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Institutional framework for the discussion of publication bias related to clinical trials

From stakeholder mapping to the hard law & soft law distinction

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Publication bias occurs when the publication of research depends on the nature and direction of the results; i.e. a study's positive, negative, or null result can influence its chances of publication. The objective of this report is the provision of an institutional framework for the discussion of impacts of interventions to reduce non-publication of clinical trials. Thereby, the hard law & soft law distinction is used to structure the societal context which guides the behaviour/interactions of stakeholders. This framework is an interim result which will be further developed in WP5 on the basis of expert workshops.

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Institutional framework for the discussion of publication bias related to clinical trials

From stakeholder mapping to the hard law & soft law distinction

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Executive summary

Background

The UNCOVER project aims at overcoming non-publication bias related to clinical trials (CTs). As an outcome of the project, recommendations will be provided which will address the change of undesired publication practice. These recommendations will serve as a contribution to evidence-based medicine and therefore eventually add to the delivery of optimum clinical care to patients.

The UNCOVER project focuses on non-publication of results of clinical trials. Non-publication is seen as a factor which derogates evidence-based medicine by hampering the process of systematically reviewing, appraising and using clinical research findings to aid the delivery of optimum care to patients.

Causes of non-publication bias can be found – to a varying degree – at all stages of the publication process. Recommendations which address the change of undesired publication practice have to deal with the variety of this causation.

Objective

The objective of this report is to provide an institutional framework for the discussion of impacts of interventions to reduce non-publication bias related to clinical trials (CTs).

Method

The methods used are desk research and concept development. Cornerstones are thereby stakeholder mapping and institutional analysis.

Results

The results are twofold. First, an updated version of the stakeholder map (version 2, following version 1 – Deliverable 1.2) is provided. Second, the impact of interventions to reduce non-publication bias related to CTs is shown on the basis of examples (“policy of medical journal”, “policy of public financier”, “standards & guides”, and “legal framework”) and represented within the stakeholder map.

1 Introduction

1.1 Background

The UNCOVER project aims at overcoming non-publication bias[1] related to clinical trials (CTs). As an outcome of the project, recommendations will be provided which will address the change of undesired publication practice. These recommendations will serve as a contribution to evidence-based medicine[2] and therefore eventually add to the delivery of optimum clinical care to patients. The UNCOVER project focuses on non-publication of results of clinical trials, since this specific type of publication bias is seen as a factor which significantly hampers evidence-based medicine. For example, Ross et al. recently indicated that fewer than half of "US National Institutes of Health" (NIH) funded trials[3] were published in a peer reviewed biomedical journal indexed by Medline within 30 month of trial completion (5).

Causes of non-publication bias can be found – to a varying degree – along all stages of the publication process. Tab. 1 gives an overview of main sources as discussed in the literature and of already existing results of the UNCOVER project. Recommendations addressing the change of the existing publication practice have to deal with the variety of this causation.

1.2 Objective

The objective of this report is the provision of a framework for the discussion of impacts of interventions to reduce non-publication bias related to CTs. This is done on the basis of the hard law & soft law distinction to structure the societal context which guides the behaviour/interactions of stakeholders. The following key questions will be considered:

[1] Publication biases can have different forms (1): e.g. non-publication (never or delayed), incomplete publication (outcome reporting or abstract bias), limited accessibility to publication (grey literature, language or database bias), or other biased dissemination (citation, duplicate or media attention bias).

[2] Evidence-based Medicine (EBM) as the process of systematically finding, appraising, and using research findings as the basis for clinical decisions (2-4).

[3] According to their sample which was limited to (i) interventional studies, (ii) registered after 13 September 2005 within ClinicalTrials.gov, (iii) primarily/partially funded by NIH, (iv) completed by 31 December 2008 (n=635).

- How does the general institutional context contribute to prevent non-publication bias related to CTs?
- How does 'soft law' contribute to prevent non-publication bias Related to CTs?
- How does 'hard law' contribute to prevent non-publication bias related to CTs?

Tab. 1: Main sources and reasons for non-publication bias related to CTs

Source	Reason
Investigators and authors	– lack of time or interest – results not important enough (i.e. lack of awareness of the benefits of publishing ALL results of CTs) – (fear of) journal rejection
Editorial review process	– editorial policies (authors anticipate rejection because of a certain qualitative, quantitative or other specific focus of a journal, lack of editorial independence) – journal peer review (unbalanced selection of reviewers, unbalanced reviews) – study results and journal editorial decisions (rejection of negative/unfavourable trials, preferring trials with statistically significant results, rejection because of type/region of research)
Readers and users of research findings	– journal editors' policy reflect readers preferences and incorporate this into the peer review process (e.g. preference for novel treatments)
Research funding bodies and commercial interests	– conflict between dissemination of research findings and commercial interest of industry sponsor

Sources: based on (1, 6-9)

1.3 Report structure

The report starts with the description of the methodology used for the development of a framework for the discussion of impacts of interventions to reduce non-publication bias. This is followed by the description and discussion of the updated stakeholder map, the 'hard law & soft law' framework and related intervention examples. The report concludes with a discussion of the key findings.

2 Methods

2.1 Methodology

Starting from the CT stakeholder map – which was developed previously in UNCOVER task 1.2 (see UNCOVER Deliverable 1.2) (10) – a further conceptual framing was added in task 3.4, which is the basis for this report. Whereas the stakeholder map is based on concepts such as role-sets and societal rationalities[4], the additional conceptual framing covers the dimension of interventions. It is based on the 'hard law' & 'soft law' distinction (11-13). That is, hard law (legislation) together with soft law (established practices, voluntary agreements, etc.) provide the institutional context guiding the behaviour/interactions of CT stakeholders (completed by a general institutional background). The interlinking of stakeholders/roles, societal rationalities and types of interventions serves as an overall conceptual framework of "middle range" in the meaning of Merton[5] to structure the discussion of impacts of interventions to prevent non-publication bias related to CTs.

