

Brussels, 4 June 2019

COST 025/19

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action “Novel tools for test evaluation and disease prevalence estimation” (HARMONY) CA18208**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action Novel tools for test evaluation and disease prevalence estimation approved by the Committee of Senior Officials through written procedure on 4 June 2019.



MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA18208

NOVEL TOOLS FOR TEST EVALUATION AND DISEASE PREVALENCE ESTIMATION (HARMONY)

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 apply Bayesian latent class models (BLCMs) in the evaluation of diagnostic tests and the true prevalence estimation. Currently the main challenge of applying BLCMs lies in the lack of adequate communication, knowledge transfer and collaboration between experts in the field and researchers working in statistics, epidemiology, diagnostics and population health. 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 120 million in 2018.

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

Epidemiological studies assessing disease prevalence are critically important to both the identification and control of pathogens in humans and animals (including zoonosis and food borne outbreaks). However, countries typically collect data in a way that is best suited for their specific needs, and non-standardized sampling strategies and diagnostic methods produce prevalence estimates that cannot be directly compared. Hence, the need for harmonization, which has been often highlighted in reports of relevant EU institutions, like the ECDC and EFSA. Despite the availability of appropriate statistical methods – Bayesian Latent Class Models (BLCMs) – that adjust for the imperfect accuracy of the diagnostic process and produce comparable prevalence estimates, the number of research studies and scientific reports that use them is small compared to the number of instances that use of such methods would have been optimal. The objective of this proposal is to coordinate and promote the implementation of BLCMs through networking and knowledge transfer between BLCM experts and researchers working in statistics, epidemiology, diagnostics and population health. Specifically, we will (a) increase the visibility and collaboration of BLCM researchers, (b) promote stakeholder engagement, (c) provide training and networking opportunities for ECIs and ITC researchers, (d) create separate training opportunities for policy makers and stakeholders, (e) establish a free online BLCMs repository, (f) set up an International society for BLCMs and (g) organize the first international conference of this society. The strongest asset of this proposal is its strong interdisciplinary nature and broad network of proposers.

<p>Areas of Expertise Relevant for the Action</p> <ul style="list-style-type: none"> ● Health Sciences: Epidemiology ● Clinical medicine: Applied mathematics, statistics, non-computational modeling ● Veterinary science: Databases, data mining, data curation, computational modelling ● Basic medicine: Applied mathematics, statistics, non-computational modeling 	<p>Keywords</p> <ul style="list-style-type: none"> ● Bayesian Analysis ● Diagnostic Accuracy ● True prevalence ● Latent Class Models ● Disease freedom
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Specific Objectives

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

Research Coordination

- Promote stakeholder engagement and foster collaboration with researchers in the field. Stakeholders and policy makers at the international/national/regional level will be involved from the beginning of the project and help to identify current needs that must be addressed.
- Establish a free online repository of existing BLCMs that will be continually updated with new developments in the field. These will be easily accessible and facilitate researcher access to model code and example data with step by step explanations of how to implement and interpret these models.
- Implement an online interactive application for the use of BLCMs for prevalence estimation and the evaluation of diagnostic tests in the absence of a gold standard.
- Create a series of open-access online training materials for researchers (especially ECIs and researchers from COST inclusiveness target countries) interested in BLCMs.
- Issue explicit guidelines for the robust and harmonized application of BLCMs for the evaluation of diagnostic tests, prevalence estimation and establishing freedom from disease.
- Establish an international society for the application of BLCMs in life sciences in order to promote collaboration of scientists working in the field and the harmonized reporting of relevant research.

Capacity Building

- Increase the visibility and integration of researchers in a variety of disciplines relevant to evaluation of

diagnostics and true prevalence estimation using BLCM. It will promote communication of ideas, fostering new strongly interdisciplinary collaborations and leading to joint funding proposal applications.

- Provide training and networking opportunities for ECIs, as well as researchers from ITCs and promote transfer of skills with particular emphasis on ECIs in ITCs as well as balance in terms of gender and geographic distribution of participants.
- Create separate training opportunities specifically for policy makers and stakeholders with the aim to update and familiarize them with current and trending methods in the evaluation of diagnostic tests and their use in the harmonization of disease occurrence measurement.
- Involve ITCs in leadership positions, support the work of ITCs in the field and seek to strengthen gender balance by involving of female scientists in future research.
- Organize the first international conference of the BLCM society and initiate the process of communicating on a biennial basis.

