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Towards recommendations to overcome publication bias related to clinical trials

From stakeholder mapping and institutional analysis to a multi-intervention strategy

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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 description of mechanisms to overcome undesired publication practice, based on scenarios developed in UNCOVER stakeholder workshops and other evidence derived from the UNCOVER project. As a result, a multi-intervention strategy is proposed.

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Towards recommendations to overcome publication bias related to clinical trials

From stakeholder mapping and institutional analysis to a multi-intervention strategy

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Background

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

The UNCOVER project focuses on publication bias arising from non-publication of clinical trials results. Non-publication is considered a factor which derogates evidence-based medicine by hampering the process of systematically reviewing, distributing and using clinical research findings to provide eventually optimum care to patients. Causes of publication bias due to non-publication of trial results can be found – to a varying degree – at all stages of clinical trial processes. 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 the description of mechanisms to overcome undesired publication practice which may result in publication bias. The report is based on scenarios developed in UNCOVER stakeholder workshops and other evidence derived from the UNCOVER project (e.g. interviews, systematic review, bibliometrics, and web crawling).

Method

The methods used are scenario workshops, desk research (including sources of evidence within the UNCOVER project: interviews, systematic review, bibliometrics, web crawling) and concept development. Thereby the distinction between “hard law” (legislation) and “soft law” (voluntary agreements, guidelines, recommendations, declarations etc.) is used as guiding principle.

Results

On basis of the integration of the results and insights from the various sources of evidence, a multi-intervention strategy to overcome publication bias due to non-publication of clinical trials results is proposed. It consists of (i) a “Global Mandatory Approach”, (ii) an “Individual Voluntary Approach”, and (iii) a “Catalytic Supplement”. These three approaches should not be seen as alternatives, but as complementary.

1 Introduction

1.1 Background

The UNCOVER project aims at overcoming publication bias[1] related to non-publication of clinical trials (CTs) results. As an outcome of the project, recommendations will be provided which will address measures to change undesired publication practice. These recommendations will serve to overcome publication bias and contribute to evidence-based medicine[2] and therefore eventually add to the delivery of optimum clinical care to patients. The UNCOVER project focuses on publication bias arising from non-publication of clinical trial results. This specific type of publication bias is considered to be 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 – at all stages of the clinical trial process. Table 1 gives an overview of main sources as discussed in the literature and as derived from the UNCOVER project. Recommendations addressing the change of the undesired publication practice have to deal with the variety of this causation.

1.2 Objective

The objective of this report is the description of mechanisms to overcome undesired publication practice, based on scenarios developed in UNCOVER stakeholder workshops and other evidence derived from the UNCOVER project (e.g. interviews, systematic review, bibliometrics, and web crawling). 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 publication bias related to non-publication of clinical trial results?
- How does 'soft law' contribute to prevent this bias?
- How does 'hard law' contribute to prevent this bias?
- How can these three dimensions be integrated in "building blocks" of recommendations, forming a multi-intervention strategy?

Tab. 1: Main sources and reasons for publication bias related to non-publication of trial results

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/unfavorable trials, preferring trials with statistically significant results, rejection because of type/region of research)
Readers and users of research findings	• journal editors' policy reflects readers preferences and incorporates 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)

2 Methodology: A systemic approach

Publication bias due to non-publication of clinical trial results is a multi-dimensional problem including scientific, economic, legal, political and overall health issues. Therefore, a systemic approach is required to adequately grasp the problem. The systemic approach provides a framework for the discussion of impacts of interventions to reduce bias related to non-publication of clinical trial results. It considers stakeholders and stakeholder's interactions on the one hand and intervention logics on the other, and results in a multi-intervention strategy to overcome undesired CT publication practice concerning.

Accordingly, the conceptualization of the multi-intervention strategy has the following cornerstones. First, it is based on the CT stakeholder map, which was developed previously (see UNCOVER Deliverable 1.2, (10)). Second, it is based on the intervention typology of "hard law", "soft law" and "general institutional context", which results from an institutional analysis (see UNCOVER Deliverable 3.3, (11)). Third, it is derived from the application of the stakeholder map and the intervention typology during the scenario assessment process (i.e. assessment of the results of the UNCOVER stakeholder scenario workshops; see UNCOVER Deliverable 5.1, (12)).