2.2 Steps in framework conceptualization

First, the existing version of the CT publication stakeholder map (10) was examined and updated. This was mainly done on the basis of the results of already existing systematic reviews covering the literature in the field of non-publication bias related to CTs, with a special focus on the study conducted as part of the UNCOVER project (1, 6, 7). The quantitative empirical basis was complemented by insights gained from interviews in qualitative studies, again with a special focus on the study conducted as part of the

[4] In Deliverable 1.2 of the UNCOVER project a first version of a stakeholder map was provided. Thereby, stakeholders are (i) localized along the functional logic of an idealized clinical trial process-chain, (ii) characterized according to an overall set of 16 roles (e.g. financier, conductor, author, editor), (iii) attributed to societal rationalities (e.g. scientific, economic, political rationality), and (iv) qualified according to generic form of interactions (e.g. law, money, knowledge).

[5] Merton provided an important theoretical background for empirical research in social science. He introduced the term "middle range theories" for approaches that "lie between the minor but necessary working hypotheses that evolve in abundance during day-to-day research and the all-inclusive systematic efforts to develop a unified theory" (14: 41).

UNCOVER project (7-9). Further input for the update of the stakeholder map was a desk research (policy documents) to comply with terms used in EU regulatory affairs; above all (15) and the proposal repealing the Directive 2001/20/EC (16).

Second, the conceptual framework for the discussion of impacts of interventions to reduce non-publication bias related to CTs was developed. Hereby the hard law & soft law distinction was used to structure the societal context which guides the behaviour/interactions of stakeholders.

Third, existing and desirable good practices of interventions to reduce non-publication bias related to CTs were identified and described to provide illustrative material for the discussion. The selection followed the general discussion on the one hand and the online availability of material on the other, since the project resources did not allow an exhaustive investigation. The stakeholder map is thereby used to identify the respective stakeholders and their related interactions.

3 Results

CT stakeholder mapping – which is accompanying three work packages (WP1, WP3, WP5) – provides the basis for the conceptual framework for the discussion of interventions to reduce non-publication bias. A first version (version 1) of the stakeholder map was presented as a result of WP1 (see Appendix) (10). Its updated version (version 2) is a result of WP3 and is presented in this report. It will be further updated in WP 5.

Already the first version of the map included stakeholder roles and generic types of stakeholder interactions (i.e. legislation-oriented interactions, monetary-oriented interactions, etc., see UNCOVER Deliverable 1.2) (10). In WP3 the hard law & soft law distinction was introduced to provide a further conceptual background to deal with these generic interactions. Subsequently, the hard law & soft law distinction has been used to describe the features of existing and desirable interventions to reduce non-publication bias. This will serve as an input for WP5.

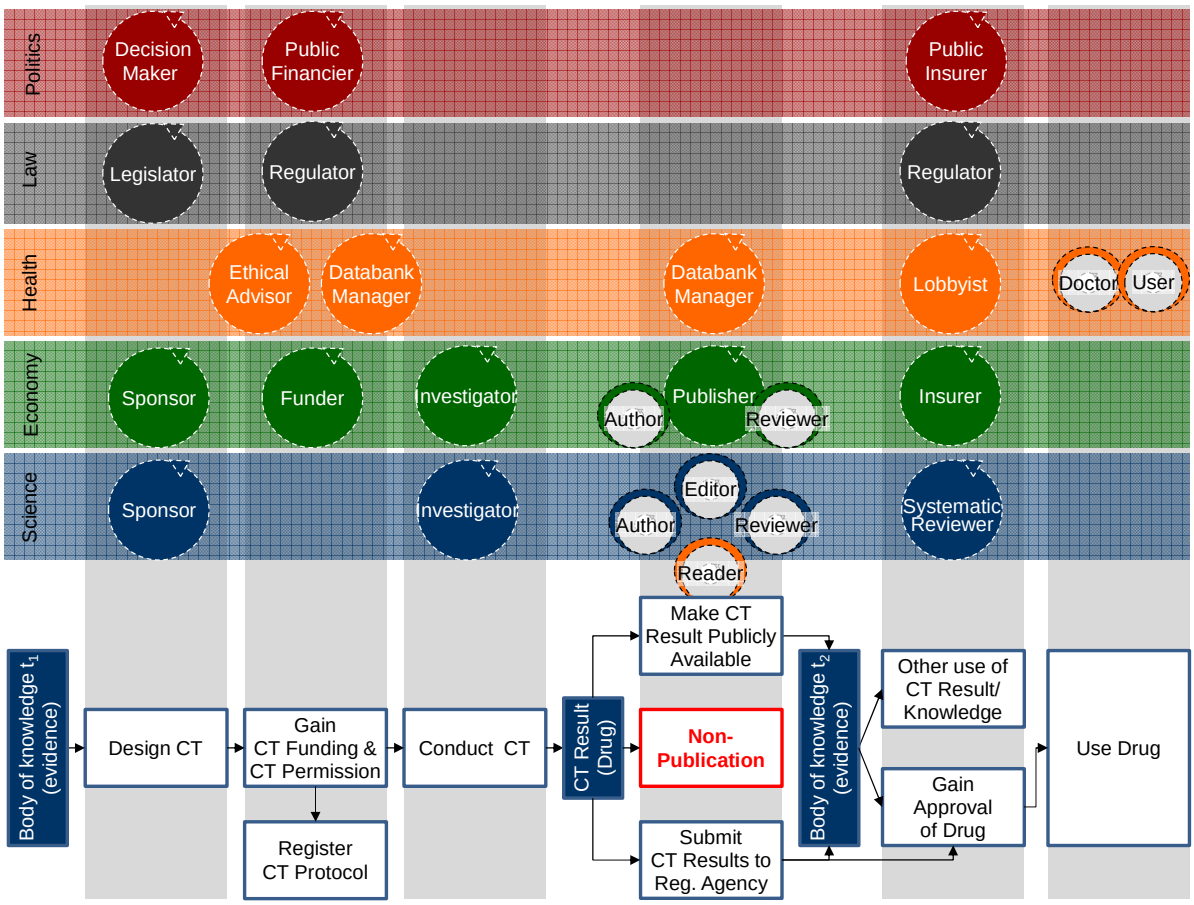
3.1 CT stakeholder map: updated version

The basic structure of the CT stakeholder map (see UNCOVER Deliverable 1.2) (10) was confirmed after a cross-check with the outcomes of recent quantitative and qualitative studies on non-publication bias related to CTs (1, 6-9). Nevertheless, an update was necessary which resulted in an extended list of stakeholders (including readers) and a few changes concerning roles (replacing 'conductor' by 'investigator', and including 'sponsor' as a distinct role).