1 S&T EXCELLENCE

1.1 SOUNDNESS OF THE CHALLENGE

1.1.1 DESCRIPTION OF THE STATE-OF-THE-ART

Epidemiological studies assessing disease prevalence are critically important to both identification of new or re-emerging pathogens and control of endemic pathogens in humans and animals (including zoonosis and food borne outbreaks), and are therefore ubiquitous across COST countries, Near Neighbouring Countries (NNCs), International Partner Countries (IPCs) and worldwide. Interpretation of the resulting data and comparison between studies is often challenging due to differences in (i) the sampling scheme and (ii) diagnostic methods that are used, which often are of varying accuracy. An additional key challenge lies in the definition of ‘disease’ that is targeted in each case (i.e. the stage of infection including or discounting any latent period) which often differs across studies, resulting in different reported diagnostic sensitivity (Se) and specificity (Sp) for the same diagnostic method. Countries typically collect data in a way that is best suited for their specific needs, and non-standardised sampling strategies and diagnostic methods produce prevalence estimates that cannot be directly compared. Hence, the need for harmonization in terms of monitoring and reporting disease occurrence has been often highlighted in reports of relevant EU institutions like the ECDC and EFSA. Harmonization of reporting will eventually improve comparability between the analytical findings derived from different studies. This goal is in line with the current EU policy on disease surveillance and control efforts. Specifically, because of the variable standards among countries even within the EU – especially for the case of non-regulated diseases – emphasis has been put on an output-based evaluation of disease control programs: i.e. the output-based standards focus on the outcome that must be achieved irrespective of the methods used. It is therefore clear that harmonization of the reported disease rates and prevalence estimates is necessary for their direct comparison between different countries and/or regions.

A prerequisite for harmonization is adjustment for the Se and Sp of the diagnostic tests, which can vary depending on the source population (i.e. country and/or regions) and sampling strategy. This means that existing diagnostic Se and Sp estimates may not be relevant to the population under consideration. In addition, for several infections with a long latent infection period (e.g. tuberculosis) the absence of a perfect reference test hampers the evaluation of new or existing diagnostic tests and often results in biased estimates of true disease prevalence. It is common for Se to be lower for individuals that are still in the early infection stages of infection, and efforts to improve this Se invariably leads to reduced Sp. Reported prevalence estimates must therefore be adjusted for the imperfect Se and Sp of the diagnostic process, which should both be specific to the population under consideration and account for all relevant latent infection stages.

Diagnostic tests should therefore be evaluated in each population (e.g. country, region, hospital, herd/flock) and for each targeted condition (e.g. infected, infectious, latently infected). Proper evaluation of tests using simple gold-standard methods requires data that are extremely expensive to obtain and may not even be feasible for infections with a long latent period. When an affordable, reliable, non-invasive reference standard does not exist, as is the case for chronic infectious diseases, a viable alternative for robust evaluation of diagnostic test accuracy involves the use of latent class models (LCMs) that do not require knowledge of the true disease status of individuals or the use of a gold-standard reference test. These latent class methods were pioneered by Hui and Walter (1980), who estimated the Se and Sp of two tests for tuberculosis based on the cross-classified results of these two tests without using either of them as a reference test. A thorough discussion of the

applicability of LCMs in diagnostic accuracy studies was first given by Walter and Irwig (1988), while the extension of these methods for prevalence estimation and certification of disease freedom has evolved considerably within the last decade. Such methods provide estimates that are directly comparable among different studies, regions and countries and thus are ideal for an output-based approach to disease measurement, control and eradication efforts within Europe and worldwide. Moreover, Bayesian LCMs (BLCMs) for diagnostic accuracy and prevalence estimation studies have been successfully implemented in a Bayesian framework for over 20 years (see, for example, Joseph et al., 1995; Johnson et al. 2001; Branscum et al., 2005; Collins and Huynh, 2014). Importantly, standards for the reporting of diagnostic accuracy studies that use Bayesian Latent Class Models – termed STARD-BLCM – have been recently published (Kostoulas et al., 2017) with the aim to facilitate improved quality of reporting on the design, conduct and results of diagnostic accuracy studies that use BLCMs. BLCMs for the evaluation of diagnostic tests and prevalence estimation are available and should be preferred because of their flexibility, the ease of interpretation of their results, and the availability of user-friendly, free software such as OpenBUGS (Lunn et al., 2009) and JAGS (Plummer, 2003) that can easily be used with standard statistical software such as R (R Core Team, 2018; Denwood, 2016).

