Brussels, 13 April 2018

COST 028/18

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action "Towards an International Network for Evidence-based Research in Clinical Health Research" (EVBRES) CA17117**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action Towards an International Network for Evidence-based Research in Clinical Health Research approved by the Committee of Senior Officials through written procedure on 13 April 2018.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA17117
TOWARDS AN INTERNATIONAL NETWORK FOR EVIDENCE-BASED RESEARCH IN CLINICAL HEALTH RESEARCH (EVBRES)

The COST Member Countries and/or the COST Cooperating State, accepting the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action (the Action), referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any new document amending or replacing them:

a. "Rules for Participation in and Implementation of COST Activities" (COST 132/14 REV2);
b. "COST Action Proposal Submission, Evaluation, Selection and Approval" (COST 133/14 REV);
c. "COST Action Management, Monitoring and Final Assessment" (COST 134/14 REV2);
d. "COST International Cooperation and Specific Organisations Participation" (COST 135/14 REV).

The main aim and objective of the Action is to encourage researchers and other stakeholders to use an Evidence-Based Research approach while carrying out and supporting clinical research, and thus avoiding redundant research. This will be achieved through the specific objectives detailed in the Technical Annex.

The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 36 million in 2017.

The MoU will enter into force once at least seven (7) COST Member Countries and/or COST Cooperating State have accepted it, and the corresponding Management Committee Members have been appointed, as described in the CSO Decision COST 134/14 REV2.

The COST Action will start from the date of the first Management Committee meeting and shall be implemented for a period of four (4) years, unless an extension is approved by the CSO following the procedure described in the CSO Decision COST 134/14 REV2.

OVERVIEW

Summary

Redundant clinical research has been published due to the absent use of systematic reviews (SR) when new research is planned. It is unethical, limits the available funding for important and relevant research, and diminishes the public's trust in research. In order to raise awareness of this inappropriate practice, the EVBRES-consortium define "Evidence-Based Research" (EBR) as the use of prior research in a systematic and transparent way to inform a new study so that it answers the questions that matter in a valid, efficient and accessible manner. New studies should be informed by SRs as to the most appropriate design and methods. EVBRES will establish an international European-based network aiming to raise awareness of the need to use of SRs when planning new studies and when placing new results in context. PhD students and senior clinical researchers' needs to learn how to find, critically appraise and update a SR, answering the same clinical question the new study plans to answer. Closely related to this is the involvement and awareness of related stakeholders, including patients, ethics committees, funding agencies and scientific journals, to require SRs before approval of new clinical studies. By acknowledging and implementing an EBR approach these stakeholders can improve their own practice and can increase the incentives for clinical researchers to use an EBR approach. Further, EVBRES will catalyse more efficient updating and production of SRs, and monitor the implementation of an EBR approach both in clinical research and among related stakeholders.

Areas of Expertise Relevant for the Action	**Keywords**
● Health Sciences: Health services, health care research	● Research Waste ● Systematic Reviews ● Evidence-based Research

Specific Objectives

To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination

● Raise awareness and acceptance of the challenge among all relevant stakeholders.
● Prepare teaching material to teach Evidence-Based Research.
● Catalyse collaboration between relevant stakeholders to increase the efficiency of updating and preparing SRs.
● Create a common agreement of how to evaluate the implementation of the EBR approach.

Capacity Building

● Formulate implications of an EBR approach for relevant stakeholders.
● Teach researchers how to be evidence-based while doing Research.
● Describe working processes and technologies used when preparing a SR that could be improved.
● Establish a common understanding of how to monitor the EBR approach in clinical Research.

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. CHALLENGE

1.1.1. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Towards an International Network for Evidence-based Research in Clinical Health Research

"*The work which deserves, but I am afraid does not always receive, the most credit is that in which discovery and explanation go hand in hand, in which not only are new facts presented, but their relation to old ones is pointed out*" Lord Rayleigh (1884)

"*New research should not be designed or implemented without first assessing systematically what is known from existing research. The failure to conduct that assessment represents a lack of scientific self- discipline that results in an inexcusable waste of public resources.*" Sir Iain Chalmers (2005)

This COST EVBRES Action aims to increase and enhance the use of systematic reviews (SR) before engaging in new clinical research and for placing new results in the context of already published results.

The PROBLEM: Unnecessary clinical research is unethical, limits the available funding for important and relevant research, and diminishes the public's trust in that research. Meta-research shows a huge waste of research activities in clinical research involving Clinical Health Researchers (CHR) from professions such as physicians, nurses, physiotherapists, occupational therapists, and others, and a long list of medical specialities including rheumatology, oncology, and neurology. Thousands of patients have been recruited to randomised clinical trials well after the intervention was known to be effective due to a lack of systematic searches and acknowledgement of prior research evaluating the same clinical question. In some cases SRs of similar trials were available, but were not included in the planning of the new study. In addition, the results from new studies are rarely placed in the context of existing evidence through a systematic synthesis of all prior results.

The SOLUTION for CHRs is to identify, update and prepare a SR on all earlier clinical studies similar to the new clinical trial planned. If the SR concludes that there is no need for further studies, any plans for a new study should be dropped. This is Evidence-based Research (EBR), an approach that can be defined as the use of prior research in a systematic and transparent way to inform a new study so that it is answering questions that matter in a valid, efficient and accessible manner. The lack of an EBR approach has already and will in the future – unless the EBR approach is implemented - continue to cost human lives, human health and support redundant and unimportant clinical research. Calculations indicate (see below) that unnecessary clinical research within only one clinical question leads to the waste of more than €23 million.