Fig. 1 shows the updated version of the stakeholder map. It conceptualizes publication of CT results as an idealized process in form of a value chain. That is, every process element represents a certain function – such as design CT, conduct CT, etc. – which creates a value. The CT value chain starts with a given body of knowledge as the first functional element, and evolves towards the use of drugs as the final functional element. Stakeholders are depicted regarding their roles towards each functional element. Additionally, five societal rationalities[6] are introduced as an ordering scheme: scientific, economic, health, legal, and political rationality.

[6] In social systems theory the concept of societal systems is used to explain macro-level phenomena. That is, each societal system is the expression of certain rationalities. Persons/organizations are orienting their decision making towards social rationalities (i.e. societal rationalities are guiding decision making) (17, 18).

Fig. 1: CT stakeholder map according to roles/functions (version 2)



Role	Description
AUTHOR	person writing or contributing to manuscripts describing clinical trials for publication; usually employed by an organization conducting a CT such as company or university hospital or research institute
DATABANK MANAGER	Entity/person providing infrastructure/service for prospective/retrospective CT registration; usually hosted by a medicines agency or a university or an intergovernmental medicines body
DECISION MAKER	entity of public administration responsible for health decisions (hard law & soft law, rules of the game)
DOCTOR	person professionally qualified & certified for medical treatment in a doctor-patient-relation
EDITOR	person who evaluates research advances and decides what to publish in a particular journal
ETHICAL ADVISOR	independent body protecting the rights of CT participants and providing public assurance; usually an ethics committee
FUNDER	organization providing funding for clinical research; usually a company or a private fund or a public fund (financier, sponsor and investigator may be the same entity)
INSURER	organization deciding about drug reimbursement in a locality; either private (company) or (semi)public insurer
INVESTIGATOR	entity (i.e. principal investigator + team) responsible for the conduct of a CT at a trial site; usually employed by a company or university hospital or research institute
LEGISLATOR	national/supranational legislative body/bodies (e.g. parliament)
LOBBYIST	person/organization working on the improvement of public health; usually consumer advocates or patient organizations
PUBLISHER	organization publishing scientific journals/books or managing databases, or mass media (print, TV, web)
READER	person who is either a CT specialist (author, investigator etc.) or an interested non-specialist
REGULATOR	competent authority approving/licensing a drug for use in a locality; usually a governmental agency
REVIEWER	person conducting scientific peer-review on behalf of an editor/publisher
SPONSOR	person/organization responsible for the initiation, management and/or financing of a CT; usually a company or university hospital or research institute
SYSTEMATIC REVIEWER	reviewer using explicit methods to identify, select, and critically appraise relevant research
USER	person who consumes health care; usually as a patient and/or as a CT participant

3.2 Hard law & soft law: understanding institutional power

For the analysis of the institutional context of non-publication bias related to CTs I used the stakeholder map and the related generic types of stakeholder interactions (10) as a starting point:

- Legislation-oriented interactions (e.g. requirements of Directive 2001/20/EC)
- Monetary-oriented interactions (e.g. financing of CTs)
- Science-oriented interactions (e.g. publishing CT results)
- Policy-oriented interactions (e.g. national health strategies, action plans)
- Further 'power'-oriented interactions (other than monetary and political power – such as informal or semiformal or formal networks between CT stakeholders, e.g. the 'International Committee of Medical Journal Editors ICMJE Recommendations')

Next, I included the distinction between 'hard law' and 'soft law' for the structuring of this complex societal context (box 1).

Box 1: Hard law & Soft law

The terms 'soft law' and 'hard law' (resp. 'soft policies' and 'hard policies') are used to characterize two different dimensions in public governance – non-legally binding and legally binding (11-13). Whereas hard law indicates public governance on the basis of legislation (including taxes, standards and other forms of binding rules), soft law means public governance by guidelines, recommendations, declarations, self-commitment, voluntary agreements, etc. In a nutshell:

- hard law changes behaviour by immediately changing the choice set of addressees (hierarchical approach)
- soft law changes behaviour *without* (immediately) changing the choice set of addressees (market approach)

In international relations, soft law proves useful were states are preferring non-treaty obligations which are simpler and more flexible than treaty-related obligations (i.e. mutual confidence-building, useful in pre-treaty processes, simpler procedures, more rapid finalization, greater confidentially). Within the European Union soft law is used to allow member states and EU institutions to adopt policy proposals without binding those member states who do not wish to be bound and/or motivate member states to do voluntarily what they are less willing to do if legally obligated. In public governance on state level soft law is used to motivate organizations as well as persons (i.e. in their professional roles) to change their behaviour in a desired direction, without simultaneously introducing legal sanctions. Especially here (i.e. when organizations/persons are concerned) soft law is used to change opportunity sets (i.e. organizational routines and community practices) which work on the basis of beliefs/attitudes.

Although soft law has no legally binding effect, its impact can be significant. Soft law may have an impact on policy development and practice precisely by reason of its lack of legal effect. Actors (states, organizations, persons) may be willing to undertake voluntarily what they are less willing to do if legally obligated. Therefore, soft law can generally be seen as a more flexible instrument – compared to hard law – in achieving policy objectives.