Despite the availability of these statistical methods, the number of research studies and scientific reports that use them is a small proportion of the number of instances where the use of such methods would have been preferable. One of the numerous striking examples is the estimation of true prevalence of depression among resident physicians, which is of critical importance since it is associated with the quality of available patient care and the risk of medical errors. Resident physicians also have a higher risk of depression and depressive symptoms than that of the general population (Mata et al., 2015). This risk is based on self-report inventories which are known to be of imperfect Se and Sp and reported prevalence estimates vary tremendously among studies from different countries. Yet, to the best of our knowledge, none of the studies have provided true prevalence estimates, choosing instead to report only the observed prevalence of depression without accounting for the imperfect accuracy of the diagnostic process (further information can be found in the meta-analysis of Mata et al., 2015).

Evidently, a gap exists between the availability of BLCMs and their uptake by researchers and clinicians that are working on problems for which these methods are relevant. There is, therefore, a need to coordinate and promote the implementation of BLCMs in both the evaluation of diagnostic tests and in estimation of true prevalence in order to provide comparable estimates of disease occurrence.

1.1.2 DESCRIPTION OF THE CHALLENGE (MAIN AIM)

The main challenge for the application of BLCMs in the evaluation of diagnostic tests and the true prevalence estimation lies in the lack of adequate communication, knowledge transfer and collaboration between experts in the field and researchers working in statistics, epidemiology, diagnostics and population health. To this end, the main objective of this Action is to create the necessary networking and training tools that will expand understanding and use of BLCMs in the fields of diagnostic accuracy, true prevalence estimation and certification of disease freedom. Organizing such a research and training network is highly relevant and timely due to:

- i. the huge expansion in collection of data in life sciences that are ideal for the application of BLCMs.
- ii. the unprecedented movement of human and animal populations – and therefore disease – beyond geographical borders, which requires internationally harmonized reporting procedures to facilitate coordination of control efforts between nations.
- iii. the increasingly limited availability of resources to estimate true disease prevalence using traditional but expensive gold-standard methods.

HARMONY aims to promote the application and development of BLCMs in order to facilitate meaningful interpretation and comparison of reported disease occurrence in a more cost-effective manner than is possible using traditional gold-standard methods.

1.2 PROGRESS BEYOND THE STATE-OF-THE-ART

1.2.1 APPROACH TO THE CHALLENGE AND PROGRESS BEYOND THE STATE-OF-THE-ART

HARMONY will address the barriers that currently limit the use of BLCMs. To serve this objective, emphasis is placed on bridging the gap between experts in the field and researchers, stakeholders and policy makers in statistics, epidemiology and public health. Importantly, this is expected to be a dynamic two-way process: BLCM experts will provide training material, easy-to-use software code and interactive web applications while, on the other hand, epidemiologists, diagnosticians, public health experts and policy makers will raise challenges that need to be addressed for the proper evaluation of diagnostics and prevalence estimation. These challenges will be accounted for and lead to modifications or the development on new approaches to BLCMs, for which we anticipate substantial uptake within the wider community.

The main strength of HARMONY lies in the diverse group of interested and relevant experts and stakeholders that will collaborate towards the practical and flexible application of BLCMs under the various related fields of diagnostic test evaluation, prevalence estimation and certification of disease freedom.

1.2.2 OBJECTIVES

1.2.2.1 Research Coordination Objectives

The overarching objective of HARMONY is to enable valid prevalence comparisons across Europe and beyond. Therefore, we aim to foster collaboration between experts in BLCMs, early career investigators (ECIs) interested in using these methods and other stakeholders and parties that are likely to benefit from the application of these methods. This COST Action will promote effective communication, training and understanding of BLCMs. Specifically, HARMONY will:

- i. Promote stakeholder engagement and foster collaboration with researchers in the field. Stakeholders and policy makers at the international/national/regional level will be involved from the beginning of the Action and help to identify current needs that must be addressed.
- ii. Establish a free online repository of existing BLCMs that will be continually updated with new developments in the field. These will be easily accessible and facilitate researcher access to model code and example data with step by step explanations of how to implement and interpret these models.
- iii. Implement an online interactive application for the use of BLCMs for prevalence estimation and the evaluation of diagnostic tests in the absence of a gold standard.
- iv. Create a series of open-access online training materials for researchers (especially ECIs and researchers from COST inclusiveness target countries) interested in BLCMs.
- v. Issue explicit guidelines for the robust and harmonized application of BLCMs for the evaluation of diagnostic tests, prevalence estimation and establishing freedom from disease. These guidelines will result in greater harmonisation in terms of (a) the way in which BLCMs are implemented and (b) reporting of results in a transparent and transferable way.
- vi. Establish an international society for the application of BLCMs in life sciences in order to promote collaboration of scientists working in the field and the harmonized reporting of relevant research.