There are several Challenges in implementing the EBR approach. First, the CHRs from all health professions, patients and related Clinical Research Support Stakeholders (CRSS) such as members of Research Ethics Committees (REC), members of Research Funding Agencies (RFA), and editors and reviewers of Scientific Medical Journals (SMJ) need to acknowledge that clinical research waste is a problem, and that EBR is an important part of the solution. Several studies indicate that the same

research question has been examined in too many studies (redundant research). Secondly, few CHRs know how to find, critically appraise, and update a relevant SR or prepare a new SR in order to justify the need for a new study or to place new results in context. A third challenge is the time, effort and funding used in updating and preparing a SR. The fact that most high quality SRs take more than a year to prepare may be a plausible argument for lack of uptake of this approach. Thus, there is a need for more efficient production, update and accessibility of systematic reviews. This is especially challenging for Low and Middle Income Countries (LMIC) as several studies show very low capacity and low funding to prepare and update SRs.

Besides these Challenges, there is a need to monitor the implementation of the EBR approach in clinical research by the means of meta-research, as meta-research aims to evaluate and improve research practices. It is important to know whether the Challenges are still an issue or not. In order to face the Challenges, stakeholders related to clinical trials should be involved, i.e. CHRs, the patients that participate in trials and that receive the new treatment, the RECs who approve the clinical trial, RFAs who financially support the new trial, and SMJs who publish the new trial. In addition, stakeholders related to production of SR, i.e. librarians and information specialists (LIS), and specialists in SR should be involved too.

The Challenges can only be met in a useful and practical manner if working processes are developed, tested and made available for all CHRs. It should be manageable to find, critically appraise, update or prepare a SR, decide if a new study is needed, and if needed how it should be designed, before initiating a new clinical study. This is what EVBRES proposes from the S&T perspective.

Thus, EVBRES is highly needed to coordinate and encourage the ongoing development and implementation of useful work processes to avoid future waste and unethical use of clinical research resources in Europe and in the rest of the world.

1.1.2. RELEVANCE AND TIMELINESS

"*If, as is sometimes supposed, science consisted in nothing but the laborious accumulation of facts, it would soon come to a standstill, crushed, as it were, under its own weight*" (Lord Rayleigh 1884).

Organizing a network for the use of an EBR approach in clinical research is highly relevant and timely. Never in the history of humanity have so many scientific papers been published daily. An evaluation in 2010 estimated that 75 new clinical trials and 11 systematic reviews are published every day, and there are no signs of this slowing down. In addition, never before has a synthesis of all earlier research within a specific area been possible. With the digital revolution, this has been possible for the last 20 to 25 years and has been evolving dramatically since. We are no longer asking for the impossible when we ask for a synthesis of prior research before a new study is conducted.

The greater awareness in the medical community, and among the public, about the need for more efficient use of the limited resources in health science, puts EVBRES in the forefront of a global movement. Three years ago the Lancet published a series of articles pointing out the great risk of waste in health science. Concurrently, initiatives such as "All Trials", "The James Lind Alliance", "The REWARD Alliance", and "World Conferences of Research Integrity" have all been established to reduce waste; and the understanding and interest in the work done by "Cochrane" has never been greater.

However, none of these initiatives focus on the EBR approach when planning a new study and when placing new results in context. This is the main advance by EVBRES current initiatives.

1.2. OBJECTIVES

1.2.1. RESEARCH COORDINATION OBJECTIVES

1. To coordinate efforts to raise awareness and acceptance of the importance of the challenge and solution among all relevant stakeholders such as CHRs, patients, and CRSS.

2. To prepare guidance and teaching material to teach Early Career Investigators (ECI) and senior CHRs how to use specific EBR related working processes. Simultaneously improve the suggested working processes via feedback from the participants.

3. To catalyse collaboration between SR specialists, LIS, engineers, programmers, CHRs and patients to implement tools to increase the efficiency of updating and preparing SRs.

4. To create a common agreement about how to evaluate the implementation of the EBR approach in clinical research practice.

1.2.2. CAPACITY-BUILDING OBJECTIVES

1. To formulate implications of an EBR approach for representatives of CHRs, patients, and CRSSs in their respective areas. These implications should be published in open access journals when agreement is reached. The process is described in more detail in 3.1.1. The formulation will include a Delphi Study with 16-18 stakeholders from CHRs, patients and CRSSs. Working Group (WG) 1 will be responsible for this objective.

2. To improve the knowledge and skills of ECIs and senior CHRs so they use an EBR approach. In order to achieve this an online EBR handbook will be prepared. Four Training Schools (TS) lasting 3 days will be arranged in Europe and three times in International Partner Countries (IPC), especially aiming at LMIC. In the last two years the experience from the face to face TSs will be used to launch online TSs. The two EVBRES conferences (2019 and 2021), and the Short Term Scientific Missions (STSM) grants would be relevant tools to improve knowledge and skills. WG2 will be responsible for this objective.

3. To describe the state-of-the-art working processes and technologies used when preparing a SR, and to identify working processes and technologies that could be improved. This will be achieved by a Delphi study involving 16-18 stakeholders from CHRs, LIS, engineers, programmers and patients. WG3 will be responsible for this objective.

4. To establish a common understanding of how to monitor the implementation of the EBR approach in clinical research. EVBRES will arrange a Delphi study involving 16-18 stakeholders with specialty in SRs and meta-research, patients (2-3 representatives), and LIS. The process is described in more detail in 3.1.1, as WG4 is responsible for this objective.

1.3. PROGRESS BEYOND THE STATE-OF-THE-ART AND INNOVATION POTENTIAL

1.3.1. DESCRIPTION OF THE STATE-OF-THE-ART

State-of-the-art related to challenge 1: Very few stakeholders for clinical research (CHRs, and CRSS) are justifying or asking for a justification of new research, or placing new results in context by the use of a SR of prior similar trials.

In a paper from 2014, Clarke and colleagues identified 24 cumulative meta-analyses showing that numerous studies had been prepared and published for no good reason, because earlier studies had already shown an unambiguous effect. When publishing clinical research results CHRs only refer to a small fraction of prior research leading to what meta-research studies have shown to be redundant research. In addition, the studies evaluating the use of systematic reviews when planning new studies unequivocally show incomplete, poor, or more typically no use of systematic reviews. Further, studies evaluating whether CHRs use systematic reviews to place their findings in context shows that very few even attempt to do so.