Whereas hard law changes the behaviour of addressees by immediately changing their choice set, soft law changes the choice set of addressees – if successful – only slowly by changing community practices and 'rules of the game' step by step. Hard law is backed by state authority. On the contrary, soft law as emergent societal phenomenon is backed by the 'use' of a certain 'rule of the game'. Only if a significant number of community members use these rules, a certain rule/practice becomes a societal reality. Soft law requires as a first step institutionalization in form of the involvement of key organizations (e.g. ICMJE agrees on 'Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals'). Note: If nobody – or only a very small number of addressees – complies with certain rules, these rules cannot be called soft law, even if key organizations are involved.

3.3 Key question (I): How does the general institutional context contribute to prevent non-publication bias?

Presently scientific publishing undergoes a fundamental change which is labelled 'open access'. This is a fundamental institutional change driven by information and communication technologies (ICTs) and their widespread application and exploitation (19-21). This changing institutional context is NOT itself preventing non-publication bias, but provides an advantageous background for initiatives such as journal's open access policies.

Second open science revolution

Existing norms of scientific behaviour are significantly affected by this change towards open access. Large scale data collection and availability challenges the traditional scientific community practices and provides new opportunities for individual researchers, and the internet enables new forms of communication and networking between professional and/or amateur scientists. This is called a "second open science revolution" (22: 7), following that of the creation of the first scientific journals. In this respect, the concept of open access covers the following (interrelated) aspects (19):

- access without payment to a version of a publication via a repository (i.e. repository mediated), often after an embargo period; with authors posting the final, accepted version of their papers without restriction of use; called *green* open access
- access without payment to the version of record of a publication via the publisher's own platform (i.e. journal mediated) providing immediate access; with authors retaining copyright under a creative commons license after paying an article processing charge (i.e. the 'author-pays' business model); called *gold* open access

- the removal of the payment barrier, so that users have a right to read an article; called *gratis* open access
- the removal of most if not all of the restrictions on the use and re-use of articles; called *libre* open access

These aspects should go together with the principles 'accessibility', 'intelligibility', 'assessability', and 'usability' of data/information (22: 14): accessible data/information are those which can easily be found; intelligible data/information provide an account of the results of scientific work (i.e. differentiated for different audiences, including favourably the non-scientific wider public); for assessable data/information recipients should be able to judge the competence and reliability of those making the claims (i.e. are claims evidence based, are they from a scientifically competent source, what interests are behind); and usable data/information is characterized by the possibility of reusing them (minimally reusable by other scientists, favourably reusable for different purposes and).

This changing institutional context is not itself a mean to reduce non-publication bias. But is serves as an advantageous background for more specific activities and initiatives which will be described on the basis of examples in the following.

3.4 Key question (II): How does 'soft law' contribute to prevent non-publication bias?

The above described ICT driven institutional development goes hand in hand with a related science-specific institutional development. Rules of games are provided which are not codified as legislation, but which unfold as 'soft law', i.e. in form of guidelines, recommendations, declarations, self-commitment, voluntary agreements, etc. and which form community practices serving as orientation standards. Soft law is seen as an effective policy intervention (box 1). In the following, recent 'soft-law' activities contributing to the prevention of non-publication bias are exemplarily described.

Soft law: open access policy of medical journal – the examples Lancet & British Medical Journal (BMJ)

Recently, the editors of 'The Lancet' expressed their commitment "to make research more widely accessible and useable in ways that contribute to sustain our broad mission to serve clinical medicine and global health" (23: 1166). They aim at offering either a '*gold* open access' or a '*green* open access' choice. The first option (*gold*) will include a creative commons license after the payment of an article processing charge of US$ 5000. The second option (*green*) will include that authors can deposit the final, accepted paper

version in any repository they choose (6 months after publication) and that 'The Lancet' will make the published paper free available on its website 6 months after publication. Both options will apply for research papers funded by the 'Research Councils UK' (RCUK) and submitted after 1 April 2013. In a reaction to this announcement, the commitment was both, welcomed and criticized (24): criticized were the restriction to work funded by particular funders (i.e. only RCUK funded research), the exclusion of already published studies (earlier than 2013) as well as the high costs.

Compared with this, the BMJ's open access approach offers a more favourable service for authors and readers according to the charge and the number of articles (immediately from 1840 onwards). The 'British Medical Journal' is a fully 'online first' publication[7]. All the BMJ's original research is published in full on bmj.com, with open access and no limits on word counts. When the print issue appears on Friday, the PDFs are available on bmj.com together with links to the respective online articles. The BMJ requires authors to pay a fee of £ 3000 per article when the authors can claim the BMF fee from their funder. Beyond that, BMJ sends the articles to PubMed Central (PMC - see box 2), i.e. a free full-text archive of biomedical and life sciences journal literature at the U.S. National Institutes of Health's National Library of Medicine. The BMJ is even running an "Open Data Campaign". Since January 2013, the BMJ has refused to publish any trial of drugs or devices where the authors do not commit to making the relevant anonymised patient level data available, upon reasonable request[8].

Box 2: PubMed Central (PMC) - Open Access Subset

Articles in the PMC Open Access Subset are still protected by copyright, but are made available under a Creative Commons or similar license that generally allows more liberal redistribution and reuse than a traditional copyrighted work. However, the license terms are not identical for all of the articles in this subset.

Source: http://www.ncbi.nlm.nih.gov/pmc/tools/openftlist/ [2013-09-12]

Soft law: open access policy of public financier - the examples FP7/Horizon 2020 & RCUK

The European Commission conducts an 'Open Access Pilot in FP7' which was launched in August 2008 and will run till the end of FP7. It aims at making EU-funded research results available to citizens at large for free in seven areas (energy, environment, health, ICTs,

[7] See for BMJ's continuous publication / open access publication (25), and http://www.bmj.com/about-bmj/evidence-based-publishing/completed-research#oapublishing [2013-09-12].

