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# Overcoming publication bias due to non-publication of clinical trial results

Recommendations to change practice and support evidence-based medicine

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The dissemination process for research findings of clinical trials is prone to bias. Publication bias is considered a 'systemic failure' produced by the many stakeholders, mechanisms and practices operating in the clinical trial and publishing process; the systemic failure needs to be approached from a system perspective. Recommendations were developed to better cope with this issue based on the empirical findings of the UNCOVER project, a conceptual framework, and the participative engagement of stakeholders. We recommend two complementary approaches (Global Mandatory Approach and Individualized Voluntary Approach) together with a Catalytic Supplement: each of the three strands comprises a variety of individual measures. Furthermore, we suggest a roadmap for the implementation of feasible interventions that considers the interdependencies of individual measures and the time frame for implementation.

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Recommendations to change practice and support evidence-based medicine

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## 1 Executive Summary

The UNCOVER project is a direct contribution to overcome publication bias due to non-publication of randomized clinical studies. It considers publication bias to be a ‘systemic failure’ produced by the many stakeholders, mechanisms and practices operating in the clinical trial and publishing process; this systemic failure must be approached from a system perspective. Recommendations were developed to better cope with the issues and problems raised by the non-publication of the clinical trials and the overall publication bias. All recommendations were based on 1) the empirical findings of the project (e.g. derived from interviews, systematic review, bibliometrics, and a web crawler); 2) software development; 3) the design of a conceptual framework (based on stakeholder mapping and the institutional context); and 4) the participative engagement of stakeholders.

All evidence acquired in the UNCOVER project indicates that a multi-intervention strategy is necessary to effectively reduce and eventually overcome publication bias due to non-publication of results of clinical trials. We recommend two complementary approaches together with a Catalytic Supplement: each of the three strands comprises a variety of individual measures. The Global Mandatory Approach focuses on a worldwide clinical trial registry, which contains all clinical trials with a unique identification number and summaries of results. This approach relies for its implementation on both hard law and soft law. The Individualized Voluntary Approach focuses on funding policy and journal policy. It is essentially a soft law approach. The Catalytic Supplement implies changes in the reward policy and an overall empowerment of healthcare professionals together with NGOs, patient organizations, education facilities, etc. The two approaches and the supplement are not to be seen as alternatives, but as complementary. Furthermore, we suggest a roadmap for the implementation of feasible interventions that considers the interdependencies of individual measures and the time frame. We believe that the process of responsible research and innovation (RRI) — which aims at stimulating a research and innovation (R&I) process that is ethically acceptable, sustainable and socially desirable — is a helpful framework to better align clinical research with the societal needs in conducting and publishing clinical trials.

## 2 Introduction

Responsible research and innovation (RRI) aims at stimulating a research and innovation process that is ethically acceptable, sustainable and socially desirable (1). It promotes societal interventions early in the research and innovation process so that ethical issues can be addressed early during the design and development of research. Early societal interventions may help to prevent undesirable developments and to better govern the positive and negative impacts of new technologies particularly when technological and scientific developments such as clinical trials (CTs) may harm consumers and citizens.

Clinical trials are embedded in a highly differentiated system involving a wide variety of stakeholders who are guided in their decision-making by various societal rationalities (e.g. scientific, economic or political rationality (2, 3)). Due to the complex nature of the system and the differing strategic goals pursued by specific stakeholder groups and individuals, the dissemination process of research findings of clinical trials is prone to bias. In clinical research “publication bias” is the established term used for biases related to the selective dissemination of evidence (4, 5). Publication bias “occurs when the publication of research results depends on the nature and direction of the results”, i.e. studies with significant or positive results are more likely to be published than those with non-significant or negative results (6). However, for the last three decades a multitude of other terms have been introduced and used to cover different aspects of bias. Depending on the source of the publication bias, i.e. the type of actor in the system and their individual interests, various types of publication bias exist (6, 7): 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).

Publication bias in its various shapes affects the overall knowledge base. It represents a major problem in the assessment of health care interventions as it threatens the validity of published research (8) and can reduce the significance of systematic reviews of drugs, medical devices, or medical procedures, a cornerstone of evidence-based medicine. Consequently, publication bias may have adverse consequences for public health due to ineffective or dangerous treatments. It also results in a waste of scarce research resources in terms of money and time as knowledge of research in futile quests is not shared and studies therefore unnecessarily repeated. Furthermore, patients and other research participants are misled in their understanding that they are contributing to scientific knowledge and the development of improved treatments (9).

The UNCOVER project is a direct contribution to overcoming publication bias related to non-publication of clinical studies that have been designed and executed as randomized controlled trials (RCTs)<sup>1</sup>. RCTs provide the best utility as input to systematic reviews, provided that RCTs are both correctly registered and completely published at least once. The UNCOVER project focuses on a specific aspect of publication bias, i.e. bias resulting from the non-publication of clinical trials. Non-publication can occur in different forms: either the results are entirely unavailable / inaccessible; or the results are submitted to a regulatory agency but are unavailable to other researchers or systematic reviewers, or other stakeholders; or some of the results remain unavailable (e.g. selective outcome reporting bias) (7).

UNCOVER's aim is three-fold:

- 1) To apply established methods 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.
- 2) To engage with stakeholders and identify strategies, barriers, and facilitating factors associated with publication bias and its consequences.
- 3) To synthesize lessons learned and recommend feasible measures to deal with publication bias.

This report focuses on the third aim of the project. It compiles recommendations for feasible measures to better cope with publication bias arising from non-publication of RCTs. It is hoped that in the end the recommended measures will ultimately change practice towards overcoming publication bias. All recommendations listed in this report are derived from the empirical findings of the UNCOVER project and the participative engagement of stakeholders and experts in the field.

The UNCOVER consortium is grateful to the numerous interview partners and participants in the three stakeholder and expert workshops<sup>2</sup> held during the course of this project. The interviewees and workshop participants provided valuable insights that enabled the identification and development of recommendations described in this report.

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<sup>1</sup> Throughout the report the terms RCTs (randomized controlled trials) and CTs (clinical trials) are used in an interchangeable way.

<sup>2</sup> The workshops included: Stakeholder Workshop I "Scenario building" (26-27 June 2013 in Vienna); Stakeholder Workshop II "Roadmapping" (25-26 September 2013 in Vienna); and Expert Workshop "Responsible Research and Innovation & Publication Bias in the health system" (25 May 2014 in Vienna).

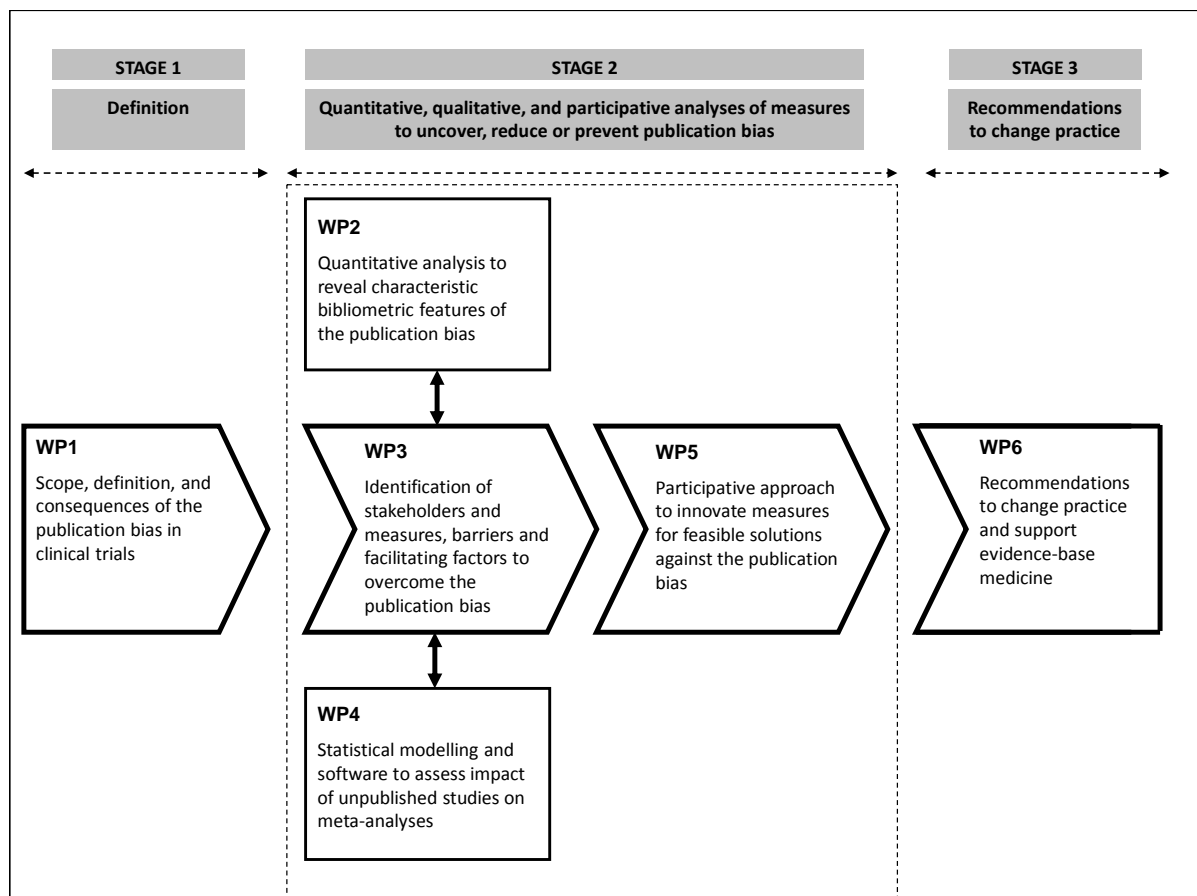


### 3 Approach

#### 3.1 Overview

In the UNCOVER project the issues of publication bias have been addressed with quantitative, qualitative and participatory means (including tools such as stakeholder maps, institutional analysis, systematic reviews, expert interviews, bibliometric analysis and the development of specific software) in an interdisciplinary approach. During the execution of the project, three stages were completed (Figure 3.1).