‘The results of empirical investigations in research synthesis imply that research ethics committees are behaving unethically by endorsing new research which is unnecessary. The performance and accountability of research ethics committees would be improved if they required those proposing research to present systematic reviews of relevant previous research in support of their applications…’

wrote Savulescu, Chalmers and Blunt in 1996. However, experience from working with ethic committees indicates that this hasn't changed today.

A recent study of RFAs and their requirements looked at the United Kingdom, USA, Canada, Australia, Denmark, and Norway, and found only one large funding agency explicitly asked for a systematic review when the applicant is arguing for the importance of a new study.

Very few SMJs explicitly demands a SR to justify the need for a new study or a SR to place new results in context. Although the Lancet has explicitly demanded a search for earlier trials to justify the need for a new study or to place new results in context since 2005, very few other SMJs have done so.

State-of-the-art related to challenge 2: Very few CHRs have the skills or knowledge to justify new research, and to put new results in context by the use of a SR of prior similar trials.

Due to the lack of knowledge and skills to prepare systematic reviews, a huge amount of redundant clinical research has been published. This is particularly a problem in LMIC, as the capacity and funding is very poor when it comes to preparing or updating SRs.

State-of-the-art related to challenge 3: Too much time and efforts are needed to produce and publish a good quality systematic review.

A recent study indicated that it on average takes 67.5 weeks for five people to prepare one systematic review. A number of reasons have been described but the basic problem is the time consuming and manual work involved in identifying, selecting, and appraising relevant published clinical research papers, and extracting data from the included studies.

State-of-the-art related to challenge 4: Waste in clinical research may be due to lack of meta-research.

Meta-research is able to identify inappropriate working processes when planning, executing, publishing and implementing clinical research. Once identified, it would be possible to correct the improper working processes, and waste in clinical research can be reduced. Without evaluation of how CHRs are planning, executing, publishing and implementing clinical research and how CRSSs are supporting clinical research, the problems and inadequate working processes will never be identified, and waste will continue.

1.3.2. PROGRESS BEYOND THE STATE-OF-THE-ART

Progress beyond SoA in challenge 1: Very few stakeholders for clinical research (CHRs, and CRSS) are justifying or asking for justification of new research, or placing new results in context by the use of a SR of prior similar trials.

This EVBRES Action will first raise awareness of the problem. Before a problem can be solved, it is important to acknowledge its existence. Thus, the immediate benefits (within the time frame scheduled) will be to identify and focus on issues related to the lack of clinical research being evidence-based. It is the intention of EVBRES to bring together representatives from the most important stakeholders in order to discuss this issue, to identify conducive and restraining factors affecting the solution, and finally to formulate implications of an EBR approach for each of the stakeholders. Primarily due to the publications of meta-research emphasizing the problem, guidance papers, TSs, and conferences on how to deal with the problem, the medium-term benefits will be a global awareness of not only the problem, but also the suggested solutions. In the longer term (more than 5 to 10 years), if the solutions have been promoted and incorporated into the execution of clinical research, fewer redundant and unnecessary studies will be conducted.

As a result of EVBRES, RECs will include the EBR approach into “Code of Conduct” documents, as part of the “Informed Consent” standards, and request that applicants have used a SR to justify the need for a new study. Likewise RFAs will demand that applicants justify the need for a new study with a SR of similar prior studies, and the Editors of SMJs will go further to also ask that the new results in any submitted paper are placed in context by the help of a SR of earlier similar trials.

Progress beyond SoA in challenge 2: Very few CHRs have the skills or knowledge to justify new research, or to put new results in context by the use of a SR of prior similar trials.

In the short-term, the immediate effect of EVBRES will be an increased knowledge and skills of EBR among ECIs and senior CHRs acquired through the TSs, handbook, EVBRES conferences and EVBRES publications. Not only will the courses help the participants, but EVBRES will get valuable experience and be able to create online courses that will reach out globally. A specific focus on identifying experts in SRs and make online courses available is very important in LMIC. In the longer term being evidence-based while performing clinical research will be just as natural as being evidence-based in clinical practice.

Progress beyond SoA in challenge 3: Too much time and efforts are needed to produce and publish a good quality systematic review.

In the short-term EVBRES will contribute to a higher interest in improving the efficient production, updating and accessibility of SRs. By a systematic description of existing work processes, the immediate possible improvements can be identified and the existing working processes can be enhanced. By involving specialist stakeholders like specialists in SRs, LIS, programmers, engineers and patients in the design of technological solutions it is possible to automate the first selection of identified studies in a literature search, the first selection of data, the first part of critical appraisal and so on to save valuable time. So far, it is not possible to state how much time will be saved, but with EVBRES's involvement, it will be possible to define where to focus automation and to calculate the time saved. Involving engineers and programmers may in the long-term lead to the improvement of existing or development of new technologies.

Progress beyond SoA in challenge 4: Waste in clinical research may be due to lack of meta-research.

Meta-research would be able to evaluate the implementation of an EBR approach in clinical research. Meta-research may also detect changes in requirements from CRSS. As there is no agreed way to evaluate this at present, and no common outcomes identified, it is not possible for EVBRES fully to evaluate the implementation of an EBR approach both in clinical practice and among other related stakeholders. Thus the accomplishment by EVBRES will be the identification of how best to perform meta-research to monitor whether CHRs and the other stakeholders are performing as hoped for or not, and to implement regular monitoring of this.

1.3.3. INNOVATION IN TACKLING THE CHALLENGE

The EBR approach is innovative in the way CHRs will use modern technology to systematically identify and synthesise earlier research when planning and/or interpreting new research. However, as this is a project focusing on process innovation, EVBRES also deals with incentives for CHRs to perform EBR. These incentives includes requirements from other stakeholders important for the scientific process such as CRSS, and expectations from patients, research colleagues, research regulators and policy makers. The working processes developed to promote EBR should not present obstacles, but rather ways to improve CHRs ethical standards and knowledge within their respective fields.