2.1 Stakeholder map

A stakeholder map was developed as a tool to visualize the complexity of non-publication of clinical trial results and to provide a basis for adequately considered recommendations on changing undesired publication practice.

As a structuring principle, a functional approach was chosen (Box 1) and clinical trial results were conceptualized as an idealized value-chain process (Fig. 1). Every process element represents a certain function – "Design CT", "Conduct CT", etc. – which creates a value. The clinical trial value-chain starts with a given body of knowledge as the first functional element and evolves towards the approval of drugs or other use of CT results as the final functional elements. Stakeholders are depicted with regard to their roles towards each functional element. Additionally, five societal rationalities are introduced as an ordering scheme: scientific, economic, health, legal, and political rationality.

The identification and mapping of stakeholders includes their clustering or grouping according to their specific roles and rationalities (scientific, economic, etc.)[4]. Most roles are adequately captured as organizations. For a few roles it seems appropriate to focus on persons. This is especially true for authors, editors and reviewers. In their case it is assumed that the "personal decision sovereignty" outweighs the "organizational decision sovereignty". For example, a researcher as part of a clinical trial team is in his/her decisions strictly guided by the organizational rules and routines, whereby the very same researcher has usually comparatively more sovereignty concerning the publishing of papers in scientific journals (unless it is an organizational instruction that publication of certain results is not permitted). Stakeholder mapping in UNCOVER recognizes therefore two categories of stakeholders: persons as stakeholders (such as authors, reviewers, doctors, patients etc.) and organizational stakeholders (such as companies, universities, hospitals etc.). Figure 1 visualizes the variety of stakeholders and their roles and Table 2 describes the roles of the stakeholders.

Box 1: The terms "stakeholder" and „function"

A stakeholder is any group, individual person, or organization that can affect, or is affected by, the achievement of a corporation's purpose (13-15). In the case of UNCOVER, a stakeholder is any organization or person that can affect or is affected by a clinical trial (CT).