[8] See for further details of BMJ's Open Data Campaign http://www.bmj.com/open-data [2013-09-12]

research infrastructure, science in society and humanities) (26, 27). FP7 grant recipients are expected to deposit peer-reviewed research articles or final manuscripts resulting from their FP7 project into an online repository and to make their best effort to ensure open access to these articles after publication. The EC open access pilot covers approximately 20% of the FP7 budget and uses the following terms for describing their *green* and *gold* open access approach (27):

- Open access publishing: the costs of publishing are covered by authors (i.e. via the funding bodies supporting them) or other sources such as university libraries; reader access without payment (*gold* open access)
- Self-archiving: authors deposit the peer-reviewed articles/manuscripts in repositories (i.e. open archives) (*green* open access)

The FP7 open access pilot focuses primarily on *green* open access, but provides beyond that the opportunity for *gold* open access by reimbursing fully open access publishing costs during the duration of FP7.

For Horizon 2020 it is considered that open access in form of *green* and *gold* models will be offered (28). All projects will be requested to provide early an electronic version of their publications into an archive (machine-readable format) either in the *gold* or the *green* form of open access. In this case, an embargo period of a maximum of six months (except for the social sciences and humanities where the maximum will be twelve months due to publications' longer 'half-life') is foreseen. Thereby the Commission will consider whether and under what conditions publication fees can be reimbursed.

The above mentioned open access announcement of 'The Lancet' is backed by a new policy of 'Research Councils UK', i.e. the 'RCUK Policy on Open Access' (29). In the UK an overarching commitment to transparency and open data and a commitment that published research findings should be freely accessible exist. The 'Royal Society' recently formulated key principles for 'intelligently open research data' which require six broad changes (22): 1) a shift away from a research culture where data is viewed as a private preserve; 2) expanding the criteria used to evaluate research to give credit for useful data communication and novel ways of collaborating; 3) the development of common standards for communicating data; 4) mandating intelligent openness for data relevant to published scientific papers; 5) strengthening the cohort of data scientists needed to manage and support the use of digital data (which will also be crucial to the success of private sector data analysis and the government's Open Data strategy); and 6) the development and use of new software tools to automate and simplify the creation and exploitation of datasets.

Fig. 2: Research Councils UK - open access path

OA Open Access

APC Article Processing Charge

AHRC Arts and Humanities Research Council

ESRC Economic and Social Research Council

Source: (29: 7)

The RCUK policy on open access applies to peer-reviewed research articles (including review articles not commissioned by publishers), which acknowledge Research Council funding, that are submitted for publication from 1 April 2013, and which are published in journals or conference proceedings.

Soft law: standards & guide provision of network - the examples CONSORT & Declaration of Helsinki & European Code of Conduct for Research Integrity

CONSORT, which stands for Consolidated Standards of Reporting Trials, encompasses various initiatives developed by the CONSORT Group to alleviate the problems arising from inadequate reporting of randomized controlled trials (RCTs). The CONSORT group includes CT trialists and methodologists, and medical journal editors. Among others, the CONSORT Statement is provided, which consists of a minimum set of recommendations for reporting RTCs (i.e. reporting how the trial was designed, analyzed, and interpreted).

The funding for CONSORT supports part-time administrative, coordination and research work. The funding history is: Medical Research Council (2012 – 2015); National Coordinating Centre for Research Methodology, UK Department of Health (2006 to 2011); US National Library of Medicine (1999 to 2004).

Box 3: CONSORT

The CONSORT website has an average of 13,621 visits per month (data for the period 2009-03 to 2010-02). Thereby 66% are new and 34% returning visitors from 197 different countries.

According to Essential Science Indicators (ESI), which lists the top one percent of all publications in each of the key scientific domains each publication year, the following CONSORT products are in the top one percent: CONSORT Statement; Explanation and Elaboration (E&E) document; and two CONSORT extension publications (CONSORT for Harms, CONSORT for Cluster Trials).

- CONSORT is endorsed by over 50% of the core medical journals listed in the Abridged Index Medicus on PubMed, including BMJ and The Lancet.

- CONSORT is endorsed by the following Editorial Groups: Council of Science Editors; International Committee of Medical Journal Editors (ICMJE); World Association of Medical Editors (WAME)

Source: http://www.consort-statement.org/ [2013-09-12]

The "Declaration of Helsinki" is a basic document providing ethical principles for medical research involving human subjects. It was developed by the World Medical Association (WMA) in 1964 and has been amended several times – most recently in 2013 (30) . The declaration is primarily addressed to physicians. Nevertheless, the WMA encourages also other stakeholders in medical research involving human subjects to adopt the Helsinki principles.

Several principles of the Helsinki Declaration are addressing the question of registration and publication and authors, editors and publishers are explicitly mentioned as crucial stakeholders beside physicians (box 4).

Box 4: Publication/registration related principles of the "Declaration of Helsinki"

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Source: (30)

The "European Code of Conduct for Research Integrity" was launched at the Second World Conference on Research Integrity held in July 2010 (31). It aims at the proper conduct and principled practice of systematic research in the medical, natural and social sciences and the humanities in the form of recommendations (i.e. not a body of law, but rather a canon for self-regulation). The code is published in collaboration by the European Science Foundation (ESF) and ALL European Academies (ALLEA), which is a European Federation of 53 National Academies of Science and Humanities.

Some of the principles of the Code of Conduct are recommendations addressing publication issues (box 5).

Box 5: Publication related principles of the "European Code of Conduct for Research Integrity"

4. Publication-related conduct
- Researchers should publish the results and interpretations of their research in an open, honest, transparent and accurate manner.
- Researchers should strive to ensure the earliest possible publication of the results of their research, unless commercial or intellectual property considerations.
- (…)
- In communication with the general public and in popular media the same standards of honesty and accuracy should be maintained; any attempt to exaggerate the importance and practical applicability of the findings should be resisted.
- (…)

5. Reviewing and editorial issues
- An editor or reviewer who has a relevant potential conflict of interest – which may be personal, academic, political, commercial or financial – should, ideally, withdraw from involvement in any publication decision. If the conflict is considered minor or unavoidable it should be disclosed to the readership.
- Reviewers should provide thorough, accurate, objective, and justifiable assessments in a timely manner.
- In the review of a manuscript, confidentiality must be maintained.