In Stage 1 “Definition”, methods of evidence-based medicine and social systems theory were joined to both acknowledge and reduce the complexity of the problem and focus on the main players in publishing clinical studies as well as their strategies. A common frame of reference was set for the subsequent work concerning both the definition and consequences of publication bias (7) and the mapping of relevant stakeholders (2, 3).



**Figure 3.1:** General structure of the UNCOVER project.

Stage 2 covered the major part of the project. It was concerned with quantitative, qualitative, and participative analyses of measures to uncover, reduce or prevent publication bias.

*Quantitative analyses:* Bibliometric analyses exploited electronically a vast amount of data from literature databases and established bibliometric features of measurable differences of registered and non-registered published studies. The identified characteristic features were considered in the analysis of two systematic reviews (10, 11). A software package called SAMURAI (“Sensitivity Analysis of a Meta-analysis with Unpublished but Registered Analytical Investigations”) was developed using the open source statistical programming language R (12). The software utilizes the available information from unpublished studies in trial registries to estimate the potential impact of these studies on the results of a given meta-analysis<sup>3</sup> (13).

*Qualitative and participative analyses:* To provide an overview of previously designed and implemented measures to counter publication bias, a systematic review evaluated the effectiveness of interventions to prevent and reduce publication bias related to clinical trials (14). To identify feasible new measures, we interviewed representative stakeholders and experts to explore motivations and barriers to counter publication bias (15). The key opinion leaders had been identified by exploiting knowledge and networks available in the UNCOVER consortium as well as by integrating bibliometrics and other web-based methods such as internet search and a web crawler for comprehensive searches and extraction of documents and sites (5, 16, 17). Finally, experts and stakeholders were invited to several workshops to collectively create multiple, alternative visions of the future (‘scenarios’) and identify both the key drivers and key activities to initiate change as well as the challenges and opportunities for individual stakeholders (18). Together with the stakeholders a roadmap was developed for a plausible scenario (see section 4.3 and (19)). At the same time, the overall conceptual architecture of recommendations (cf. Stage 3) was validated by the stakeholders (20).

Stage 3 was dedicated to develop recommendations to change practice and to support evidence-based medicine. It conceptualised the multi-level structure of recommendations by integrating the findings and lessons learned in the UNCOVER project. It incorporated expert opinion from both inside and outside the UNCOVER consortium, as well as relevant input from a wider range of stakeholders.

As both the systemic and the participative approach constituted major elements of the overall approach of the UNCOVER project, they are described in more detail below.

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<sup>3</sup> Meta-analyses combine results from individual studies to estimate an overall size effect and play an important role in systematic reviews.

## 3.2 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.

### 3.2.1 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 (Figure 3.2). 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.

**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 (21-23). 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 (24). 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”)<sup>4</sup>. 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” (27: p.23).

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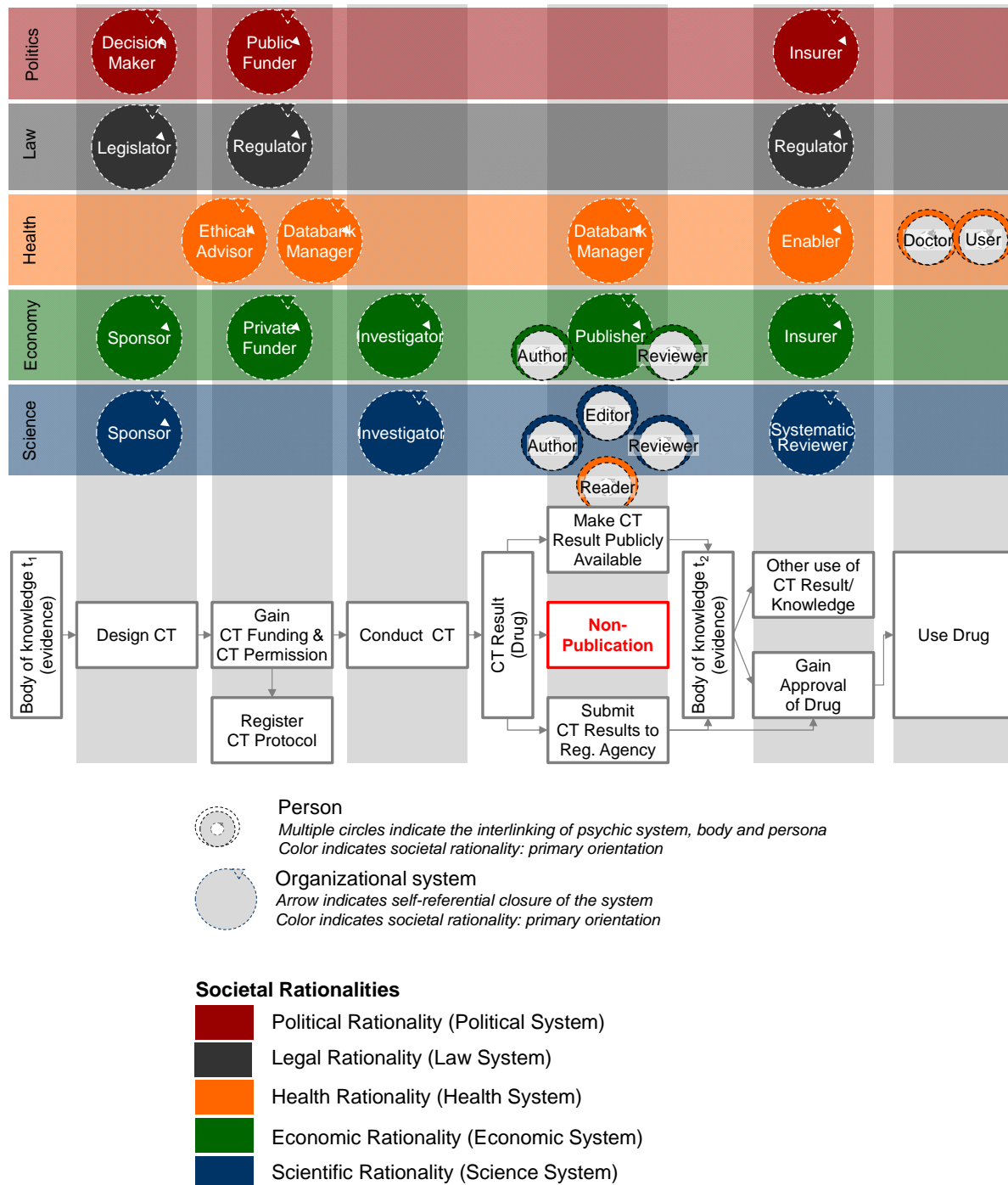
<sup>4</sup> For experiences with the value-chain concept in the health sector, see (25, 26).

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” (28, 29). 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 societal rationalities are considered: 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.)<sup>5</sup>. 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 3.2 visualizes the variety of stakeholders and their roles and Table 3.1 describes the roles of the stakeholders.

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<sup>5</sup> For the evolution of the stakeholder map within the UNCOVER project, see (2).



**Figure 3.2:** CT stakeholder map according to roles/functions<sup>6</sup> (for a description of the stakeholders see Table 3.1).

<sup>6</sup> 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) (30: p.3). As a consequence, signals from the environment must be transferred into the system's own references (otherwise, the signal remains "noise" for the addressed system).

**Table 3.1:** 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

### 3.2.2 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 (31-33). 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 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 confidentiality). 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 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.

The interlinking of the stakeholder map and logics of interventions serves as an overall conceptual framework of “middle range” in the meaning of Merton<sup>7</sup> to structure the discussion of impacts of interventions to prevent publication bias due to non-publication of clinical trial results.

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<sup>7</sup> 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” (34: p.41).

### 3.3 Participatory approach

The stakeholders, mechanisms and practices operating in the clinical trial and publishing process seem to be involved in producing a ‘systemic failure’ (35). Within UNCOVER, a range of experts and stakeholders was specifically asked which institutions or organizations they consider influential in overcoming publication bias (15). Out of ten stakeholder groups<sup>8</sup>, only four consider themselves as important in preventing publication bias (ranked by count): the research community, regulatory agencies, policy decision-takers (incl. EC), and research funding agencies. The majority, however, considers other stakeholders as (more) important for preventing publication bias in clinical trials and is thus ‘shifting the burden’.