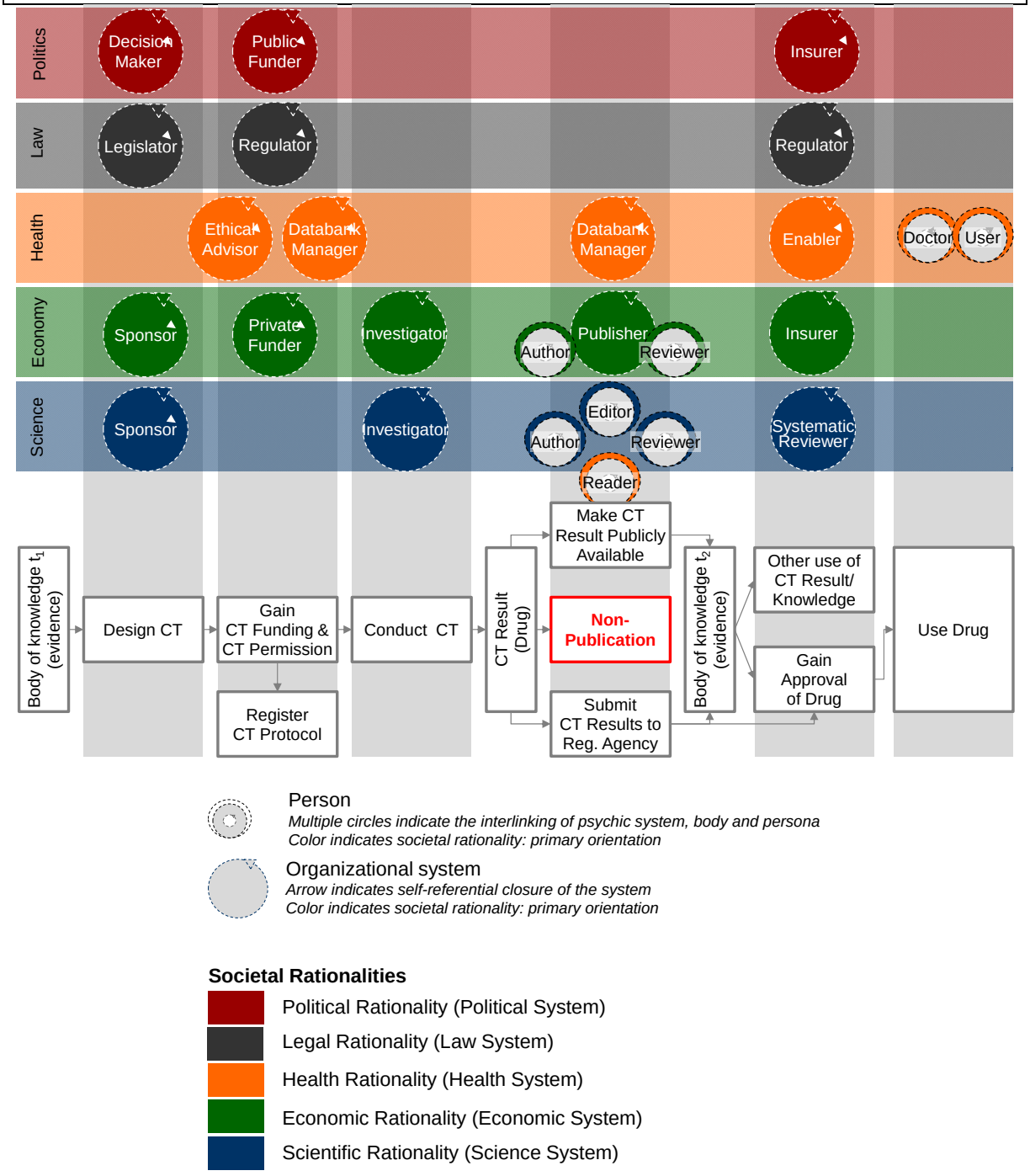
Function and role: In social system theory, the term function denotes at the micro-level (person, organization) the relation of an actor to a certain situation and the history of that relation (16). In the case of UNCOVER, the actors are the stakeholders, and the situations are defined by the value-chain elements (such as "Prepare CT", "Conduct CT", and "CT follow up")[5]. The specific functional characteristics of the actors are condensed into roles. "The role is that organized sector of an actor's orientation which constitutes and defines his participation in an interactive process. […] When we recognize that roles rather than personalities are the units of social structure, we can perceive the necessity of an element of 'looseness' in the relation between personality structure and the performance of a role" (19: p.23).

Function and societal rationality: It is a further cornerstone of social system theory that the dominant type of system-building on the societal macro-level relates to functions (and not to social status, rank, and hierarchical order), resulting in societal systems such as "science", "economy" and "politics" (20, 21). Each of these societal systems is an expression of a certain rationality; e.g. functional rationality or societal rationality. Actors orient their decision making towards societal rationalities (i.e. societal rationalities are guiding decision making). In the case of UNCOVER five

[4] For the evolution of the stakeholder map within the UNCOVER project, see (22).

[5] For experiences with the value-chain concept in the health sector, see (17, 18).

societal rationalities are considered: scientific, economic, health, legal, and political rationality.



See for a stakeholder description Table 2.

Fig. 1: CT stakeholder map according to roles/functions[6]

[6] In social systems theory, each system is conceptualized as open and closed at the same time, whereby closure of the system is understood as referring to itself (i.e. self-referential closure) (23: p.3). As a

Tab. 2: Stakeholder roles involved in the process of clinical trials and publication of trial results

Role	Description
AUTHOR	person writing or contributing to manuscripts describing clinical trials for publication; usually employed by an organization conducting a CT such as a company, a university hospital or research institute
DATABANK MANAGER	entity/person providing infrastructure/service for prospective/retrospective CT registration; usually hosted by a medicines agency, a university or an intergovernmental medicines body
DECISION MAKER	entity of public administration responsible for health decisions (hard law and soft law, rules of the game)
DOCTOR	person professionally qualified and certified for medical treatment
ENABLER	person/organization working on the improvement of public health; usually health care professionals, health education facilities, consumer advocates, patient organizations or other health related NGOs
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, a private fund or public fund (funder, sponsor and investigator may be the same entity)
INSURER	organization deciding about reimbursement of drugs, medical devices etc. in a locality; either private (company) or (semi)public insurer
INVESTIGATOR	entity (i.e. principal investigator and team) responsible for the conduct of a CT at a trial site; usually employed by a company, a university hospital or research institute
LEGISLATOR	national/supranational legislative body/bodies (e.g. parliament)
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, medical devices etc. 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

consequence, signals from the environment must be transferred into the system's own references (otherwise, the signal remains "noise" for the addressed system).