Source: (31: 14)

Soft law: requirement policy of journals/editors – the example ICMJE Recommendations

The International Committee of Medical Journal Editors (ICMJE) provides recommendations to biomedical journals for the conduct and publication of scholarly work. The ICMJE Recommendations were first published in 1978 (at that time as URMs Uniform Requirements for Manuscripts). The present version, now named "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" was released in 2013 (32).

In September 2005, the ICMJE implemented a policy that requires the prospective registration of clinical trials as a precondition for publication in the member journals[9]. Presently, ICMJE clinical trial registration policy requires prospective registration of all interventional clinical studies, but does not require results reporting for registered trials. It is acknowledged that the Food and Drug Administration Amendments Act of 2007 (FDAAA; U.S. Public Law 110-85, Title VIII), mandates the posting of summary results data for certain trials in ClinicalTrials.gov[10]. The ICMJE accepts registration in the following registries:

www.anzctr.org.au

www.clinicaltrials.gov

www.ISRCTN.org

www.umin.ac.jp/ctr/index/htm

www.trialregister.nl

https://eudract.ema.europa.eu/

In addition to these registries, the ICMJE accepts registration in any of the primary registries that participate in the WHO International Clinical Trials Portal http://www.who.int/ictrp/network/primary/en/index.html. The ICMJE policy requires registration in a WHO primary registry rather than solely in an associate registry (for-profit

[9] This was backed by the U.S. Federal law to require trial registration, starting with the Food and Drug Administration Modernization Act of 1997 (FDAMA). It included a mandate that the National Institutes of Health (NIH) had to establish, maintain, and operate a public resource for information on efficacy studies of drugs. The first version of the Clinical Trials Data Bank was launched 2000. At that time, the data bank included primarily NIH-sponsored trials. Subsequently, FDA Guidance for industry was issued (one of the milestones was in October 2003; i.e. FDA acknowledged the listing of the 1000th industry sponsored trial in ClinicalTrials.gov). See http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ParticipatinginClinicalTrials/ucm143647.htm

[10] See http://www.icmje.org/faq_clinical.html [2013-11-20]

entities manage some associate registries) because it is critical that trial registries are independent of for-profit interests.

Box 6: URMs/ICMJE Recommendations

The International Committee of Medical Journal Editors ICMJE (previously known as the Vancouver Group) is a group of medical journal editors who meet annually. ICMJE is not an open membership organization but rather a small working group of general medical journals.

Occasionally, the ICMJE will invite a new member or guest when the committee feels that the new journal or organization will provide a needed perspective that is not already available within the existing committee. Open membership organizations for editors and others in biomedical publication include the World Association of Medical Editors www.WAME.org and the Council of Science Editors www.councilofscienceeditors.org .

The ICMJE participating journals/organizations are (in August 2013):
– Annals of Internal Medicine
– British Medical Journal
– Chinese Medical Journal
– Journal of the American Medical Association
– Nederlands Tijdschrift voor Geneeskunde (The Dutch Medical Journal)
– New England Journal of Medicine
– New Zealand Medical Journal
– The Lancet
– Revista Médica de Chile
– Tidsskrift for Den Norske Lægeforening (The Journal of the Norwegian Medical Association)
– Ugeskrift for Laeger (Journal of the Danish Medical Association)
– U.S. NLM
– World Association of Medical Editors

Source: http://www.icmje.org [2013-09-12]

3.5 Key question (III): How does “hard law” contribute to prevent non-publication bias?

Public governance by hard law – legislation and law based regulation including taxes, standards and other forms of binding rules – is without doubt a potential powerful intervention to prevent non-publication bias. In Europe, the European Medicines Agency (EMA) provides preliminary grounds for the desired mandatory registry of CTs on the basis of EudraCT (EU CT database) together with the ‘Detailed guidance on the request to the competent authorities for authorization of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial’ (33) based on Article 9(8) of Directive 2001/20/EC (15).

Hard law: mandatory registration – the example EudraCT

The detailed guidance on the request to the competent authorities for authorization of a CT (33) – specifying directive 2001/20/EC – mentions several documentations important for non-publication bias (Tab. 2). This is especially true for the CT protocol and the EudraCT number. The guide says:

> 2.2 "Before submitting an application to the national competent authority, the applicant should obtain a unique EudraCT number from the EudraCT Community Clinical Trial System (…). This number identifies the protocol for a trial, whether conducted at a single site or at multiple sites in one or more Member States. To obtain the EudraCT number automatically from the database the applicant will need to provide a few items of information." (33)

Tab. 2: Request for a CT authorization – required documentation (excerpt)

Document	Description
EudraCT number	unique EudraCT number from the EudraCT Community Clinical Trial System
CT application form	unique, EU-wide clinical trial application form
CT protocol	a document that describes the objective(s), design, methodology, statistical considerations and organization of a trial (relevance, anticipated benefits and risks, participant justification/informed consent etc.)
Investigator's brochure	a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study
IMP dossier	gives information related to the quality of any IMP (i.e. including reference product and placebo)

IMP (investigational medicinal product): a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial

Source: (33)

The EU Clinical Trials Register website https://www.clinicaltrialsregister.eu/ provides access to information on interventional CTs from 1 May 2004, when national medicine regulatory authorities began populating EudraCT, the application that is used by national medicines regulatory authorities to enter clinical trial data. The website was launched on 22 March 2011. Users are able to view:

- description of phase II-IV adult clinical trials where the investigator sites are in EU Member States or the European Economic Area (EEA)
- description of paediatric clinical trials with investigator sites in the EU and trials which form part of a paediatric investigation plan (PIP), including those where the investigator sites are outside the EU

The EU Clinical Trials Register website does not:

- provide information on the results of clinical trials (this will come later)

- provide information on non-interventional clinical trials of medicines (observational studies on authorized medicines)
- provide information on clinical trials for surgical procedures, medical devices or psychotherapeutic procedures.