More specifically, the innovation in tackling the challenges will be: (a) changes in the requirements from the CRSS; (b) working processes to find, critically appraise and use systematic reviews when planning a new study and when placing new results in context; and (c) working processes to update or prepare systematic reviews. With a long term perspective, the innovation would be (d) technologies such as automation of the screening process of literature search results, better indexing of literature in databases, identification of sources, quality control and other means to achieve a more efficient production and updating of systematic reviews. In addition, (e) standardised methods and outcomes to evaluate how CHRs and related stakeholders implement the EBR approach.

1.4. ADDED VALUE OF NETWORKING

1.4.1. IN RELATION TO THE CHALLENGE

Networking will increase the awareness of the problem due to the involvement of an international group, and due to the dissemination and promotion of the EBR approach through TSs, EVBRES conferences and participation in other international conferences. Through this increased awareness, an acknowledgement of both the challenge and the solution will be the next step. By the use of social media in relation to EVBRES's activities and production, the awareness and acknowledgement will increase faster, and a more in-depth discussion and development of the solutions will be one of the important outcomes.

By networking the solutions will be developed and strengthening by the many different perspectives and be based on experiences from different contexts. By this plurality the handbook, the TSs, the Delphi studies, and the EBR Conferences will deal with the most important questions, and the learning material will be of higher quality and more relevant. As the training is of higher quality and much more relevant it will last longer and have a bigger impact as it will be used more in daily research practice. When it comes to the realization of the suggested solutions there is not "one way only", but some principles that should be developed to the benefit for a higher percentage of the participants or users of TSs, learning material and alike. In addition, the EBR approach may reach out to many more due to an international network.

By networking LMIC will be included in the process as their need for an evidence-based research approach in clinical research is even higher than in High Income Countries (HIC).

A SR is and should be prepared with no language restrictions and the working process for a SR should thus also be the same all over the world. The improvement of the working processes and enhancement and development of technologies to produce or update SRs should therefore be internationally based. It is important that this kind of development activity is done with full awareness of other individuals and groups related initiatives and knowledge. There is, so to speak, no need to "invent the wheel" several places simultaneously.

Meta-research is an important, if not the most important prerequisite to improve quality of practice. The decisions on how to measure the implementation of an EBR approach among CHRs and related stakeholders needs to be taken in an international forum. Firstly, it is better to have several perspectives, as an international group will ensure. Secondly, the selected methods and outcomes will have higher status based upon an international group, and thus the results will have higher impact.

1.4.2. IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

As already mentioned, the Lancet published a series of articles, describing possible reasons for waste in clinical research. EVBRES is directly related to the challenges described in this series, and more specifically to the following statements: (a) more than 50% studies designed without reference to systematic reviews of existing evidence, and (b) most new research is not interpreted in the context of systematic assessment of other relevant evidence. Thus, EVBRES can be regarded as a part of the movement to reduce waste in clinical research, since EVBRES is the only group dealing with the mentioned challenges.

Besides EVBRES, a number of different organizations are dealing with other challenges mentioned in the Lancet series (See table).

Phases of Research Production	Some Interested Groups
1. Questions & priorities	James Lind Alliance (JLA), Cochrane, EVBRES
2. Design, conduct and analysis	Equator-Network (SPIRIT), COMET & OMERACT, EVBRES
3. Regulation and management	Trial Forge
4. Accessibility	AllTrials, ClinicalTrials.Gov, International Clinical Trials Registry Platform (ICTRP)
5. Reporting	Equator-Network (CONSORT, ARRIVE, PRISMA, and many other), EVBRES

The "James Lind Alliance" is involved in prioritizing research questions based upon the input from patients. Even though they are using SRs in their prioritization of research questions, they are not

promoting nor developing working processes for CHRs to perform EBR, nor are they involved in monitoring the implementation of an EBR approach among CHRs and related stakeholders. Cochrane was established in 1993 to promote evidence-informed health decision-making by producing high quality, relevant, accessible systematic reviews and other synthesized research evidence. However, their focus is to produce and disseminate SR for the use in clinical practice, and (for the moment) not on how the research they are using in their SR is produced. The Equator-network is an umbrella organization for the different reporting guidelines. The reporting guideline for clinical studies (CONSORT) states "Ideally, the introduction should include a reference to a systematic review of previous similar trials or a note of the absence of such trials." However, even though CONSORT states the same principle as EVBRES they are not focusing on how to do it, or in developing working processes or technologies for updating or preparing SRs. The COMET (Core Outcome Measures in Effectiveness Trials) initiative brings together people interested in the development and application of agreed standardised sets of outcomes to be used in clinical research. Thus they are focusing on how to design the study, and in that way are related to EVBRES's point that a new study should be designed based upon an updated SR, but COMET is not focusing on how to do it, or developing working processes or technologies for fulfilling this or to update or prepare SRs. OMERACT has the same purpose but solely within the medical speciality of Rheumatology, thus has the same relation to EVBRES as COMET. Trial Forge will make trials more efficient by looking for marginal gains across all trial processes, from research question to implementation into routine care. While Trial Forge is aiming to make the production of clinical trials more efficient, EVBRES aims to diminish redundant clinical trials and make the production and updating of SR more efficient. AllTrials calls for all past and present clinical trials to be registered and their full methods and summary results reported. However, their focus is on promoting the publication of all clinical trials, not on finding and using those having been published. Even though the problems are related because both not finding or not publishing all trials may lead to redundant studies, the problem and thus the solution is different.

None of the above mentioned groups deal with the same challenge as EVBRES, thus EVBRES is needed. However, knowing the work of each other, and collaborating when possible will make sure that none of the groups is doing the same work at the same time, and will increase the effect of both groups initiatives.