The need to overcome this systemic failure in combatting publication bias, to adequately address the complexity of the issue and to ultimately chart pathways to change current practice was anticipated in UNCOVER’s participatory approach which emphasized the critical importance of learning through interaction by experts and stakeholders. This approach aimed to develop a viable ‘breakthrough’ scenario for overcoming publication bias in clinical trials.

Within this context, roadmapping aimed to sketch viable pathways for long term sustainable ‘systemic innovation’ required for overcoming publication bias in clinical trials – recognizing the need for the development of an entire socio-technical ‘transformation’ system, including the institutional, market, policy, educational and regulatory and technological issues.

#### ***Towards responsible health research and innovation***

Uncertainty and complexity are key characteristics of the current situation of publication bias, as there are many stakeholders involved with varying interests as well as different measures and coalitions. In the light of this diagnosis, responsible research and innovation (RRI) provides a useful framework, or governing perspective, to analyse and structure a ‘solution space’ where action needs to be taken. Responsible research and innovation refers to “a transparent, interactive process by which societal actors and innovators become mutually responsive to each other with a view on the (ethical) acceptability, sustainability and societal desirability of the innovation process [...] in order to allow a

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<sup>8</sup> Patient organizations, pharmaceutical industry, regulatory agency, political decision-makers, research funding agencies, journal publisher / editor (incl. open access), research organization, health technology assessment (HTA), trial registry, and experts in the field.



proper embedding of scientific and technological advances in our society” (1, 36). More concretely, it encompasses:<sup>9</sup>

- a deliberate focus of research and innovation to achieve a social or environmental benefit;
- the consistent involvement of society, including the public and non-governmental groups, who are mindful of “health” as a public good;
- assessing and effectively prioritizing social, ethical and environmental impacts, risks and opportunities, both now and in the future, alongside the technical and commercial;
- oversight mechanisms which are better able to anticipate and manage problems and opportunities and which are also able to adapt and respond quickly to changing knowledge and circumstances; and
- openness and transparency as an integral component of research and innovation.

When faced with high levels of uncertainty and complexity in the future, foresight offers itself as a system of inquiry. System foresight (37) was identified as a useful methodology and practice within UNCOVER because it

- has as its object large social institutions and the associated systems of organizations (such as industry, education, or research);
- entails a participatory process involving diverse categories of actors and stakeholders;
- aims to deliver a shared normative narrative of the future (often, a vision or visionary scenario) as a guide to action.

Successful transition towards more responsible research and innovation are either advanced or impeded by various stakeholders (38). Change requires a certain level of commitment, support or at least acceptance by relevant stakeholders which depends on the extent to which stakeholders manage to align their diverging expectations, needs and interests.

No single actor can ultimately induce transformation by him- or herself. Transformative scenario building is a useful method process to work with complex problematic situations that actors want to transform but cannot transform unilaterally or directly (39: p.17). Transformative scenario building uses stories about possible futures to influence what

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<sup>9</sup> See <http://www.responsible-research.co.uk/index.php/home>

<http://www.onlineethics.org/Topics/RespResearch.aspx>

<http://renevonschomberg.wordpress.com/implementing-responsible-research-and-innovation/>

could happen. It also focuses on producing new cross-system relationships and new system-transforming intentions.

Alignment of stakeholders involves learning about the different perspectives on the problem and its solutions. This requires a process in which stakeholders with different backgrounds, knowledge, values and expertise interact and exchange their knowledge and ideas. This kind of participatory processes should facilitate mutual learning by generating, articulating and evaluating divergent knowledge claims and viewpoints. Hence, they should provide ample opportunity to scrutinize conflicting viewpoints and claims, rather than for instance negotiating or compromising preferences. After all, negotiation or compromising is only possible when people know what their own, and other people's preferences are. Common action does not require fully shared perspectives, but only congruent perspectives. Congruency means that options incorporating the different perspectives can be envisaged (40, cited in 41).

A multi-stakeholder dialogue can support processes of alignment and in doing so, future options and solutions for transformation of systems can be meaningfully explored (41). With multi-stakeholder scenario-building, participants often do not a priori share a common vision or underlying set of values, which means that a shared base, or least appreciation, has to be created through the scenario process and dialogue (38).

### ***Scenario-based design***

A key element within UNCOVER's participatory approach was thus to design and facilitate a collaborative future-oriented environment for stakeholders in which the potential for overcoming some of the barriers and challenges to stakeholder engagement and collaboration could be revealed. Experts and stakeholders were invited to engage in a multi-step process which encompassed the visioning of a 'healthy future' with a time horizon 2050, building scenario frames (18) for realizing transformative change towards 2030 and roadmapping feasible solution paths (19).

Developing scenarios and roadmaps within a public policy context has to articulate a future pathway that is desirable from a societal perspective (42). A long-term normative vision emerges as the result of some form of congruence or consensus among participants and therefore claims a degree of representativeness or, at least, of inter-subjective agreement to guide action (37).

Building scenarios towards realizing the long-term vision subsequently served as a 'heuristic device' to generate a number of strategically important initiatives which a range of stakeholders might pursue with the shared aim of improving information on and dissemination of clinical trial outcomes. It was a means to open up appraisal of options to a broader range of views, perspectives and framings (42). Scenario-building also enabled

stakeholders to break away from conventional thinking with a focus on mental models and strategic dialogue and think beyond current issues in operational contexts and broader issues. By looking in a sustained way into the future, it enabled different and potentially radical insights about how needs for providing transparency about clinical trials and their outcomes might be addressed more appropriately and effectively in the future.

Invited stakeholders finally engaged in roadmapping a feasible transformation scenario based on the three key questions: (1) Where do we want to go? (2) What are the ways of getting there? And (3) what should we do from now on?

### *Interim conclusions*

The unique value of constructing a normative vision, scenarios and back-casted roadmap together with a set of experts representing all stakeholder groups was to provide a space for debate and deliberation about options and preferences. Scenario-building and roadmapping brought forth a broad scope and range of interventions. Ultimately a more integrated set of viable pathways compared to existing strategies<sup>10</sup> emerged which echoes the need to steer transitions towards more systemic and thus sustainable institutional and policy arrangements and setting priorities (42).

The participatory process also provided a mechanism for considering the robustness or responsiveness of new ideas and strategies in a range of possible futures, and helped to build confidence in future collaborations among stakeholders.

## 4 Recommendations

Due to the multi-dimensionality of the problem of publication bias related to non-publication of clinical trial results, **we recommend**

1. **a three-pronged multi-intervention strategy** to overcome publication bias in clinical trials (general recommendation);
2. **individual measures** of the multi-intervention strategy (specific recommendations); and
3. **a roadmap** that integrates individual measures into a feasible implementation plan with a time frame for activities (roadmapping recommendations).

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<sup>10</sup> E.g. Song *et al.* (6) identified six measures for the prevention of publication bias: 1) Changes in publication process, 2) Prospective registration of trials, 3) Open access policy, 4) Right to publication, 5) Research sponsors' guidelines, and 6) Confirmatory large-scale trials.

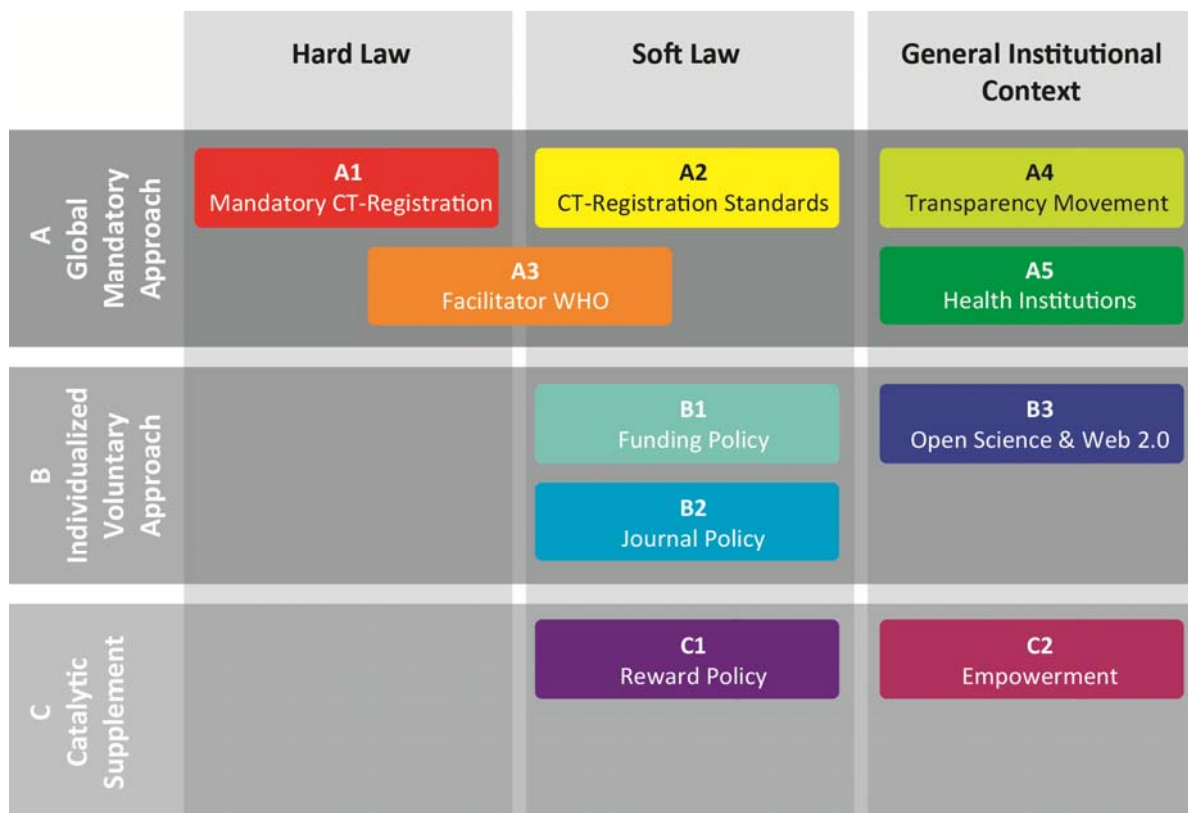
In the following sections we describe the general architecture of the three-pronged multi-intervention strategy and its building blocks (section 4.1), we detail individual measures of the multi-intervention strategy (section 4.2) and we suggest how some of these individual elements could be combined in a feasible roadmap (section 4.3).