In 2012, a proposal for the amendment of the Directive 2001/20/EC was published by the European Commission. It suggests among others a new authorization procedure for CTs, including a "harmonized authorization dossier" together with a "single portal EU database" free of charge for sponsors (16: 4). The assessment of the proposal indicates that the proposed option of the facilitating of GCP[11] inspections would put sponsors under an obligation to register publicly all clinical trials whose results are used subsequently in an application for authorization of a clinical trial or for marketing authorization for a medicinal product (34: 39).

Last but not least, the EMA committed to issue a policy on proactive publication of clinical-trial data in January 2014. In a recent update the EMA concludes: "The Agency has embarked on the development of a policy on publication and access to clinical-trial data because it believes that the release of data is about establishing trust and confidence in the system. The Agency is also firmly of the opinion that availability of data broadens the scientific knowledge base, fosters innovation and encourages investment in the development of medicines and ultimately benefits public health." (35: 1)

[11] Good Clinical Practice

4 Summary & Outlook

4.1 Key findings

It was shown that a broad variety on soft law interventions exist which (potentially) reduce non-publication bias related to CTs and that hard law made a step forward in the same direction. Examples were presented for:

- Open access policy of medical journals and of public financiers
- Standards and guide provision of professional networks
- Requirement policy of journals/editors
- Mandatory registration of CTs

Already known

The variety of these interventions is already discussed in the literature, whereas the most relevant stakeholders have been identified in WP1 of the UNCOVER project.

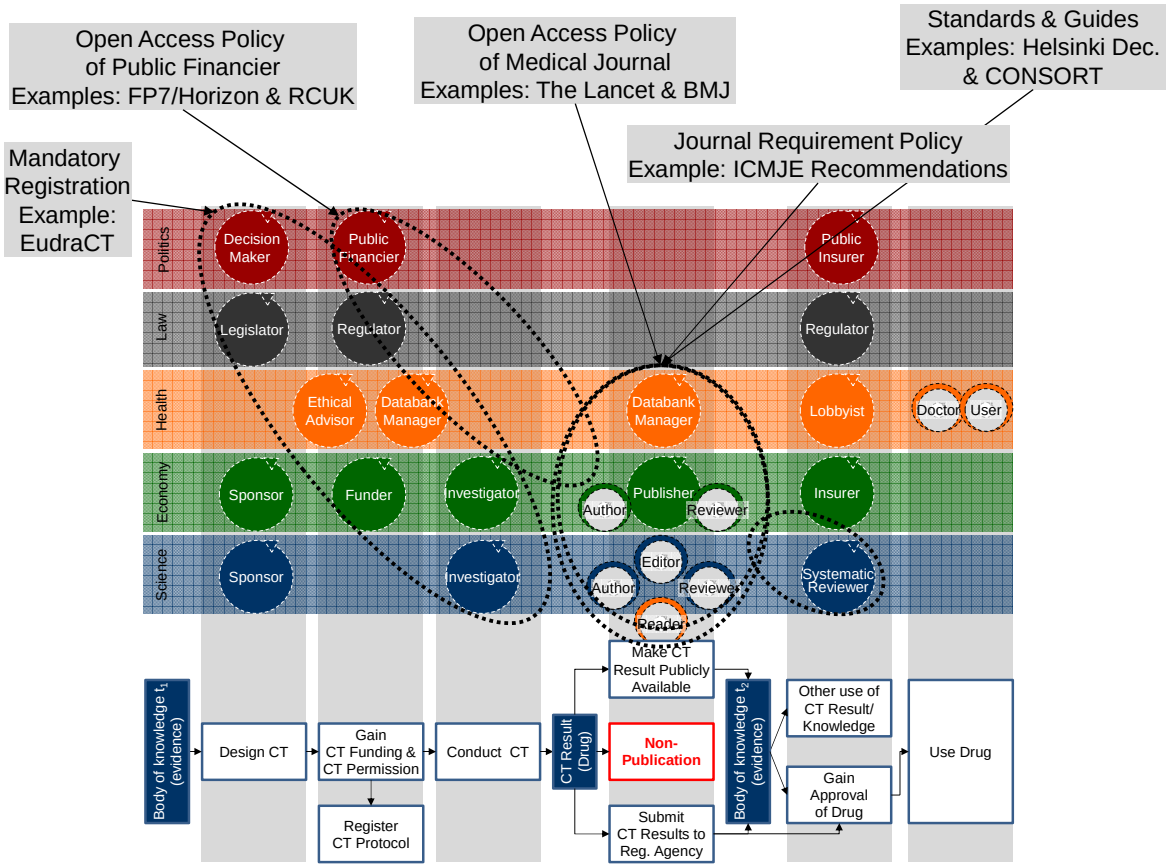
Value added

The provision of a multidimensional conceptual framework for the discussion of impacts of interventions to reduce non-publication bias related to CTs adds a special value – by integrating a functional (i.e. value chain), a role specific, a societal (i.e. societal rationality) and an interventional (i.e. hard law & soft law) dimension (Fig. 3).

4.2 Limitations

This report addresses primarily the European perspective. This entails limitations in two respects. First, non-publication bias is not a regional but a global problem and accordingly there are interventions required on the global, the European AND on the national level. Second, this report presents an exemplary insight in the institutional context and the existing/optional measures to prevent non-publication bias, whereby the selection followed the general discussion and the online-availability of material, since the project resources did not allow an exhaustive investigation.