2. IMPACT

2.1. EXPECTED IMPACT

2.1.1. SHORT-TERM AND LONG-TERM SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS

The short-term scientific impact (within the time frame of EVBRES) is a better understanding and acknowledgment of how to avoid an idiosyncratic, preference-based and strategic driven choice of citations in clinical research protocols and reports by CHRs. Further, the short-term scientific impact will be an acknowledgement of the need to use an EBR approach for CRSS when evaluating the importance of submitted applications or clinical trial protocols or reports. Finally, the short-term scientific impact may be an explicit understanding by LIS of their important role in supporting the production and updating of SR.

In the long-term (within 5 to 10 years) the scientific impact is a public and clearly stated expectation from patients and the society as a whole that no new clinical trials should be performed without prior systematic review of existing evidence. At the same time, RECs will have included an EBR approach in their "*Code of Conduct*" documents, in their requirements for achieving ethical approval, and as part of their standard "*informed consent*" documents. The RFAs will include an EBR approach in their requirements to achieve financial support, and they may use the EBR approach to formulate their own funding agenda. Likewise, SMJs will expect that a manuscript for a protocol include documentation of the use of a SR when the authors try to justify the need for the new study. In addition, a manuscript reporting the results of the clinical trial includes both the SR as part of the Introduction and as part of placing the new results in context in the Discussion. All these improvements will lead to a greater demand for knowledge and skills by the CHRs for how to perform EBR, because it will become increasingly more and more difficult to recruit patients, get ethical approval, funding or be published without having used a SR to justify the new study and place new results in context. For LIS, the impact of EVBRES will in the long-term mean that they have achieved a clear and unique role in the preparation

and updating of SRs, and – not at least – a pivotal role in performing research on how to search for literature and related topics.

The short-term and long-term socioeconomic impact will be preparation and publication of fewer but at the same time necessary clinical trials. A simple calculation may illustrate the economic impact of EVBRES. In a study from 2005, Fergusson and colleagues showed that at least 4,500 patients have participated in unnecessary and redundant clinical trials. With less patients participating in redundant research, less adverse events and even deaths will occur. In a study from 2003 it was estimated that one test patient in a clinical trial may cost €5.300, thus the amount of waste related alone to the research question examined in the study from 2005, would be €23,850,000. This is a very conservative estimate in all parts of the calculation. The extra costs in preparing a SR when planning a new study is minimal in comparison. A typical SR may cost one or maybe two man-years, i.e. €230,000. Thus, the extra cost of preparing a SR is less than 0.01% of the expense of performing redundant studies.

There is no short-term technological impact, but in the long-term, the involvement of programmers, engineers, and LIS together with CHRs, patients, and specialists in SR, will lead to the development of technologies able to speed up the time for preparing SRs. It could be expected that an update or development of new technologies dealing with literature searches, screening of search results, first raw evaluation of internal validity of identified studies, extraction of data from included studies, and analyses would have been further developed and in use in the long-term.

2.2. MEASURES TO MAXIMISE IMPACT

2.2.1. PLAN FOR INVOLVING THE MOST RELEVANT STAKEHOLDERS

The key stakeholders participating in all aspects of EVBRES will be CHRs and patients. The work to raise the awareness, acknowledgement and a change in procedures and requirements will in addition involve the CRSS (WG1). The work to improve knowledge and skills among ECI, CHRs, will involve specialists in SR and LIS (Expert stakeholders) in addition to key stakeholders (WG2). The work to achieve a more efficient production and updating of SR will in addition to key stakeholders involve specialists in SR, LIS, Programmers and Engineers (Expert stakeholders) (WG3). Finally, the work initiated to monitor how CHRs and CRSS implement an EBR approach to clinical research and related supporting systems, will in addition to the key stakeholders involve specialists in SR and Meta-research and LIS (Expert stakeholders) (WG4).

2.2.2. DISSEMINATION AND/OR EXPLOITATION PLAN

The COST EVBRES Action's overall dissemination and exploitation plan is to involve representatives from the different stakeholder groups in EVBRES in order to make sure a more relevant and understandable message from EVBRES to the target groups. Specifically the target groups are (1) CHRs (both ECI and seniors), (2) Patients (including patients receiving treatment, patients participating in clinical trials, and patients participating in clinical research as co-researchers), (3) CRSS, (4) Policy makers, (5) The Industry developing and marketing pharmaceutical, surgical and other interventions to the benefit of the patients, and society as a whole.

Even though dissemination and exploitation is the focus for WG1 and WG2, all four WGs will be part of the dissemination plan. This means that all WGs must use the webpage, and social media accounts for EVBRES on a regularly basis, i.e. all WG must post something on all channels on a regular basis. In addition, they should post a message every time something important for the WG has happened. Further, all WGs will publish scientific papers related to the goal of the WG, and based upon a close collaboration with both the CRSS and Expert stakeholders involved in the WG.

Specifically, WG1 has the overall responsibility for the Dissemination and Exploitation Plan. That means WG1 can help and assist the other WGs deal with this. Further, WG1 involves the CRSS and patients in three Delphi studies resulting in a paper from each presenting the implications for each stakeholder group of the EBR approach. The conferences identified for promoting EVBRES include central conferences for clinical research such as Cochrane Colloquium, Evidence-based Health Care, Evidence Live, COMET, conferences for patients, for members of REC, for RFA, Congress on Peer Review and Scientific Publication, and more generic conferences such as World Conference of Research Integrity. EVBRES expect to participate in at least 5-6 of these international conferences each year. Finally WG1

will, together with EVBRES Management Committee (MC) Core group identify relevant messages to submit to the media including newspapers, radio and television.

WG2 will focus on teaching ECIs and senior CHRs how to perform EBR. The dissemination activities will thus be TSs both face-to-face and later online, EVBRES's own conference, and an online handbook. The TSs will be held in Europe each year but also in international partner countries. It is expected that 25 to 30 people will attend each TS, and in total seven workshops are planned. Parallel to this WG2 will follow the same procedure as WG1 to develop EBR working processes, and publish guidance ("how-to") papers about these methods. During 2018 and 2019 the Handbook will be prepared, and it will be published in 2020. Finally, EVBRES will arrange two international EBR Conferences in Europe (2019 and 2021). About 120 people are expected to participate in 2019 and 200 in 2021.

