health care. 2009; www.yps-publishing.co.uk. Accessed 25.01.2012.

7. European Network for Health Technology Assessment. HTA core model for medical and surgical interventions 1.0R. 2008; Websource: http://www.eunethta.net/upload/WP4/Final%20Deliverables/HTA%20Core%20Model%20for%20Medical%20and%20Surgical%20Interventions%201%200r.pdf. Accessed Accessed: August 30, 2010.

8. The HuGENet Writing Group. The HuGENET™ HuGE Review Handbook, Version 1.0. 2006; http://www.hugenet.ca. Accessed 2-28-09.

9. Kunz R, Lühmann D, Windeler J, Lelgemann M, Donner-Banzhoff N. Glossar zur Evidenzbasierten Medizin: AG Glossar des Deutschen Netzwerk EbM; 2006:13.

10. German Center for Evidencebased Nursing. Glossar epidemiologischer Fachbegriffe2004:12.

11. Universität Basel. Epidemiologisches Glossar2006:16.

12. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). Glossar zu den Allgemeinen Methoden 3.0. Vol Version 1.02008:27.

13. Liesegang TJ. The distortion of commercial research reported in the peer-reviewed literature. *Can J Ophthalmol.* Aug 2009;44(4):367-369.

14. Gregoire G, Derderian F, LeLorier J. Selecting the language of the publications included in a meta-analysis: is there a tower of Babel bias? *Journal of Clinical Epidemiology.* 1995:159-163. http://www.mrw.interscience.wiley.com/cochrane/clcmr/articles/CMR-340/frame.html. Published PubMed.

15. Kirkham JJ, Dwan KM, Altman DG, et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *BMJ.* 2010:c365. http://www.mrw.interscience.wiley.com/cochrane/clcmr/articles/CMR-14331/frame.html. Published PubMed.

16. Ernst E, Resch KL. Reviewer bias: a blinded experimental study. *The Journal of laboratory and clinical medicine.* Aug 1994;124(2):178-182.

17. Greenberg SA. How citation distortions create unfounded authority: analysis of a citation network. *BMJ (Clinical research ed.).* 2009;339(Journal Article):b2680.

18. The Cochrane Collaboration. Glossary. 2012; http://www.cochrane.org/glossary. Accessed 24.04.2012.

19. Chapman AL, Morgan LC, Gartlehner G. Semi-automating the manual literature search for systematic reviews increases efficiency. *Health Info Libr J.* Mar 2010;27(1):22-27.

20. Gotzsche PC, Kassirer JP, Woolley KL, et al. What should be done to tackle ghostwriting in the medical literature? *PLoS Med.* Feb 3 2009;6(2):e23.

6 Appendices

6.1 Literature search Task 1.1

Search Date: 10.10.2011

PubMed – general

#1 Search "Publication Bias"[Mesh] OR "dissemination bias"[tiab] OR "publication-bias"[tiab] OR "publication bias"[tiab]	3308
#2 Search "Publishing/standards"[Mesh] OR "Biomedical Research/standards"[Mesh] OR "Evidence-Based Medicine/standards"[Mesh] OR "Information Dissemination/methods"[Mesh] OR "Peer Review"[Mesh]	23766
#3 Search #1 AND #2	327
#4 Search #1 AND #2 Limits: Comment, Editorial, Letter, Review	153

PubMed – identical indexing as Song et al. publication

#1 Search "Publication Bias/statistics and numerical data"[MeSH] AND ("Information Dissemination"[MeSH] OR "Evidence-Based Medicine/standards"[MeSH Terms] OR "Biomedical Research/standards"[MeSH Terms])	10*

*(6 references imported into EndNote; other 4 reference contained in "PubMed – general" search)

Cochrane Methodology Register Database (CMRD) via the Cochrane Library:

#1 (citation OR database OR indexing OR dissemination OR "grey literature" OR "gray literature" OR language OR "media attention" OR "multiple publication" OR "duplicate publication" OR "outcome reporting" OR "place of publication" OR "time lag bias"):ti and (bias):ti in Methods Studies	54*

*53 references imported into EndNote; the remaining reference was contained in "PubMed – Song indexing" search

6.2 Data extraction form Task 1.1

Data was extracted into an excel spreadsheet:

"Data Extraction Form Task 1.1.xlsx"

Figure 1: Data extraction form Task 1.1

	A	B	C	D	E	F	G
1	Rcrd#	Author or Source	Term	Stat	Valu	Category	Definition
2	44	Buchkowsky, S	author–industry rela	I	X	stakeholder	An author was considered to be affiliated with an industry-funding source if the sponsor of the study was industry or a mixed source and the identity of the pharmaceutical company matched the affiliation of one or more authors. For trials with a nonprofit or undeclared sponsor, a possible affiliation with an industry funding source was considered when the study drug supplies were provided by, and one or more authors were affiliated with, that particular pharmaceutical sponsor.
3	236	Liesegang, T	bias, general	I	X	EBM	In this editorial, bias refers to types of systematic errors in the collection, analysis, or interpretation of research data that distort the o
4	19	Arida, A	time lag bias (early-	I	X	publication bias	I have reservations about his suggestion that publication lag is a more exact term than publication bias in efficacy trials. Stern and
7	40	Bowden, J	dissemination bias	I	X	publication bias	When presented with data collected from a study, there are often multiple statistical methods that could be employed in the
8	40	Bowden, J	publication bias	I	X	publication bias	An implicit assumption made when fitting model (1) is that the n studies form a representative sample of all studies conducted into this research topic. However, it is often only possible to include studies that have been published in research journals. While it may
9			benefit assessment	I	X	stakeholder	
10	44	Buchkowsky, S	funding bias	I	X	publication bias	The pharmaceutical industry has become a major source of funding for clinical drug trials resulting in concern about the negative effects of the commercialization of research. 1-7 Potential financial conflicts of interest in biomedical research exist, and most journals now require investigators to declare any relationship that may threaten their impartiality. While we fully support the need to disclose author–industry relationships that would not otherwise be obvious, we are also interested in closer affiliations. We have
11	53	Carter, A	publication bias	I	X	publication bias	Publication bias is a form of selection bias defined by MeSH as the influence of study results on the chances of publication and the tendency of investigators, reviewers, and editors to submit or accept manuscripts for publication based on the direction or strength of the study findings [1]. Interest has focused mainly on bias associated with the direction of the findings being positive (i.e., finding a significant difference between two or more of the groups studied) for primary outcome(s) of the study because of the concern
		Cochrane Collabora	Cochrane Collabora	I	X	EBM	An international organisation that aims to help people make well informed decisions about health by preparing, maintaining and ensuring the accessibility of systematic reviews of the benefits and risks of healthcare interventions.