#### 4.1 General recommendation: A multi-intervention strategy

All evidence acquired in the UNCOVER project indicates that a multi-intervention strategy is required for effectively overcoming publication bias arising from non-publication of clinical trials results. To overcome publication bias, we recommend two approaches together with a Catalytic Supplement comprising a variety of building blocks and individual measures (Figure 4.1):

- Global Mandatory Approach
- Individual Voluntary Approach
- Catalytic Supplement

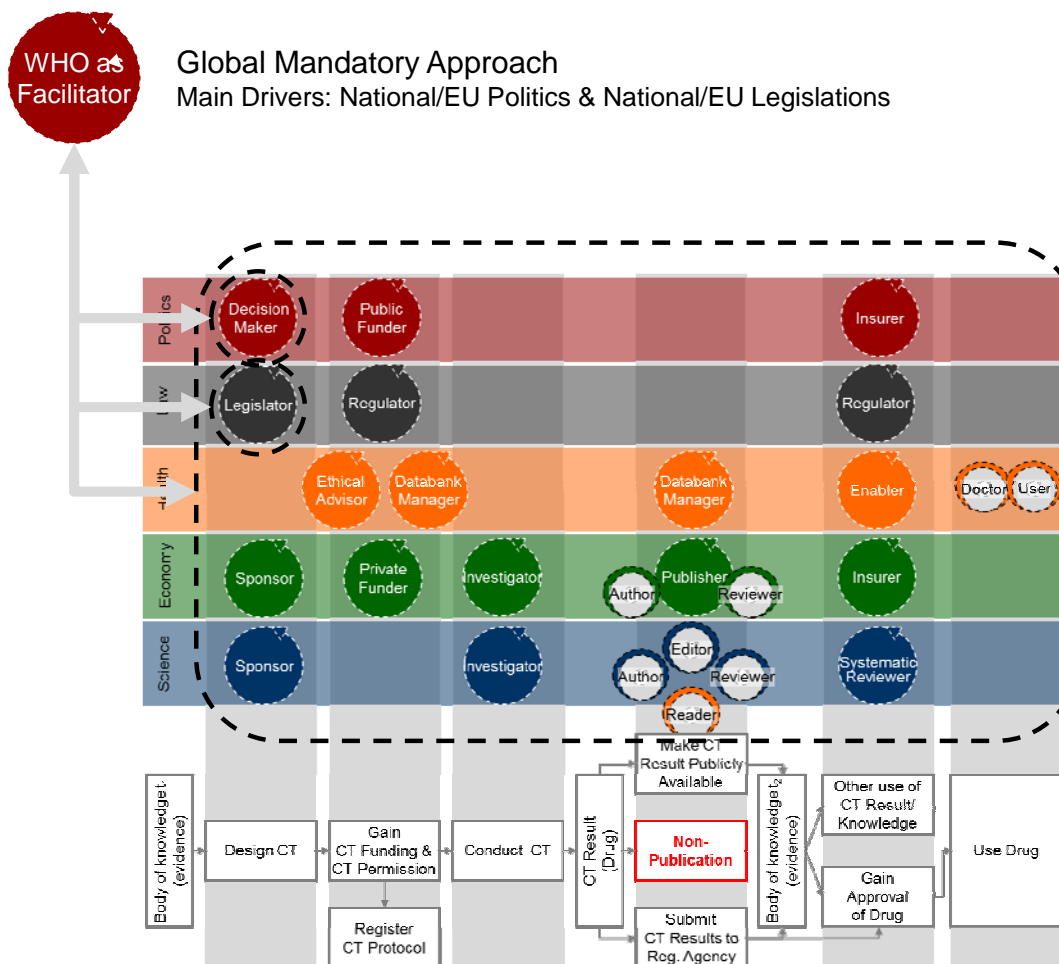
These three approaches should not be seen as alternatives, but as complementary.



**Figure 4.1:** Three interlinked approaches to overcome publication bias related to non-publication of results of clinical trials and their building blocks.

The **Global Mandatory Approach** (Figure 4.2) 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).

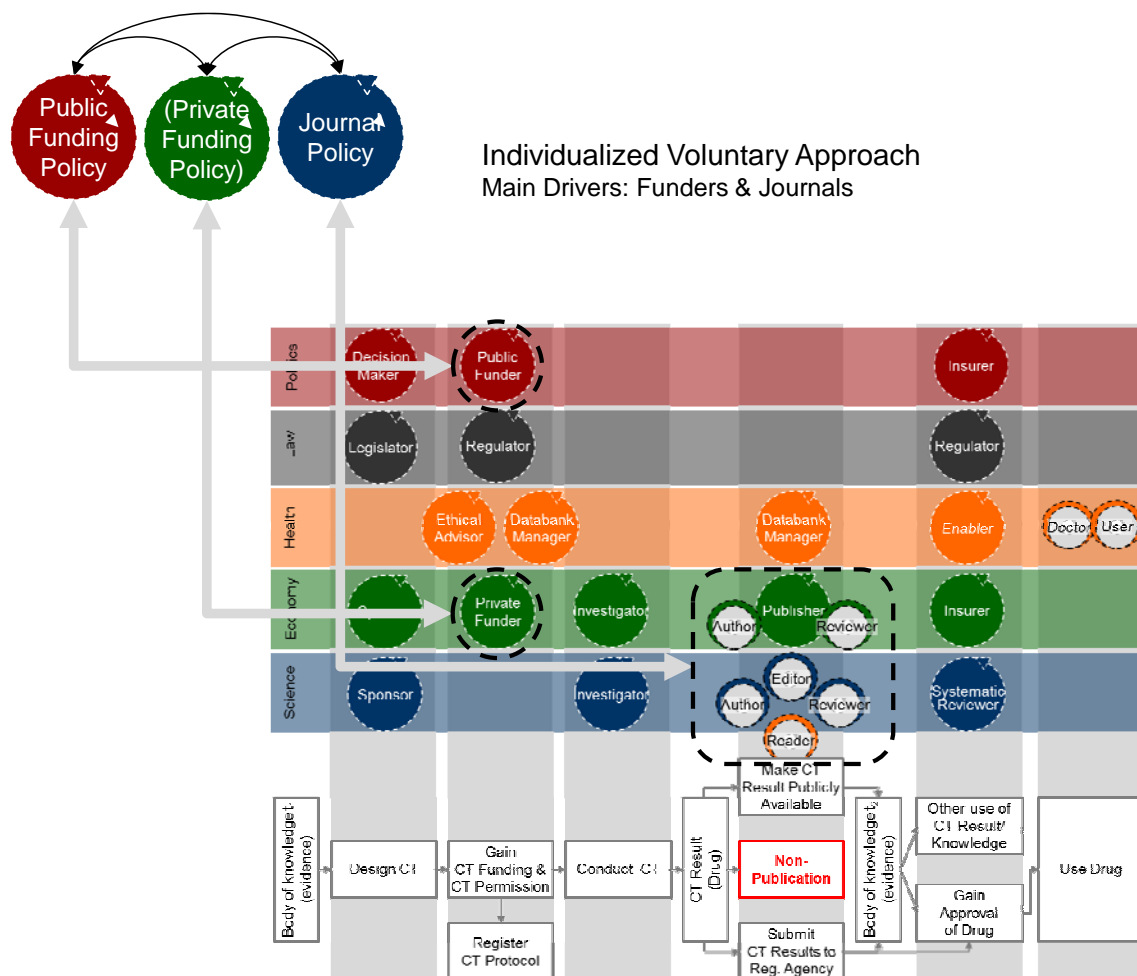


**Figure 4.2:** Global Mandatory Approach. For an explanation for colours and symbols, see Figure 3.2.

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.