2.2 Intervention logics

Starting from the above described CT stakeholder map, a conceptual framework for the identification of logics of interventions was developed. It is based on the 'hard law' and 'soft law' distinction (Box 2), supplemented by the general institutional context. Whereas hard law follows the mandatory and legislation logic, soft law follows the voluntary and agreement logic.

Box 2: "Hard law" and "soft law"

The terms 'soft law' and 'hard law' (i.e. 'soft policies' and 'hard policies', respectively) are used to characterize two different dimensions in public governance – non-legally binding and legally binding (24-26). 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 behavior by immediately changing the choice set of addressees (hierarchical approach)
- soft law changes behavior *without* (immediately) changing the choice set of addressees (market approach)

In international relations, soft law proves useful where states prefer 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 to motivate member states to do voluntarily what they are less willing to do if legally obligated. In public governance at the state level, soft law is used to motivate organizations as well as persons (i.e. in their professional roles) to change their behavior 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.

The interlinking of the stakeholder map and logics of interventions serves as an overall conceptual framework of "middle range" in the meaning of Merton[7] to structure the discussion of impacts of interventions to prevent publication bias due to non-publication of clinical trial results.

[7] 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" (27: p.41).

3 Results: Towards a multi-intervention strategy

All evidence acquired in the UNCOVER project indicates that a multi-intervention strategy it required for effectively overcoming publication bias arisen from non-publication of clinical trials results.

3.1 Multi-intervention strategy

The multi-intervention strategy proposed here includes three interlinked approaches to overcome publication bias related to non-publication of results of clinical trials, comprising a variety of building blocks and individual measures (Fig. 2):

- Global Mandatory Approach
- Individual Voluntary Approach
- Catalytic Supplement

These three approaches should not be seen as alternatives, but as complementary.