WG3 focus on how to improve the production, update and accessibility of SRs. The work will eventually end with 2 or 3 papers presenting the-state-of-the-art regarding existing methods of the efficient production of SRs, and promising developments that could further increase the efficiency of the production, updating and accessibility of SRs. The results will also be part of the Handbook and TSs.

WG4 will focus on how to monitor the implementation of an EBR approach among CHRs, and CRSS. The work of WG4 will end up with a series of publications presenting how to monitor the implementation, and the results of the monitoring.

2.3. POTENTIAL FOR INNOVATION VERSUS RISK LEVEL

2.3.1. POTENTIAL FOR SCIENTIFIC, TECHNOLOGICAL AND/OR SOCIOECONOMIC INNOVATION BREAKTHROUGHS

EVBRES has the potential to introduce a fundamental new way to handle and use citations when planning new studies and when placing new results in context. All studies examining how CHRs choose references show that the choice to day is idiosyncratic, and based upon preferences and strategic considerations. Several studies have for example showed that positive, supportive and significant studies are significantly more often referred to than those that are negative, critical and non-significant.

As mentioned above (2.1.1) EVBRES can have a socioeconomic impact since fewer patients will be exposed to treatment already shown to be ineffective or unnecessary placebo treatment when participating in trials, and unnecessary use of resources can be avoided. Thus, the socioeconomic breakthrough will be a new way to approve new clinical trials from RECs and RFAs. "The performance and accountability of research ethics committees would be improved if they required those proposing research to present systematic reviews of relevant previous research in support of their applications, and to summarise the results of these reviews in the information prepared for potential participants" as Savulescu and co-authors put it in 1996. In addition, the RFAs will have an effective tool to select the relevant and necessary clinical trials to support.

In terms of technological breakthroughs, EVBRES will by involving Programmers, Engineers, LIS and specialists in SRs act as catalyst for development of automation software to increase an efficient production and update of SRs.

3. IMPLEMENTATION

3.1. DESCRIPTION OF THE WORK PLAN

3.1.1. DESCRIPTION OF WORKING GROUPS

Working Group #1: The Dissemination and Exploitation Working Group

Description: As the aim of WG1 is dissemination and exploitation of the EBR approach, WG1 involves CHRs and patients, and the CRSS. By dissemination meetings, use of scientific and public media, social media, a Delphi study for each stakeholder group (i.e. 3 Delphi studies) and publications describing the implications of an EBR approach for each stakeholder, the output and results of WG1 will be possible.

Each Delphi study includes between 12 to 18 participants always including two CHRs representatives and two patient representatives in each group, and consists of five stages. Stage 1: A SR of all published studies evaluating how CHRs, RECs, RFAs or SMJs are performing when it comes to using or asking for a SR when justifying a new study and when placing new results in context. In stage 2 each group meets at a workshop to discuss the results from the SR. In stage 3 a multi-round Delphi process (no more than 3 rounds) will be performed in order to identify areas needed to be adjusted in accordance to the EBR approach. In stage 4 a workshop for all participants will finalize the Delphi study. In stage 5 the implications of EBR for each group will be published. The representatives will be selected from COST Action full member countries by contacting common organizations in each country for each group.

Output(s): The EBR approach will be a topic on international scientific conferences for CHRs (for example WCRI, EBHC, and others), in publications in scientific journals (Articles, Letters to editor, Essays and the like). Further, the EBR approach will be placed on the agenda for meetings within RECs, RFAs and SMJs.

The awareness among patients and patient organizations will be noticeable as the EBR approach will be on their agenda for conferences, meetings, their websites and in their social media releases. Based upon earlier experience, a current estimate would be that 1/1,000/quarter will respond to the call for implementing the EBR approach in clinical research and CRSS. The increased activity on several social media, at conferences, advertising of TSs, publications (an EBR related paper reached an Altmetric score of 175 within 1 week of publication in 2016), it could be expected that EVBRES will reach out to (i.e. someone reading and considering EBR) 100/1,000/quarter. Thus up to 400 clinical ECIs, senior CHRs, and members of CRSSs, will be affected the first year of EVBRES. Add to the mentioned activities the newly involved commitment 800 may be reached the second year, 1,600 the third year, and more than 3,000 the fourth year.

Milestones/deliverables:

1. Amendments to the RECs documents (“Code of Conduct”, “Informed Consent”)
2. Adjustments of RECs requirements: all new clinical trials should be justified by a SR
3. Adjustments of RFAs requirements: all new clinical trials should be justified by a SR
4. Adjustments of SMJs formats for how to include results from a SR in the Introduction
5. Adjustments of SMJs formats for how to place new results in context by a SR in the Discussion
6. Patient organizations and groups demand an EBR approach when new clinical research is prepared
7. More than 3,000 CHRs and members of CRSS have been reached (at least 1/3 from LMIC)

Working Group 2: Development and teaching of methods to be evidence-based doing clinical research.