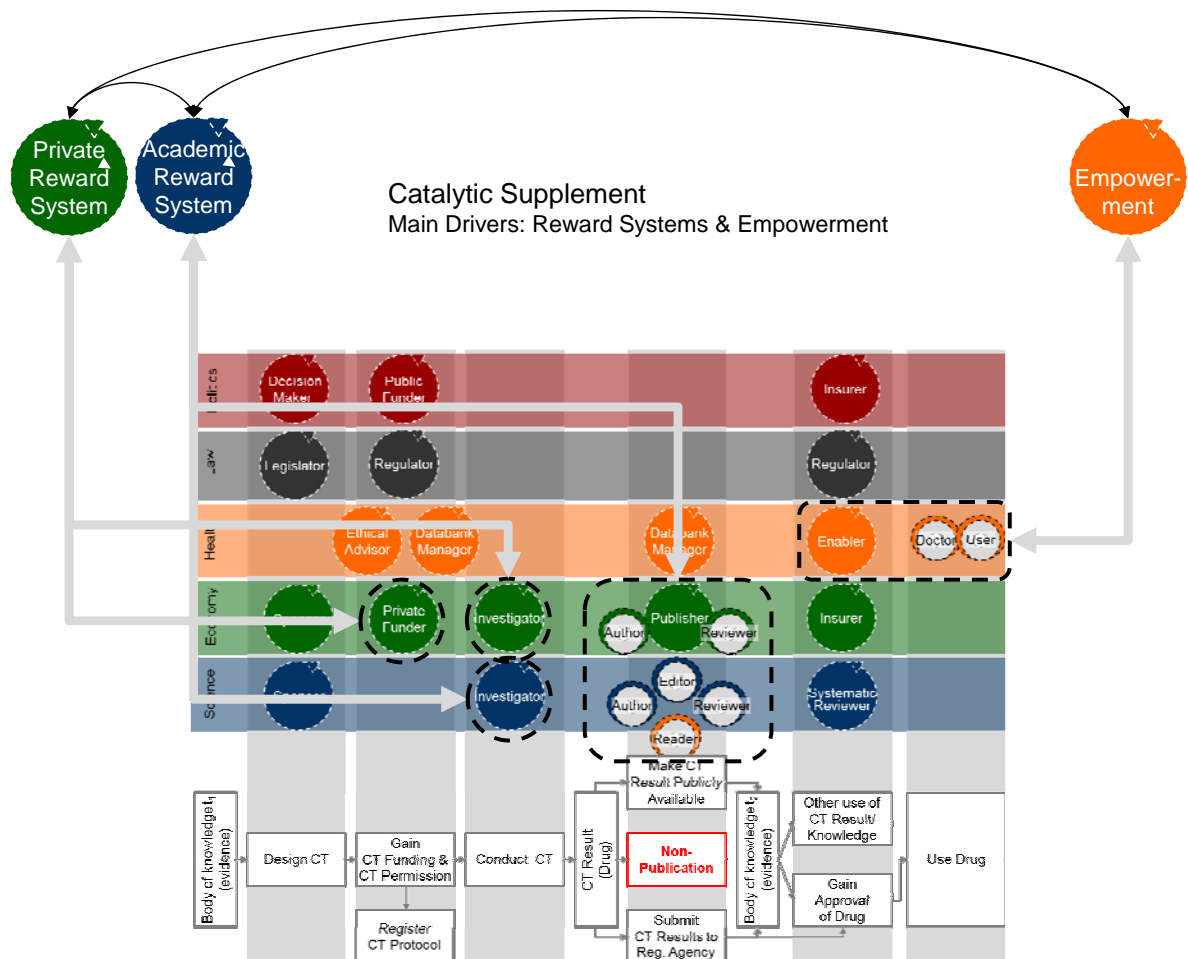
The **Individualized Voluntary Approach** focuses on funding policy and journal policy. It is essentially a soft law approach which will unfold its efficiency in the interlinking of funding and journal policy (Figure 4.3).



**Figure 4.3:** Individualized Voluntary Approach. For an explanation for colours and symbols, see Figure 3.2.

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.

A **Catalytic Supplement** (Figure 4.4) to the Global Mandatory Approach and the Individualized Voluntary Approach is a change in the reward policy and an overall empowerment.



**Figure 4.4:** Catalytic Supplement. For an explanation for colours and symbols, see Figure 3.2.

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.

#### 4.2 Specific recommendations: Individual measures

The three approaches of the multi-intervention strategy for overcoming publication bias require a set of practical measures for their implementation. Table 4.1 provides an overview of recommended measures and indicates how they correspond to the overall architecture of recommendations. In addition to the identified building blocks of the strategy we suggest measures that should support the overall learning process related to publication bias. The individual measures will be characterized in more detail in the following sections.

**Table 4.1:** Building blocks of the multi-intervention strategy and individual measures.

Building blocks		Individual measures
A1	Mandatory CT-registration incl. mandatory publishing of result	<ul style="list-style-type: none"> <li>All clinical trials should be registered in one worldwide meta-registry and catalogued using a unique trial identification number.</li> <li>The World Health Organization (WHO) should be responsible for the administration of this single worldwide trial registry.</li> <li>Regulatory agencies should not accept any trials for approval of drugs, medical devices etc., unless these have been prospectively registered. In addition, reporting of results should also be a prerequisite for the acceptance of trial results by these agencies.</li> <li>Approval institutions and funders, in addition to ensuring that trials are registered, should review the quality of entries (quality management) and should secure compliance with mandatory data requirements.</li> <li>The results of clinical trials must be publically available (at least as summaries).</li> </ul>
A2	CT-registration standards	<ul style="list-style-type: none"> <li>Global harmonized standards should be developed for trial registration and results of clinical trials.</li> </ul>
A3	Facilitator WHO	<ul style="list-style-type: none"> <li>The WHO should be strengthened as a facilitator.</li> </ul>
A4	Transparency movement	<ul style="list-style-type: none"> <li>Medical journals should increase transparency.</li> <li>The public “call for transparency” (e.g. through awareness raising campaigns) should be done justice<sup>11</sup>.</li> </ul>

<sup>11</sup> A broad awareness raising campaign, the “All Trials Registered – All Trials Reported Campaign” ([www.alltrials.net](http://www.alltrials.net)) has already been signed by more than 450 organisations and 63,000 individuals. This



Building blocks		Individual measures
A5	Health institutions <sup>12</sup>	<ul style="list-style-type: none"> <li>Health care professionals together with civil society organisations (patient organisations, consumer advocates, etc.) should raise general awareness and knowledge of the general public with the objective to empower citizens to become “informed, autonomous, critical and respected” partners.</li> </ul>
B1	Funding policy	<ul style="list-style-type: none"> <li>Funding bodies should support trial registration and mandatory reporting of results. Funding (public or private) for clinical trials should be dependent on the trials being prospectively registered.</li> <li>Funding of future applications for grants should be dependent upon the prospective registration record of the applicant.</li> <li>Funding bodies should support the implementation of The European Code of Conduct for Research Integrity.</li> <li>Funding bodies should include researchers’ data sharing activities in their assessment.</li> </ul>
B2	Journal policy	<ul style="list-style-type: none"> <li>Journals (via editors) should revise their policies on information contained in abstracts and in reference lists to contain the unique trial identification number.</li> <li>Journal editors should only accept manuscripts based on registered trials.</li> <li>Editors and peer reviewers should check that the trial registration number is stated in all publications.</li> <li>Journals should follow their own rules seriously and also set consequences if researchers are not willing to share data.</li> <li>Medical journals should increase transparency.</li> <li>Trial registration numbers should be stated in all publications.</li> </ul>
B3	Open science & Web 2.0	<ul style="list-style-type: none"> <li>Automated issue management systems should be used in awareness raising campaigns (see also C2).</li> </ul>
C1	Reward policy	<ul style="list-style-type: none"> <li>There should be incentives for making data publically available.</li> </ul>
C2	Empowerment (& awareness raising)	<ul style="list-style-type: none"> <li>Awareness of publication bias and its detrimental effects should be raised among all stakeholder groups and the general public.</li> <li>Automated issue management systems should be used in awareness raising campaigns (see also B3).</li> <li>Awareness of the issue should be increased through the assessment of the extent of publication bias.</li> <li>The consequences of publication bias on the estimated effects of a meta-analytic summary effect should be assessed.</li> </ul>
-	Fostering future learning	<ul style="list-style-type: none"> <li>Cooperation within stakeholder groups should be reinforced.</li> <li>Ongoing and future strategies to counter publication bias should be evaluated.</li> </ul>

initiative was set up by the British Medical Journal (BMJ), the James Lind Initiative, the Centre for Evidence-Based Medicine, and transparency activist Dr Ben Goldacre (43). This measure will not be further characterized in the report.

<sup>12</sup> Generally, as health (care) institutions are major actors in the field of clinical trials and publishing of trial results, they are implicitly addressed in the implementation of most of the recommended measures either as actors or as affected parties.