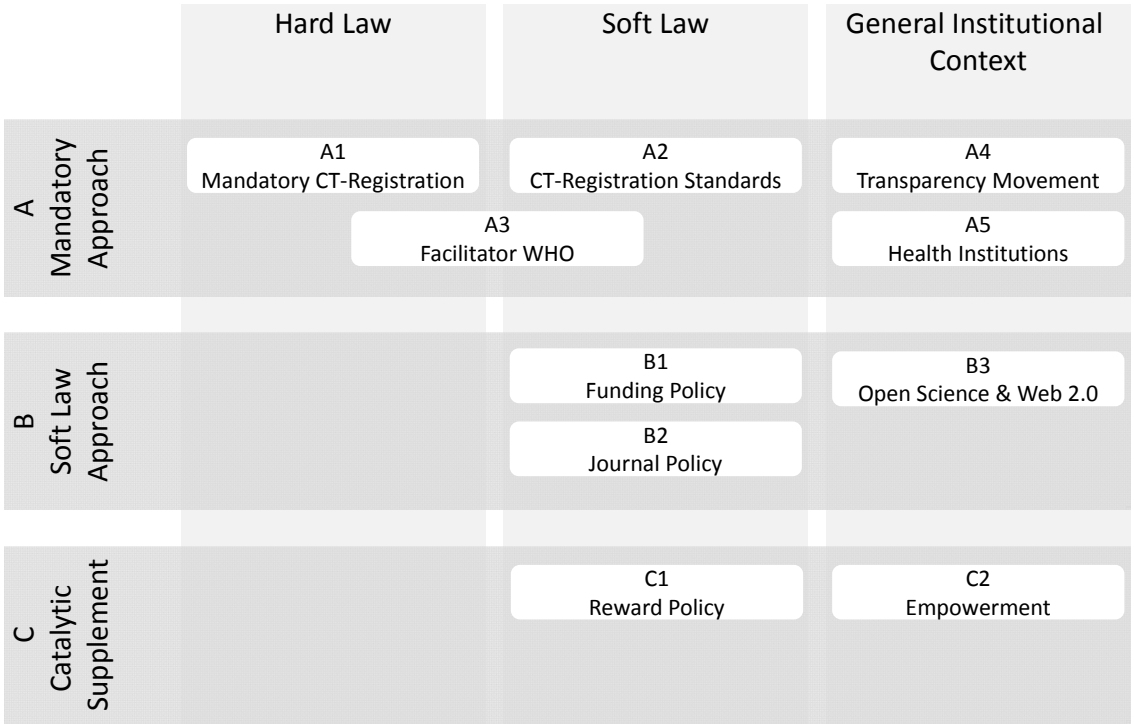
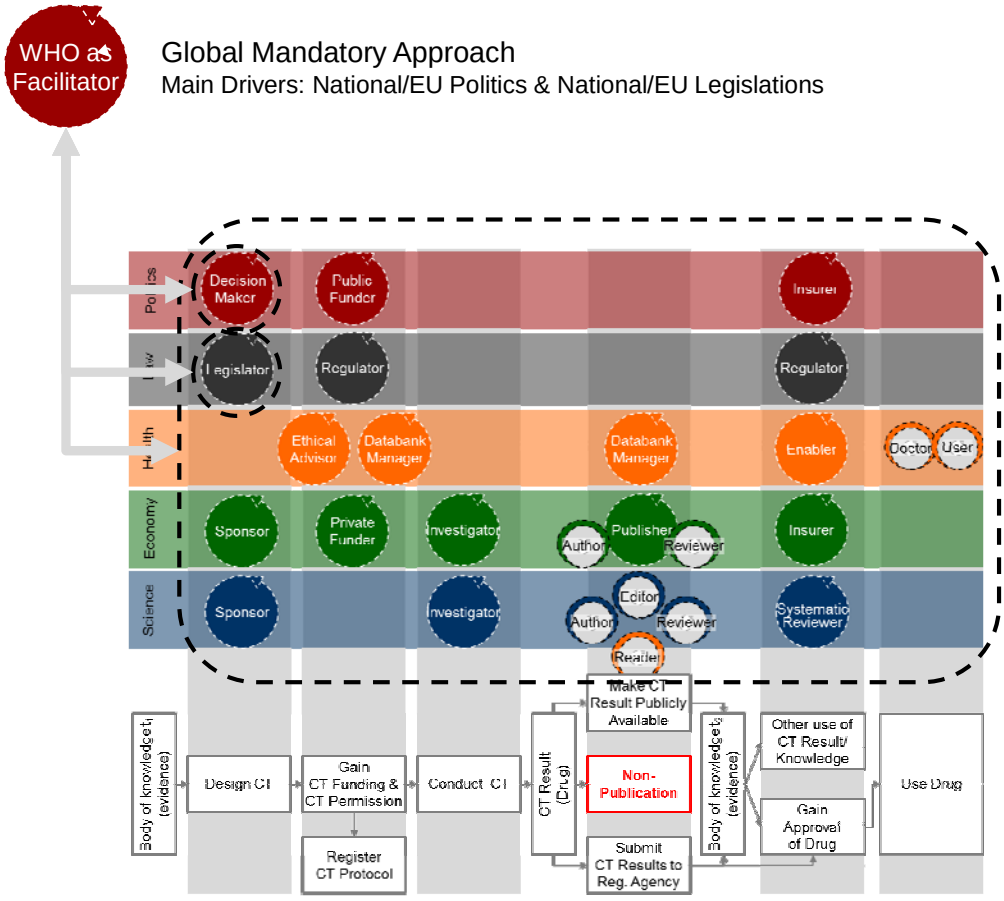


Fig. 2: Three interlinked approaches to overcome publication bias related to non-publication of results of clinical trials and their building blocks.

3.2 Global Mandatory Approach

The **Global Mandatory Approach** (Fig. 3) focuses on a worldwide CT-registry, which contains all clinical trials with a unique number as well as at least summaries of results of all of these clinical trials. We are aware that the basis for such a registry already exists in the form of the WHO International Clinical Trials Registry Platform (ICTRP), but also that these efforts require stronger support by nation states worldwide and the EU. This approach combines hard law and soft law.