Fig. 3: Examples of interventions to reduce non-publication bias



4.3 Outlook

The findings of this deliverable are representing an interim result which will be further developed in WP5. This will be done in the course of scenario workshops aiming at the clarification of 'what can/should be done' (i.e. interventions) by whom (i.e. stakeholders) to prevent non-publication bias in the future on the basis of expert assessment.

5 References

1. Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton AJ, et al. Dissemination and publication of research findings: an updated review of related biases. Health Technology Assessment. 2010;14(8).
2. Belsey J. What is evidence-based medicine? Newmarket and London: Hayward Group Ltd., 2009.
3. Rosenberg W, Donald A. Evidence based medicine: An appraoch to clinical problem solving. BMJ. 1995;310:1122-6.
4. Sackett DL, Rosenberg WMC, Gray JAM, Haynes BR, Richardson WS. Evidence based medicine: What it is and what it isn't. BMJ. 1996;312:71-2.
5. Ross J, Tse T, Zarin D, Xu H, Zhou L, Krumholz H. Publication of NIH funded trials registered i clinical trials.gov: Cross sectional analysis. BMJ. 2012;344:d7292.
6. Thaler K, Nußbaumer B, Van Noord M, Kien C, Griebler U, Gartlehner G. The effectiveness of interventions for reducing publication bias. Deliverable 3.2 of the UNCOVER FP7 funded project under contract number 282574, 2013.
7. Wager E, Williams P. 'Hardly worth the effort'? Medical journals' policies and their editors' and publishers' views on trial registration and publication bias: Quantiative and qualitative study BMJ. 2013;347:f5248.
8. Smyth RMD, Kirkham JJ, Jacoby A, Altman DG, Gamble C, Williamson PR. Frequency and reasons for outcome reporting bias in clinical trials: Interviews with trialists. BMJ 2010;341:c7153. 2010.
9. Kien C, Van Noord M, Wagner-Luptacik P. Perspectives of stakeholders on publication bias. Deliverable 3.4 of the UNCOVER FP7 funded project under contract number 282574, 2013.
10. Buchinger E. Stakeholder map. Deliverable 1.2 of the UNCOVER FP7 funded project under contract number 282574, 2012.
11. Abbot KW, Snidal D. Hard law and soft law in international governance. International Organization. 2000;54(3):421-56.
12. Brennan G, Brooks M. On the 'cashing out' hypothesis and 'soft' and 'hard' policies. European Journal of Political Economy. 2011;27:601-10.
13. Eurofund. European industrial relations dictionary. http://www.eurofound.europa.eu/areas/industrialrelations/dictionary [2013-09-11], 2013.
14. Merton RK. On sociological theories of the middle range. In: Szompka P, editor. Robert K Merton: On social structure and science. Chicago-London: The University of Chicago Press; 1996 [1968]. p. 41-50.
15. OJEC. Directive 2001/20/EC: Implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Brussels: Official Journal of the European Communities, 2001.
16. EC. Proposal for a regulation of the European parliament and of the council on clinical trials on medical products for human use, and repealing Directive 2001/20/EC. Brussels: European Commission, 2012 Contract No.: COM(2012) 369 final.
17. Luhmann N. Social systems. Stanford: Stanford University Press; 1995 [1984].

18. Luhmann N. Observations of modernity. Stanford: Stanford University Press; 1998 [1992]
19. Finch J, Bell S, Bellingan L, Campbell P, Donnelly P, Egginton R, et al. Accessibility, sustainability, excellence: How to expand access to research publications. Working Group on Expanding Access to Published Research Findings, 2012.
20. G8. G8 Open Data Charter. UK Presidency of G8 2013.
21. EC. Digital Agenda: Turning government data into gold (Press release IP-11-1524). Brussels: European Commission, 2011.
22. Boulton G, Campbell P, Collins B, Elias P, JHall W, Graeme L, et al. Science as an open enterprise. London: The Royal Society Science Policy Centre, 2012.
23. The-Lancet-Editors. The Lancet journals welcome a new open access policy. The Lancet. 2013;381:1166-7.
24. Glynn JR, Thomas SL. Open access policy. The Lancet. 2013;381:2028.
25. Godlee F, Delamothe T, Smith J. Continuous publication: The next logical step. BMJ. 2008;336:1450.
26. EC. Commission decision on the adoption and a modification of special clauses applicable to the model grant agreement: Special clause 39. Brussels: European Commission, 2008 Contract No.: C(2008) 4408 final.
27. EC. Open access pilot in FP7. Brussels: European Commission, 2008.
28. EC. Towards better access to scientific information: Boosting the benefits of public investments in research. Brussels: European Commission, 2012 Contract No.: COM(2012) 401 final.
29. RCUK. RCUK policy on open access and supporting guidance. Swindon: Research Councils UK, 2013.
30. WMA. World Medical Association declaration of Helsinki: Ethical principles for medical research involving human subjects. Ferney-Voltaire/France: World Medical Association, 2013 [1964].
31. ESF, ALLEA. The European code of conduct for research integrity. Strasbourg-Amsterdam: European Science Foundation, ALL European Academies, 2011.
32. ICMJE. Recommendations for the conduct, reproting, editiong, and publication of scholarly work in medical journals. International Committee of Medical Journal Editors, 2013.
33. OJEC. Communication 2010/C 82/01: Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial. Brussels: Official Journal of the European Communities, 2010.
34. EC. Impact assessment report on the revision of the 'Clinical Trial Dorective' 2001/20/EC. Brussels: European Commission, 2012 Contract No.: SWD(2012) 200 final ; COM(2012) 369 final.
35. EMA. European Medicines Agency updates on development of its policy on publication and access to clinical-trial data. London: European Medicines Agency, 2013.

6 Appendix: Stakeholder Map (version 1)

In Deliverable 1.2 (10) a first version of the stakeholder map was provided (Fig. 4). A slightly updated version is presented within this deliverable (Fig. 1).

Fig. 4: Stakeholder map (version 1)