#### 4.2.1 Mandatory trial registration (A1, A2)

Prospective registration of clinical trials has been at the forefront of reducing publication bias for more than a decade. The European Medicines Agency (EMA) established the EudraCT clinical trial database in May 2004. For complying with the authorization process details of trials of investigational medicinal products have to be entered in EudraCT. Since March 2011 limited information on the trial's method is publically available on EudraCT. The National Library of Medicine (NLM) maintains the *ClinicalTrials.gov* database where, as a result of a U.S. law, clinical trial information has to be submitted not later than 21 days after enrolment of the first participant (44). In addition, the International Committee of Medical Journal Editors and other journals require registration of clinical trials prior to enrolment of the first participant (44).

To enforce trial registration, in 2005 the International Committee of Medical Journal Editors (ICMJE) started to consider registration as a prerequisite for consideration of publication in peer-reviewed journals (45). Despite this policy, ICMJE-member journals show a lack of monitoring and enforcement of this policy (46) and many journals have not implemented this policy at all (47-53). Although research ethics committees are often suggested as an important institution to enforce trial registration, currently trial registration is required as a prerequisite for ethical approval only in the UK (since 2013) (54, 55).

Another mechanism to enforce trial registration is stated in the current proposal of the Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC(56) as well as in the U.S. Test Act (57). For achieving licensing of a new drug only studies which have been prospectively registered will be considered.

As a result of the current activities concerning trial registration, we recommend that **all clinical trials should be registered in one worldwide meta-registry and catalogued using a unique trial identification number**. These identification numbers should be used and searchable in databases (such as Web of Science) and become part of the fields used in referencing publications of trials in other works (i.e., Authors, Title, Journal, Date, Trial number). This would permit the recognition of data as coming from a single trial as one entity, rather than considering each new publication as a stand-alone piece of data, and enable the linking of publications resulting from the data of a single trial.

Furthermore, **we recommend that global harmonized standards should be developed for trial registration and results of clinical trials**. The first step would be to develop a system of unique trial numbers. For example, the publishing industry began to use the ISBN (International Standard Book Number) in the 1970s making it possible to identify unique

books worldwide. This example shows that publishers and funders must support the use of unique trial identification codes and be willing to finance them with small contributions.

Mandatory trial registration is necessary so that the community can recognise what research has been conducted and where results of that research are available (or when they are not available what impact the result might have on the state of knowledge in a clinical area, see the software SAMURAI (12, 13)).

The actors related to these recommendations are researchers and organisations responsible for maintaining the trial registries. On the one hand, researchers (or authors) are faced with the cost of their time in entering protocol data about their trials into registries and following up with trial results. On the other hand, the usefulness of trial registries is dependent on their adequate use, and the entry of data into fields needs to be monitored by an external organisation. This involves a large administrative burden.

**We recommend that the WHO is responsible for the administration of the single worldwide trial registry** because WHO has the mandate of many countries and a current funding model that allow distribution of the costs fairly between multiple countries (see section 4.2.3 for more details on strengthening the WHO as a facilitator). This would require synchronisation of the WHO ICTRP with other current trial registration facilities such as the US clinicaltrials.gov and the European EudraCT and those from other countries (in their languages).

Furthermore, **we recommend that journals (via editors) revise their policies on requested information in abstracts and bibliographic records to contain the unique trial identification number.**

Similarly, owners of large bibliographic databases (e.g. Thomson Reuters for Web of Science) should modify their databases to contain trial numbers and allow for bibliometric analyses based on these numbers.

Two issues must be addressed in order for trial registries to be useful – they must be used by all trialists and they must be used properly. Thus two questions arise: who should enforce the USE of trial registries for all clinical trials, and who should enforce the PROPER USE of clinical trial registries?

**We recommend that regulatory agencies do not accept any trials for approval processes unless these have been prospectively registered.** Similarly, **we recommend that funding (public or private) for clinical trials is dependent on the trials being prospectively registered.** Furthermore, **we recommend that the funding of future applications for grants should be dependent upon the prospective registration record of the applicant** (including the availability of results, see section 4.2.2).

Mandatory fields are the spaces in the trial registries where an input is absolutely required – it cannot be left blank. Analyses of registries, however, have shown that entries are often too vague to be useful (i.e., nonsense or non-specific information is entered, such as “drug x” as name of drug, etc.). We believe that **approval institutions and funders**, in addition to ensuring that trials are registered, **should review the quality of entries** (quality management) and should secure compliance with mandatory data requirements.

A precondition of the implementation of mandatory trial registration is that there is a sophisticated quality management system with harmonised data relations. Another technical aspect that will influence the success of mandatory trial registration is whether the unique trial numbers are used in databases and for referencing scientific publications and that the database works technically and legally (worldwide in all countries).

The stakeholders that are affected by mandatory trial registration include: the scientific community; trialists and researchers; health care professionals; intermediaries; funders (including governmental, NGOs, and private); consumers and patients; reimbursement agencies; health insurance funds – social insurance agencies; pharmaceutical companies; EMA; publishers; editors; peer reviewers.

#### 4.2.2 Mandatory publishing of results (A1, A2)

**The results of clinical trials must be publically available.** The current system of sporadic publishing of clinical trial results in the form of academic papers published in scientific journals is inadequate because the barrier to releasing results is too high (time of writing manuscripts, acceptance process, peer review). Many studies show that a high proportion of results of trials are never published.

Two broad categories exist for the availability of trial results: 1) results in summary form (such as in tables, similar to the current presentation in scientific publications or in publically available drug-approval documentation); and 2) data available for re-analysis. **We recommend, at a minimum, that results are available in summary form.** Ideally, result data should be available for re-analysis by independent researchers; however the barriers and costs of this type of access to results may currently be too high to ensure proper implementation.

There are two major stakeholders who are responsible for conducting clinical trials: researchers and trialists working in their own fields with grant support from government funders, NGOs, or their own hospitals; and trialists working for or closely with pharmaceutical companies looking to gain approval for new drugs or to achieve broader approval for current drugs (in terms of applicable conditions or patient population). In order that both groups are adequately motivated to allow the release of the results of

their trials three additional stakeholders should be employed as actors: ethics committees; funding agencies; and regulatory agencies.

In regards to summary form trial results: **we recommend that BOTH trial registration and reporting of results should be a prerequisite for the acceptance of trial results by regulatory agencies.** A summary of the results of the primary and secondary outcomes of clinical trials should be attached to the entry in the trial registry database and available within one year of the trial completion and this must be a pre-requisite for funding and for approval of drugs, medical devices or medical procedures (see section 4.2.4). For example, we recommend that funding bodies make a proportion of funding for clinical trials available only AFTER results are made publically available. In addition, regulatory agencies may withdraw approvals where results are not made available in a timely manner and ethics committees could make future approval of clinical trials for individual investigators dependent on their past record of making trial results available.

Several other strategies in cooperation with other stakeholders can support the registration and mandatory reporting of results (see sections 4.2.4, 4.2.5, 4.2.6).

In regards to the availability of patient-level data for re-analysis: the major issue of concern relate to privacy and ownership of data and technical considerations. One current initiative, run by Yale University in the US (YODA - Yale University Open Data Access project) may serve as a model for future development (58). In terms of privacy, ethical considerations regarding the identity of patients must be addressed. Likewise, the public availability of data that “belongs” to private pharmaceutical companies may result in a competitive disadvantage for those companies and therefore to a reduction in willingness to fund clinical research. A technical consideration is that a very large amount of digital storage space is required for storing the data. The costs for this could be shared, for example, via a subscription mode where access to the data involves a small fee. Furthermore, in order to encourage the set-up of data-repositories a system mimicking the current journal impact factor points system could be implemented, with a competitive reward system for “good practice” of presenting data and results.

Several measures aiming at mandatory publishing of trial results have already been introduced. For example, the current U.S. law requires results to be reported within one year of study completion in the *ClinicalTrials.gov* database (44). The EU Clinical Trial Regulation, which should be implemented in 2014, also requires the reporting of the results of clinical trials in the EudraCT database within 12 months after completion of clinical trial (56, 59).

Publication policies of the European Medicines Agency (EMA) and some pharmaceutical companies point in the same direction.

In 2012, the EMA stated that it is committed to the “proactive publication of data from clinical trials supporting the authorisation of medicines once the marketing-authorisation process has ended, which the EMA does not consider commercially confidential”. After a workshop organized by the EMA in November 2012, followed by several meetings of advisory groups, the EMA has published the final advice of these groups on the topics of protecting patient confidentiality, clinical trial data formats, rules of engagement, good analysis practice, and legal aspects as well as a draft policy on the publication and access to clinical trial data(62, 63) and an implementation plan will be discussed in May and will be delayed until September 2014 (64).

Some pharmaceutical companies have agreed on publishing the results of clinical trials in a database which can be accessed upon request. In January 2014 the portal [www.ClinicalStudyDataRequest.com](http://www.ClinicalStudyDataRequest.com) was created and includes data from clinical trials from GlaxoSmithKline, Roche, Boehringer Ingelheim, Sanofi, Novartis and ViiV Healthcare (65). Johnson&Johnson was the first pharmaceutical company to start collaboration with the Yale University Open Data Access (YODA) project in January 2014. YODA will give access to the data to other researchers who request it (58).

#### 4.2.3 Strengthening WHO as facilitator (A3)

**The WHO should be strengthened as a facilitator** (by nation states which provide funding) to maintain and curate the single database for clinical trial registrations and results. The WHO has already developed and published a list of 20 mandatory fields for the WHO Trial Registration Data Set. These do not include any reporting of trial results (in summary form or otherwise). Standards should be developed by self-organisation of the WHO and networks must support the WHO in implementing and improving the already existing dataset.