On the one hand, it is the goal that nation states worldwide implement CT law on the basis of global harmonized standards. Thereby, US and EU should act as first movers and serve as role models by synchronizing the US clinicaltrials.gov and the European EudraCT with ICTRP. The WHO as facilitator should monitor the progress of nation states' implementation of mandatory CT-registration and eventually promote the achievement of a globally accepted declaration on CT-registration (international treaty law).



For an explanation for colors and symbols, see figure 1.

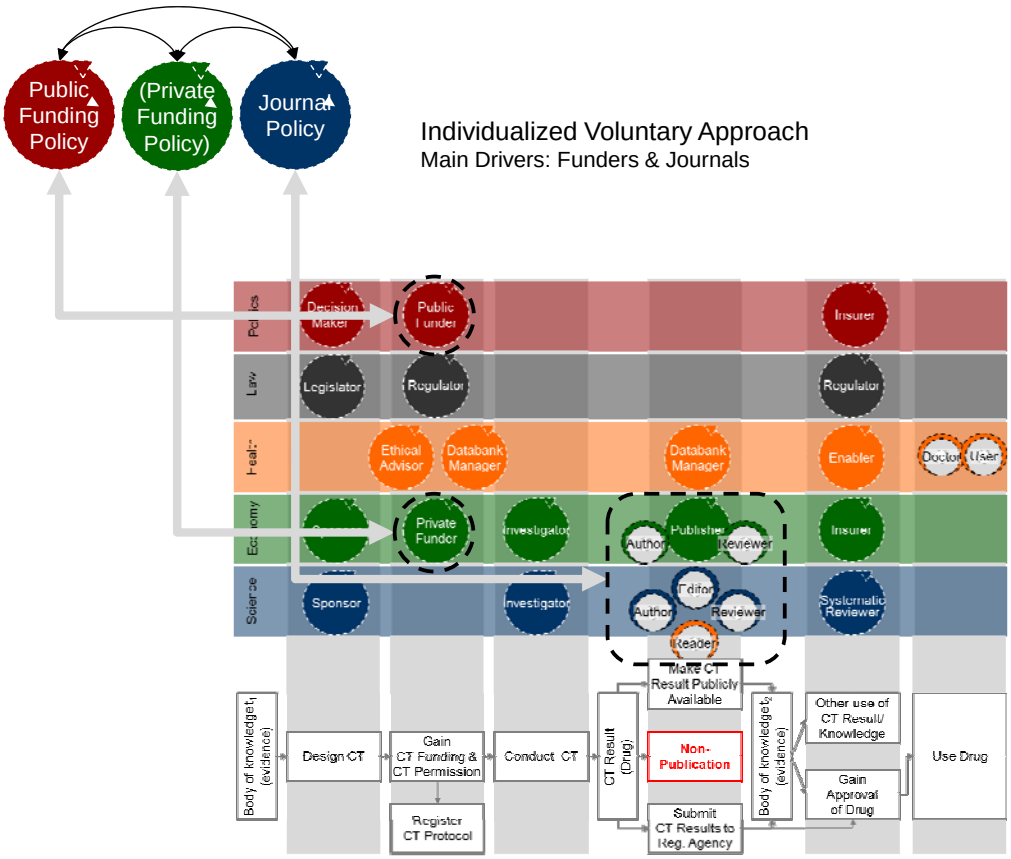
Fig. 3: Global Mandatory Approach

On the other hand, these global harmonized standards should be developed in a step-by-step process including learning and feedback with participation of different stakeholders from investigators, authors, financiers/funders, publishers, editors, and reviewers to lobbyists, NGOs, doctors, health care professionals, and patients. To facilitate the process, the WHO should provide a forum for the integration and supervision of the development of global harmonized standards.

Simultaneously, the general institutional context should gradually improve by taking up the "call for transparency". This should be mirrored in health institutions, such as regulatory bodies and educational and training facilities, and in the professional assessment of the nature and effects of non-publication of clinical trial results.

3.3 Individualized Voluntary Approach

The **Individualized Voluntary Approach** focuses on funding policy and journal policy. It is essentially a soft law approach which will unfold its efficiency in the interlinking of funding and journal policy (fig. 4).