Description: The solution to the challenge is the use of SRs before initiating a new study and when placing new results in context. However, a number of issues may impede this solution. The goal of WG2 is to identify the concrete challenges for CHRs to find and critically appraise (for currency and quality), and/or update an existing SR or prepare a new SR regarding their clinical research question. Next, it is the goal of WG2 to teach clinical ECIs and senior CHRs how to overcome these obstacles. Both can be done in the same process. The first three TSs will include both training in how to implement EBR, and identification of obstacles, difficulties, and lack of knowledge by the use of Delphi studies. Up to three Delphi studies, with 12-18 participants, including two patient representatives will be performed. In stage 1, the preparation of a “Scoping Review” (Scoping reviews are an approach to summarizing the breadth and nature of research activity in a field) will identify published working processes of how to use a SR in the Introduction and in the Discussion (placing new results in context). It will be a Scoping Review not a SR, as the aim is to identify methods not evaluate results. At stage 2, the participants (20-25 in total for each TS) the results of the SR will be discussed in a session where all teachers, patient representatives and TS participants take part. In stage 3 all participants, teachers, and patient representatives participate in a Delphi process aiming at identifying the best working processes to implement an EBR approach (max 3 rounds). In stage 4 a selection of participants in the TS, patient representatives and teachers finalize the Delphi and in stage 5 a number of “Guidance” papers are selected. As EVBRES is planning seven TSs, the first 3 of these will be part of this combined process. The planned publications from each TS will be combined before papers are written and submitted. The planned online versions of the

TSs will be launched in the last 1 or 2 years of EVBRES, in order to gain as much knowledge from Delphi studies as possible. WG2 is also responsible for planning and execution of EVBRES's Conferences in 2019 and 2021, as well as the Handbook.

Output(s): The most important output is interest from clinical ECIs and senior CHRs to participate in the TSs and the planned Delphi study (A minimum number of participants will be 12 for each TS). If enough interest is found, it would be possible to accomplish all seven planned TSs, and thus the 3 planned Delphi studies. TSs are planned to be held each year in Europe, and in international partner countries.

The first EVBRES Conference in EBR is expected to have 120 participants in 2019 and 200 in 2021.

The "*EBR Handbook for Clinical Research*" will be freely available online (approximately 250 pages). Very specific and concrete working processes related to the EBR and the clinical research context will be available to all ECIs and senior CHRs through the TSs, the publications in scientific journals, the Handbook, EVBRES website and indirectly by information in the social media.

Milestones/deliverables:

1. Published specific working processes for applying the EBR approach to clinical research
2. An online handbook presenting the background and the working processes for applying the EBR approach to clinical research
3. More than 100 ECIs and senior CHRs have completed the TSs
4. Two EVBRES conferences has been accomplished (2019 and 2021)

Working Group #3: Improve Efficiency in Producing and Updating Systematic Reviews

Description: One important reason for clinical research not being evidence-based, is the fund demanding and time consuming efforts needed to prepare a SR. Thus, it seems untrustworthy to argue that all CHRs should find, update or prepare SRs while it is so effortful to prepare one. The aim of WG3 is to identify promising areas where it seems possible to improve the efficient production and update of SRs. This is done by the use of a Delphi study process. The Delphi study includes between 12-18 participants (specialists in SRs, LIS, Programmers, Engineers), including two CHRs representatives and two patient representatives. In stage 1 a Scoping Review is prepared in order to identify already published suggestions for how to prepare SRs in a more efficient way. In stage 2 a face to face meeting between all participants is arranged in order to discuss the results from the Scoping Review. In stage 3 all participants will take part in a Delphi process to identify more suggestions for how to improve the production of SRs and to suggest a prioritization among the suggestions. In stage 4 the Delphi study will be finalized and the most relevant working processes to further develop tools and software to improve production and updating of SRs will be identified and prioritized. In stage 5 the results from stage 4 will be published in one or two papers.

Output(s): Awareness of the need to increase the efficiency when producing and updating systematic reviews. EVBRES will participate in the identification and description of possible solutions and work as a catalyst to improve an efficient production of systematic reviews.

Milestones/deliverables:

1. Identification and prioritization of working processes and technologies to achieve a more efficient updating and production of SRs
2. Closer relationship between stakeholders of importance for an efficient updating and production of SRs

Working Group #4: The Meta-Research Group

Description: The concept of EBR was developed as an answer to results from several meta-research studies. As EVBRES promotes the concept of EBR, it is important to know and understand the state-of- art, or in other words: to monitor the implementation of an EBR approach among CHRs and CRSS. This is of great importance for all the activities of EVBRES, as it will determine the focus of the different working groups, and the focus of EVBRES as a whole. The aim for WG4 is thus to identify ways to evaluate clinical research practice and initiate the implementation of these

methods. This is done by the use of a Delphi study. The Delphi study will include 12-18 participants (specialists in SRs, LIS, plus two CHRs representatives and two patient representatives). In stage 1 a Scoping Review will identify existing meta-research methods and outcomes to evaluate if CHRs have implemented the EBR approach or not. In stage 2 participants meet face to face to discuss the results of the Scoping Review. In stage 3 all participants take part in a Delphi process to prioritize the identified methods and outcomes, add new suggestions for methods and outcomes, and suggest a standard procedure for monitoring the implementation of EBR in clinical research. In stage 4 they all meets face to face to finalize the Delphi study, to agree upon a monitoring plan and to prepare for the publication of the identified methods and outcomes. In addition, the group will execute the agreed upon monitoring plan.

Output(s): The most important output is a standard plan to monitor the implementation of EBR in clinical research. That plan involves how to evaluate, what kind of trials to evaluate, and which outcome to use. In addition, the frequency of the monitoring will be decided. Based upon these principles at least 4 or 5 different publications will be presented at different international conferences before publication, and on the EVBRES website.

Milestones/deliverables:

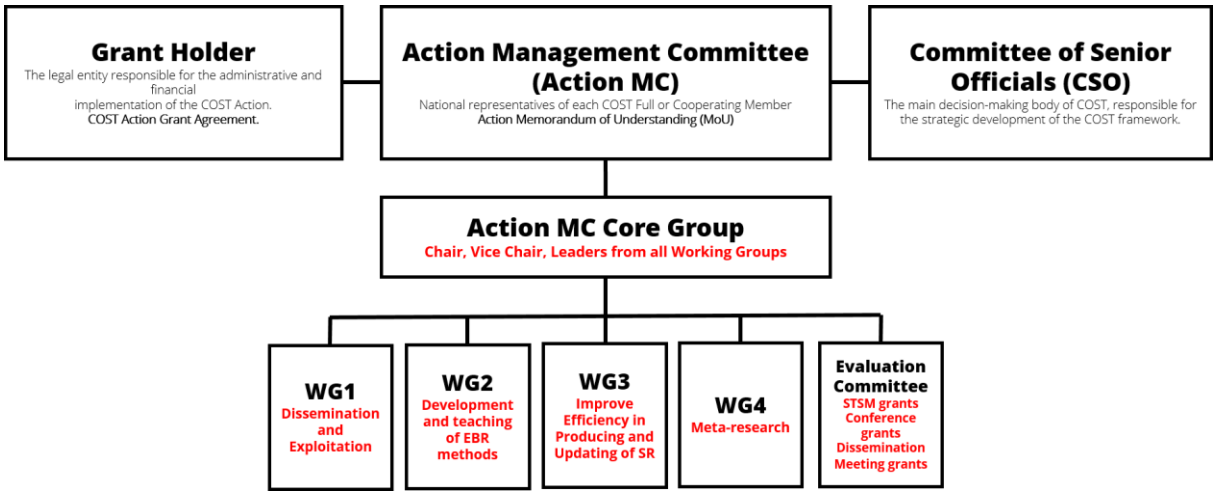
1. A list of monitoring methods and outcomes of relevance for monitoring the implementation of EBR in clinical research and among CRSSs
2. A standard monitoring plan is decided upon to evaluate the implementation of an EBR approach in clinical health research and among CRSSs.
3. Publishing results from the execution of the monitoring plan

3.1.2. GANTT DIAGRAM

3.1.4. RISK AND CONTINGENCY PLANS

Risk identification	Likelihood	Contingency plan / mitigation measure
Partners unable to fulfil their commitments	Highly likely to happen for some of the partners	○ The number and competences of participants involved in the consortium makes it possible to let someone else take over, in case someone is not able to fulfil their commitment.
Lack of coordination between interdependent activities may cause delay	Less likely to happen	○ Both EVBRES MC Core Group and the four WG leaders will be responsible for supervising work progress, and when necessary making adjustments.
May be difficult for representatives from CRSS to find time to participate	Highly likely to happen	○ The suggested Delphi studies in WG1 are meant as means to involve these stakeholders as much as possible, without demanding too much time on their behalf. ○ A useful outcome of the Delphi study does not need representatives from all partner countries, thus if someone is prevented from participating it would be possible to identify someone else from other partner countries. ○ Some of the partners are already part of CRSS or related hereto.
Too few enrolled in the Training Schools	Less likely to happen	○ If less than eight people sign up for the first three TSs, the course will be cancelled and the next course will be the next announced. Those having signed up will defer to next course. ○ For the last four TSs, an online solution will implemented instead.
Delayed recruitment of stakeholders related to efficient production and update of SR	Less likely to happen, as many of these stakeholders is already identified	○ The outcome of the Delphi study does not need representatives from all partner countries, thus if someone is prevented from participating it would be possible to identify someone else from other partner countries.
If the Meta-research Delphi study is delayed	Less likely to happen	○ The preparation of meta-research study will then be based upon already existing/used study methods and outcomes.
If too few (less than 50) enrol for the EVBRES conference	Unlikely to happen	○ The conference will be altered into a less resource demanding workshop
Conference Grants / Dissemination meetings	Unlikely to happen	○ The conference grants/dissemination meetings will only be distributed if there are applicants. ○ The STSM will only be distributed if there's any ECIs at TSs applying for them.

3.2. MANAGEMENT STRUCTURES AND PROCEDURES



EVBRES is organized with an Action MC Core Group as the executive organ for EVBRES supported by an annual meeting of the Action MC. The Action MC Core Group have two face-to-face annual meetings in January and August, and a monthly online meeting (except for July and December). The Action MC meets every year in January, face to face.

Action MC appoints an Evaluation Committee responsible for the STSM grants, the Conference grants and Dissemination Meeting grants. Each of the WGs have a leader appointed by the Action MC. Each WG and the Evaluation Committee have face-to-face meetings in January and August, and the WGs a monthly online meeting (except from July and December). In WG1 one person will be appointed as responsible for the 3 Delphi Studies (including workshops). In WG2 one person will be appointed as responsible for the TSs (including the Delphi Studies), one responsible for EVBRES Conference, and one responsible for the EBR Handbook. In WG3 and WG4 the leader of each is also responsible for the outputs of the WGs.

January and August is planned to be when EVBRES members are meeting, when the TSs and Action Conference will be held, and when the face-to-face meetings in the Delphi studies will take place.

EVBRES will follow the management structure and procedure given by the document COST 132/14 REV 2 Rules for Participation in and Implementation of COST Activities.

Patients represent a unique stakeholder position when it comes to the concept of EBR. First EVBRES needs the perspective of the patient that ultimately will receive the tested treatment in the new clinical studies. Secondly, EVBRES needs the perspective of the patients invited to participate in a clinical trial. Finally, EVBRES needs the perspective from patients invited to participate as co-researcher in clinical research. Thus, EVBRES will include patient representative in all Delphi Studies, in the planning of the TSs, EVBRES Conference and the handbook.

3.3. NETWORK AS A WHOLE

The EVBRES–consortium have today involved more than 130 different stakeholders including patient representatives covering North America, South America, Africa, Asia, Australia, New Zealand, and Europe. The EVBRES Action involves Europe including inclusiveness target countries, near neighbouring countries and international partner countries to build a strong European and Global cooperation, since the lack of an EBR approach clearly is a worldwide challenge.

The aim of this network is to increase the use of SRs before engaging in new clinical research and when placing new results in context. This involves primarily the involved stakeholders: clinical health researchers, patients, members of research ethic committees, research funding agencies, editors and reviewers of scientific medical journals, librarian and information specialists and specialists in SR. Thus,

the inclusion of representatives of all stakeholders is not only crucial to the success of the network, but also involving all of these stakeholders can create a maximum synergy.

The described organization, suggested network tools, and the intentional choice of processes inviting everyone to fully participate and to be heard, no matter who you are or where you are from, will help in achieving EVBRES's goals.