The WHO could be given a mandate by nation states and become better empowered to enforce and maintain the central trial registry. In this case the actors would be the nation states and the WHO itself and the stakeholders affected are other groups in the health care field.

#### 4.2.4 Funding policy (B1)

**Funding bodies should support trial registration and mandatory reporting of results.** In the future, a priori registration and mandatory reporting of results have to become prerequisites for receiving grants from funding bodies. Funding bodies should retain a certain amount of the grant until it has been proven that the results of the clinical trial have been publically reported. The implementation of this funding policy would only

require a small extra effort of time and personal resources regarding the adapted funding requirements. It has to be recognized that funding bodies cooperate in national networks and new strategies have to be coordinated among each other.

**Funding bodies should support the implementation of The European Code of Conduct for Research Integrity.** Several *Guidelines for Good Clinical Practice*, such as The Declaration of Helsinki (DoH) issued by the World Medical Association (66) and The European Code of Conduct for Research Integrity (67) discuss the ethical obligation of publishing research results. Funding bodies have the necessary leverage to ensure that research institutions accept and implement these guidelines and should base grants on the condition that institutions have implemented these guidelines.

**Funding bodies should include researchers' data sharing activities in their assessment.** Currently the impact factor is the major assessment for assessing the quality of a researcher. Research funders have the potential to implement a different performance matrix and therefore contribute to change the reward system. Funding bodies should consider in their assessment the principal investigators track record in making trial data publically available, publishing detailed study protocols and reuse of original data sets.

#### 4.2.5 Journal Policy (B2)

**Journal editors should only accept manuscripts based on registered trials.** To enforce trial registration, the International Committee of Medical Journal Editors (ICMJE) stated in 2005 to consider registration as a prerequisite for consideration of publication in peer-reviewed journals (45). ICMJE-member journals should retake their vows and they should reject manuscripts based on non-registered trials. Several smaller journals have not implemented this policy yet, due to several reasons (54). We encourage especially associations of medical science journals to inform their members of the necessity of implementing such an editorial policy.

**Medical journals should increase transparency.** Peer review is a highly subjective process; personal knowledge (68), private interests of reviewers (69, 70), a preference towards interesting topics and favourable results (71) can affect the review. To increase transparency in the peer and editorial review process, the reasons for rejecting a manuscript should be made publically available alongside with the abstract.

Medical journals should have a vested interest in publishing reproducible research. One way to shape the norms towards more transparency is to foster open access to data strategies. Such strategies have been already adopted by several journals amongst others *The British Medical Journal (BMJ)*, *The Annals of Internal Medicine*, *PLoS Medicine*, and the *BioMedCentral Publisher Group* (72). We recommend that journals follow their own rules seriously and also set consequences if researchers are not willing to share data.

**Trial registration numbers should be stated in all publications.** Editors and peer reviewers should monitor that all publications have the trial registration number stated in the abstract. This enables systematic reviewers to easily identify and compare the published results with the study protocol in a publically accessible database to assess outcome reporting bias.

#### 4.2.6 Reward Policy (C1)

**There should be incentives for making CT data publically available.** The pharmaceutical industry's as well as academia's reputation have suffered during the last years due to research misconduct, such as researchers falsifying data and leading to retraction of articles (73) or pharmaceutical industry holding back data (74). Some pharmaceutical companies have taken steps to increase their credibility (see chapter 2.1). We recommend that the assessment of drugs, medical devices or other treatments by health insurance agencies should also include the indicator of the completeness of the evidence base, which can only be a check of registered trials and published results). In academia, performance measures (e.g. impact factor, received research grants) used for career advancement should also include a researcher's record in making data publically available.

#### 4.2.7 Awareness & Empowerment (A4, A5, B3, C2)

**Awareness of publication bias and its detrimental effects should be raised among all stakeholder groups and the general public.** Raising awareness of the detrimental effects of publication bias on the health care system as well as on the waste of time and resources is a first step for prevention (6). The scientific community itself and the general public should be targeted. Health care professionals together with civil society organisations (patient organisations, consumer advocates, etc.) should raise general awareness and knowledge of the general public with the objective to empower citizens to become "informed, autonomous, critical and respected" partners. These civil society organisations should receive funding to fulfil their objectives. Trial registries should continue their cooperation with research funders to inform researchers about complying with the rules of registering and reporting the results of clinical trials.

**Automated issue management systems should be used in awareness raising campaigns.** Based on our research results of the "web crawler" we recommend communication managers and PR experts to use technical features such as automated issue management systems to become visible in the community.

**Awareness of the problem should be increased through the assessment of the extent of publication bias.** Currently, when researchers are conducting a systematic review or a



meta-analysis, the extent of publication bias in this certain field is usually assessed via statistical methods (e.g. funnel plots) and via a search in a trial registry. To raise awareness of the problem the number of registered clinical trials which cannot be included in the assessment of the evidence based due to non-published articles or reported data in the trial registry should be reported prominently in the abstract of a systematic review.

**Sensitivity analyses using registered but unpublished studies should be used to assess the impact of unpublished studies on meta-analyses.** The non-publication of trials is a serious threat to the validity of systematic reviews and meta-analyses. SAMURAI is a statistical program that can utilize information from registries to test their potential impact of unpublished studies on meta-analyses using different outlook assumptions (75). We recommend systematic reviewers applying this tool for conducting sensitivity analyses and for gauging the impact of unpublished but registered studies upon the meta-analytic summary effect of a set of published studies. These analyses should also be used in drug regulatory applications.

#### 4.2.8 Fostering future learning

**Cooperation within stakeholder groups should be reinforced.** On the European and the international level, networks have been created to build a basis for mutual exchange and to create common standards or procedures to face the challenge of differing health care and research systems (e.g. local ethic committees, national funding bodies, etc.) across Europe. Several initiatives have recently been implemented to foster exchange between organizations across member states. Initiatives involve research ethics committees (EURECNET – European Network of Research Ethics Committees), bodies conducting Health Technology Assessments (EUnetHTA – European Network on Health Technology Assessment), and research institutions engaged in investigator-driven clinical trials (ECRIN – European Clinical Research Infrastructures Network). In addition, Science Europe, an association of European Research Funding Organisations (RFO), and Research Performing Organisations (RPO) supports its member organisations in their efforts to foster European research. On an international level, the International Clinical Trials Registry Platform (ICTRP) focuses on the exchange and establishment of common standards and principals in registering clinical trials (76). These networks provide an important exchange between different member states as well as international cooperation, especially in the field of trial registry and should receive further funding.

**Ongoing and future strategies to counter publication bias should be evaluated.** Many interventions that should supposedly reduce publication bias and that have been advocated by researchers and organizations over many years are not supported by any study data. We require more and larger controlled studies of systems or interventions.

Especially, the current trends in making clinical trial data publically available (e.g. EMA, pharmaceutical companies) demand the monitoring of its usage by systematic reviewers and funders and the assessment of the potentially added value in using individual patient-level data.

### 4.3 Roadmapping recommendations

In order to structure the approaches and measures to overcome publication bias in a systematic manner, it is recommended to move along an ‘ideal’, yet feasible roadmap (Figure 4.5) with selected key measures and key stakeholders in three major phases. A more complete list of recommended individual measures was detailed in the previous sections.

A feasible transformation scenario to overcome publication bias in clinical trials can be structured into three major phases.

- Phase 1 (from the present until 2020) is mainly characterized by the Individualized Voluntary Approach with a focus on funding policy and journal policies and a Catalytic Supplement with a focus on change in the reward policies and overall empowerment.
- Phase 2 (2020-2025) is mainly characterized by the Global Mandatory Approach with a focus on a worldwide CT-registry, facilitated and orchestrated by the WHO.
- Phase 3 (2025-2035 and beyond) is mainly characterized by global cooperation and harmonization of laws and standards.