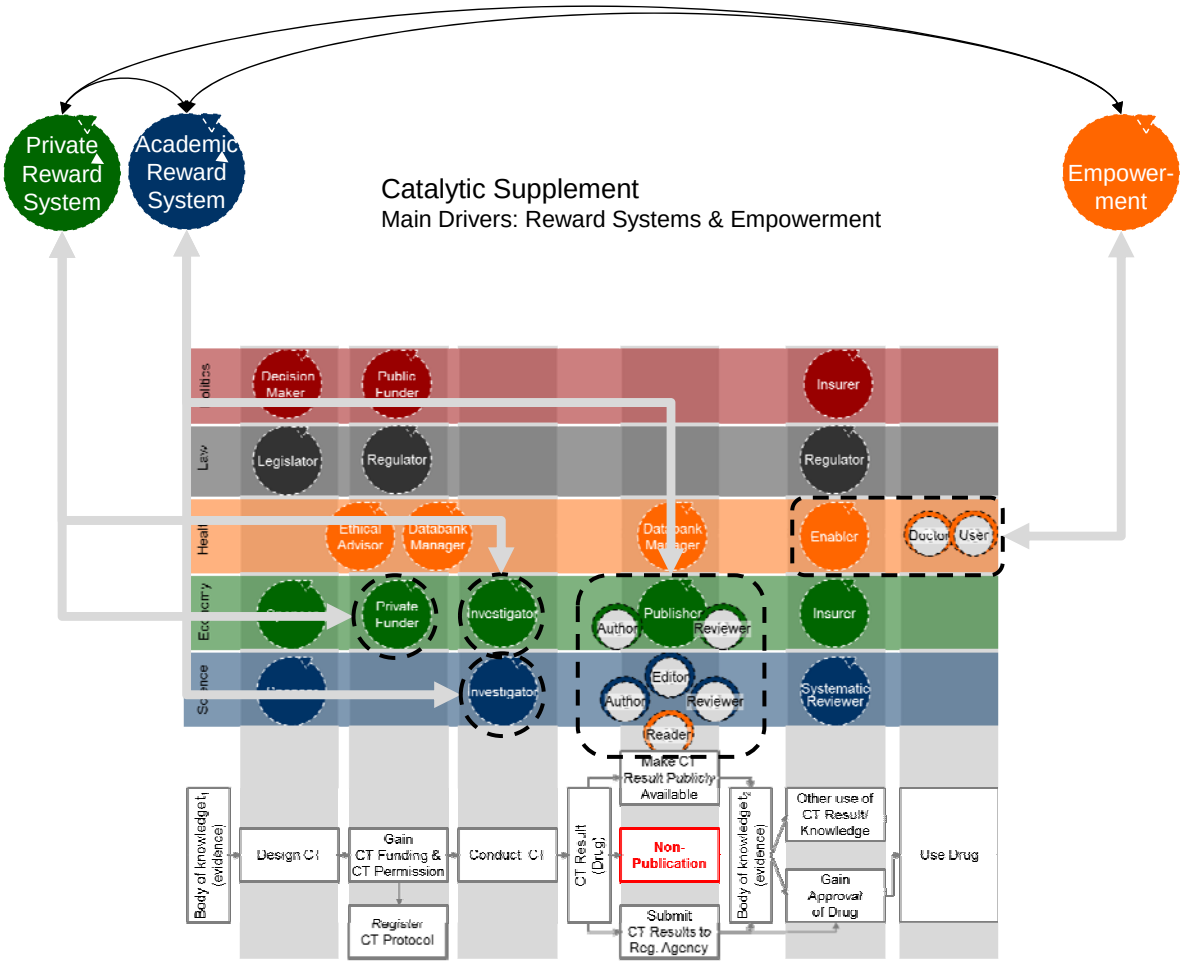
For an explanation for colors and symbols, see figure 1.

Fig. 4: Individualized Voluntary Approach

Public funders should require that researchers publish clinical trial results by following principles such as The European Code of Conduct for Research Integrity. There are already several national initiatives (e.g. the Research Councils UK Policy on Open Access) which demonstrate that public funders are aware of their leverage power and that they are ready to use it. Ideally, the proactive up-taking of fostering the publishing of all kinds of results (successful as well as unsuccessful CTs etc.) by journals could be a signal towards private funders to consider themselves a "publish all kinds of results" policy. The general institutional context in form of the open science movements backed by Web 2.0 (from professional online-databases to wiki-type crowd-source information) supports these developments.