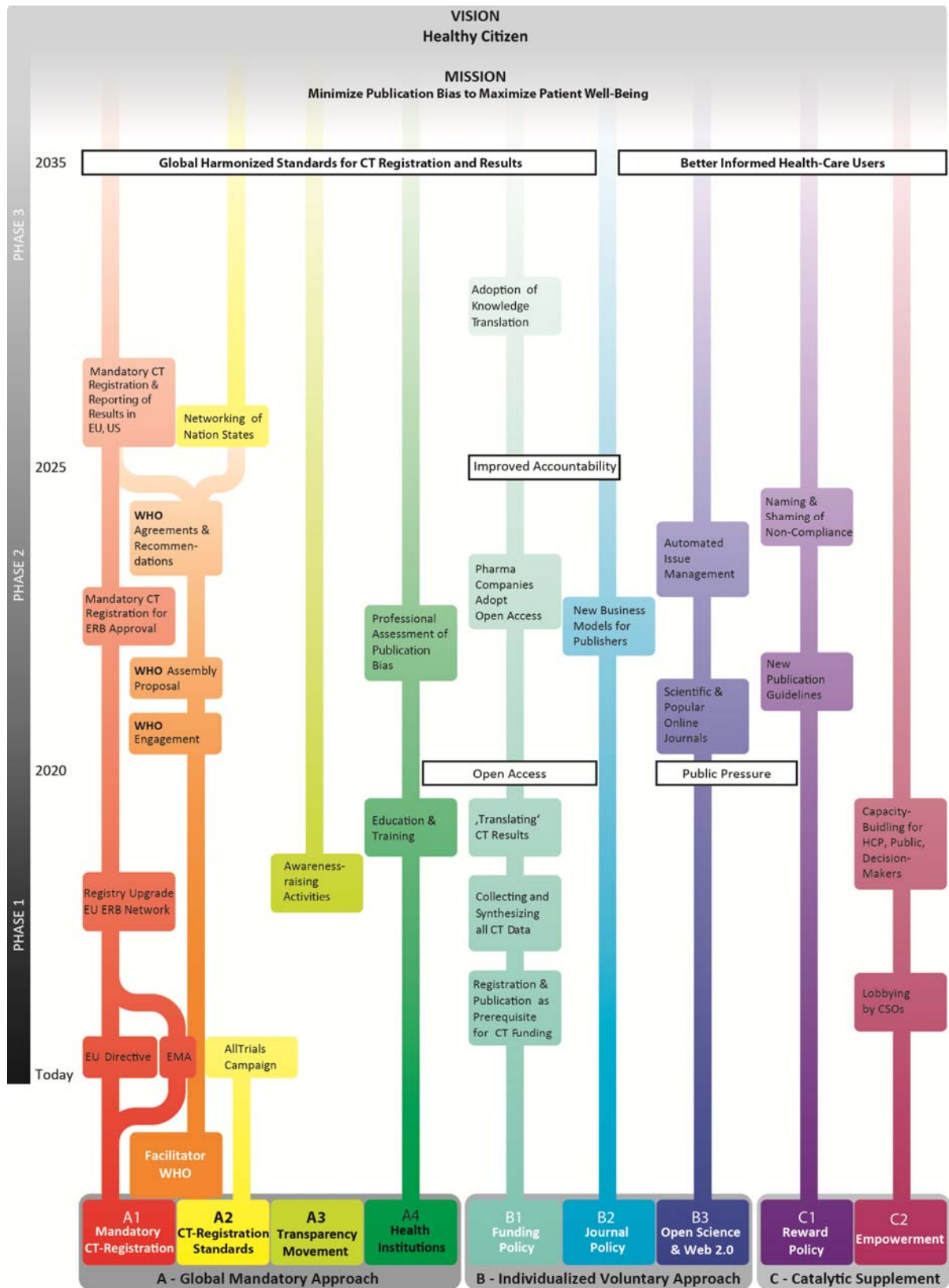
**Phase 1** (*from the present until 2020*) is mainly characterized by raising public awareness due to lobbying by civil society organizations such as patient groups, consumer advocates etc. Funding policy plays a central role for improving CT data availability and knowledge translation. Registration and publication will become a prerequisite for CT funding, as well as CT data collection and synthesis. In terms of capacity-building, CT results are increasingly ‘translated’ into user-friendly information for health care providers, decision makers, the interested public, etc. Health institutions increase education and training activities and upgrade existing registries. Overall, increasing public pressure results in buy-in from regulators and legislators.

**Phase 2** (*2020–2025*) is characterized by consensus-building among regulators and legislators worldwide in the sense of the Global Mandatory Approach. The World Health Organization (WHO) assumes a key facilitating role with proposals and agreements which gradually paves the way for global collaboration. Key stakeholders show improved accountability in their reward policies. Pharmaceutical companies adopt open access principles, notwithstanding naming and shaming in case of non-compliance. In the wake of

the open science movement, publishers adopt new business models and new publication guidelines. More and more online journals (scientific and popular) appear. Automated issue management is used by public relations (PR) experts and also by activist scientists in the health domain for systematic information retrieval, lobbying and agenda setting.

**Phase 3** (2025-2035 and beyond) finally sees the European Union and the United States in the lead to implement mandatory CT registration as well as globally harmonized CT registration standards due to intensive networking among nation states. CT knowledge translation is a pervasive phenomenon which ultimately leads to better informed health care users.

Figure 4.5 depicts in a stylized manner the various temporal pathways towards minimizing publication bias and maximizing patient well-being. Although the vertical lines suggest linear or even isolated developments, measures actually frequently interlink horizontally with other measures, providing or receiving necessary inputs for or from other measures.



**Figure 4.5:** Feasible roadmap to overcome publication bias (CSO: civil society organisations; CT: clinical trial; EMA: European Medicines Agency; ERB: Ethical Review Board; HCP: health care professionals).

## 5 Conclusions

For the last decades, various preventive measures have been implemented to counter publication bias. The most prominent strategies currently pursued are prospective registration of clinical trials and reporting of results, as well as awareness raising campaigns, such as the AllTrials campaign<sup>13</sup>. However, setting up trial registry systems, reporting standards, publication guidelines and the like as isolated measures is likely to suffer from a lack of compliance, poor data quality, etc. as long as these interventions are not embedded in a comprehensive strategy that takes into consideration the systemic dependencies and rationalities of actors and mechanisms at work in clinical research. This effect is intensified when the policies behind the interventions do not carry the force of law and non-compliance with the policies does not entail legal sanctions or penalties. This is confirmed by a systematic review that assessed the effectiveness of particular interventions (e.g. trial registration, peer review process) to counter publication bias. It found little evidence that current measures are successful in dealing with the problem (14). In line with this, only a few stakeholder groups are convinced that they actually have influence when it comes to preventing publication bias (15). Not surprisingly, there is evidence that publication bias has even increased over the years despite the existing wealth of knowledge on the matter and suggested remedial measures that have been researched and debated for many years (9, 77).

To effectively reduce and eventually overcome publication bias, we believe that it is necessary to apply a systemic approach and implement individual measures as orchestrated sets of interventions that are carefully aligned with the social system context. We suggest the implementation of several interlinked and complementary approaches that comprise bundles of individual measures and rely on hard law as well as soft law interventions.

Although non-publication of trial results is widely considered as unethical, to date no researcher or trialist can be legally forced to publish research results. However, as the medical field is a highly regulated system, all researchers and trialists are subject to 'hard law' and, to some extent, also to 'soft law' when they conduct clinical trials and work to meet obligations of funding and regulatory agencies. We conclude that the implementation of legally binding measures is vital to change current practice in scientific publishing of trials results. Although such regulations may not necessarily result in a higher quantity of publications in peer-reviewed journals, they can be powerful enough to

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<sup>13</sup> See [www.alltrials.net](http://www.alltrials.net)

reinforce open access to information on clinical trials, including their results. As especially pharmaceutical firms — major actors in the field of clinical trials — are bound to their business models rather than transparency and therefore reluctant to disclose knowledge of promising treatments in an early stage of drug development, legally binding regulations seem to be the only promising means to bring about a change in scientific publishing of clinical trial results.

Based on the evidence gathered in the UNCOVER project, we believe also that a focus on the ethical dimension of publication bias against the broader notion of responsible research and innovation (RRI) can bring about a significant and sustainable change in the publishing process of trial results in the long run.

Responsible research and innovation aims at stimulating a research and innovation (R&I) process that is ethically acceptable, sustainable and socially desirable (1). It promotes societal interventions early in the R&I process so that ethical issues can be addressed early during design and development of research. Early societal interventions in the R&I process may help to prevent undesirable developments and to better govern the positive and negative impacts of new technologies. RRI is a policy issue that can be applied for various sectors, including the health sector, and for any technological and scientific development (such as a clinical trial) that concerns consumers and citizens in general.

The issue of publication bias in clinical research has mainly been addressed from a scientific perspective (i.e. from “inside” science), dealing with societal needs and values through expert representatives from the medical and related areas. Declarations and codes of conduct interpret the assumed needs and views of the society. Ethics review boards are designed to protect the rights and welfare of human subjects in clinical trials by critically overseeing clinical research on humans and to comment on ethical questions raised by medical universities or hospitals. Their work is guided by international regulations and guideline (e.g. Declaration of Helsinki, ICH-GCP Guideline for Good Clinical Practice) and national law related to clinical trials and other medical issues. Furthermore, the European Code of Conduct for Research Integrity comments on the ethical obligation to publish research results (67). These approaches define what is ethically acceptable and socially desirable.

Societal engagement promotes the empowerment of the society and will support the position of the public with expert stakeholders in the discussion of the process of clinical trials and the publication of the trial results. We believe that the process of responsible research and innovation (RRI) which aims at stimulating a research and innovation (R&I) process that is ethically acceptable, sustainable and socially desirable (1), is a helpful framework to better align clinical research with actual societal needs in conducting and publishing clinical trials. RRI thus encourages us to change our perspectives and look at science from the “outside”. Although publication bias has been widely discussed in the

scientific community, not all relevant stakeholders are aware of publication bias and its detrimental consequences (15, 78). Therefore, drawing attention to publication bias not only among the scientific but also non-scientific stakeholders must be a first step, before societal actions can be expected to take place. Ongoing transparency movements and awareness campaigns go in this line.

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