3.4 Catalytic Supplement

A **Catalytic Supplement** (fig. 5) to the Global Mandatory Approach and the Individualized Voluntary Approach is a change in the reward policy and an overall empowerment.



For an explanation for colors and symbols, see figure 1.

Fig. 5: Catalytic Supplement

A change in the reward policy means that the academic reward system changes towards the appreciation of publication of all kind of results (e.g. inclusion in the impact factor system, performance measures used for career advancement should also include a researcher's record in making data publicly available), and the business and funders reward system change likewise. Overall empowerment means that health care professionals together with NGOs, patient organizations, education facilities etc. raise general awareness and provide knowledge to better inform health care users – who are then better respected by the professional health care experts and who are able to behave as advanced demanders within the health care system.

4 Summary

4.1 Key findings

It was shown that a according to the variety of causations of non-publication of clinical trial results a systemic approach is required to grasp the problem adequately. This insight is reflected in the multi-intervention strategy, which is recommended to overcome undesired clinical trial publication practice.

Already known

The variety of these interventions is already discussed in the literature.

Value added

The development of a systemic framework adds a special value providing a theory based and empirically proved concept as a basis for a multi-intervention strategy to overcome non-publication of clinical trial results.

4.2 Limitations

First, this report addresses primarily a European and US perspective, but proposes the WHO as facilitator to refer to the international and even global dimension of the problem of non-publication of clinical trial results. Second, the interlinking of the building blocks of the multi-intervention strategy to overcome undesired publication practice remains somewhat fuzzy, since the project resources did not allow further exhaustive investigations.

4.3 Outlook

Further research dealing with intervention strategies to overcome publication bias related to clinical trials should collect and analyze empirical evidence of impacts of individual measures and of favorable and unfavorable feedbacks of interlinked measures.

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. Buchinger E. Deliverable 3.3 of the UNCOVER FP7 funded project under contract number 282574: Framework for the discussion of publication bias prevention: From stakeholder mapping to the hard law & soft law distinction. 2013.
12. Wagner-Luptacik P, Nußbaumer B. Scenario building: Results of scenario workshop 1. Deliverable 5.1 of the UNCOVER FP7 funded project under contract number 282574, 2013.
13. Freeman R. The stakeholder approach revisited. Zeitschrift für Wirtschafts- und Unternehmensethik. 2004;5(3):228-41.
14. Freeman R. Strategic management: A stakeholder approach: Boston: Pitman; 1984.
15. Mitchell RK, Agle BR, Wood DJ. Toward a theory of stakeholder identification and salience: Defining the principle of who and what really counts. Academy of Management Review. 1997;22(4):853-86.
16. Parsons T. The social system. : New York: The Free Press; 1964 [1951].
17. Porter ME, Olmsted-Teisberg E. Redefining health care: Creating value-based competition on results: Harvard: Harvard Business School Press; 2006.

18. Burns LR. The health care value chain: Producers, purchasers, and providers: San Francisco: Wiley; 2002.
19. Parsons T, Shils E, Allpor tG, Kluckhohn C, Murray H, Sears R, et al. Some fundamental categories of the theory of action. Toward a general theory of action. : Cambridge: Harvard University Press; 1962 [1951]
20. Luhmann N. Social systems. Stanford: Stanford University Press; 1995 [1984].
21. Luhmann N. Observations of modernity. Stanford: Stanford University Press; 1998 [1992]
22. Buchinger E. Deliverable 1.2 of the UNCOVER FP7 funded project under contract number 282574: Stakeholder map. 2012.
23. Luhmann N. Essays on self-reference. : New York: Columbia University Press; 1990.
24. Abbot KW, Snidal D. Hard law and soft law in international governance. International Organization. 2000;54(3):421-56.
25. Brennan G, Brooks M. On the 'cashing out' hypothesis and 'soft' and 'hard' policies. European Journal of Political Economy. 2011;27:601-10.
26. Eurofund. European industrial relations dictionary. http://www.eurofound.europa.eu/areas/industrialrelations/dictionary [2013-09-11], 2013.
27. 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.