1.2.2.2 Capacity-building Objectives

HARMONY will:

- i. increase the visibility and integration of researchers in a variety of disciplines relevant to evaluation of diagnostics and true prevalence estimation using BLCM. It will promote communication of ideas, fostering new strongly interdisciplinary collaborations and leading to joint funding proposal applications.
- ii. provide training and networking opportunities for ECIs, as well as researchers from COST Inclusiveness Target Countries (ITCs) and promote transfer of skills with particular emphasis

- on ECIs in ITCs as well as balance in terms of gender and geographic distribution of participants. The Action has also secured the participation from COST Near Neighbour Countries (NNCs) and International Partner Countries (IPCs).
- iii. create separate training opportunities specifically for policy makers and stakeholders with the aim to update and familiarize them with current and trending methods in the evaluation of diagnostic tests and their use in the harmonization of disease occurrence measurement.
 - iv. involve ITCs in leadership positions, support the work of ITCs in the field and seek to strengthen gender balance by involving of female scientists in future research.
 - v. organize the first international conference of the BLCM society and initiate the process of communicating on a biennial basis.

2 NETWORKING EXCELLENCE

2.1 ADDED VALUE OF NETWORKING IN S&T EXCELLENCE

2.1.1 ADDED VALUE IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

Despite the increasing uptake of BLCMs in tackling current challenges in disease prevalence estimation, there is complete absence of coordinated efforts for major international and/or Europe-based initiatives in this field. Research that is based on BLCMs is presented as part of other conferences held in the field of Life Sciences, but the general nature of these conferences precludes in-depth discussion of the important nuances of these methods. Workshops and/or short-term training sessions are occasionally organized from the few (i.e. three to five) organized groups of experts, but with limited impact in the wider community.

One of the critical and strategic objectives of this Action is therefore to establish a formal framework of scholars, in Europe and beyond, that work on the development of BLCMs. The foundation of the relevant Society and its biennial conference will engage an international network of scholars and sustain exchange of knowledge. The society will also promote a structured approach to training opportunities by offering international training schools semi-annually with the goal of attracting interested researchers (especially ECIs) from various disciplines.

Last but not least, the Action will create and sustain links for effective communication and collaboration between (i) BLCM researchers, (ii) policymakers and (iii) other relevant interested stakeholders. The latter is crucial because one of the main limitations in the expanded use of BLCMs is the gap between experts and the researchers and stakeholders that would benefit most from the application of such methods.

2.2 ADDED VALUE OF NETWORKING IN IMPACT

2.2.1 SECURING THE CRITICAL MASS AND EXPERTISE

HARMONY will fully exploit the networking tools of COST among European and International researchers, stakeholders and policy makers. Fifty-five proposers were backing this Action from thirty-seven countries (30 COST countries of which 19 ITCs, 1NNCs and 6 IPCs). The proposers of this action can be divided in two groups: (a) a group of experts that have been working extensively on BLCMs as well as Bayesian methods more generally and (b) a group of researchers with a solid (although more general) background in epidemiology that have started or are interested in working on BLCMs. The latter group will provide input to the former group on the requirements that are not presently covered by BLCMs and must be addressed. The latter group has also established connections with international, european and national stakeholder and policy institutions which will connect to the workings of the Action. The communication between the two groups of proposers is critical to the success of HARMONY and is ensured by HARMONY's structure and networking activities. The network includes partners from Europe and IPCs that are specialist in both BLCMs and epidemiology. There is a strong interdisciplinary nature in this Action, which is crucial to serve the

strong interaction and communication required for the development and robust application of fit-for-purpose BLCMs.

Importantly, connection between ECIs and more experienced researchers will be strengthened: the average time after PhD completion for the proposers in this Action is 12.3 years. Beyond the proposers, the Action's network is built on further expansion that will promote both growth and interaction between existing members. To this end HARMONY will try to establish and maintain as many direct links among participants as possible, with emphasis on bridging science with policy, which is fundamental to the success of disease control and eradication efforts.

2.2.2 INVOLVEMENT OF STAKEHOLDERS

HARMONY will prioritize the extension of its network to engage the most relevant stakeholders. Three main stakeholder groups will be targeted:

1. Researchers and scholars from universities and research institutes from Europe and beyond (NNCs, IPCs). Many of the proposers involved in the network at the time of application are internationally recognised experts in the field of BLCMs. Importantly, most of them have already established links to stakeholder groups and the involvement of other stakeholders will develop from this core group. The Action will significantly strengthen connections among them and engage new members as official partners who are either active or interested in BLCMs.
2. Policymakers at the International, Europe and national level.
 - a. International level: WHO, OIE, FAO.
 - b. Europe: ECDC, EFSA
 - c. National: public officials responsible for human, animal and public health policy working at the national peers of ECDC and EFSA, in central or regional government.
3. Small and Medium-Sized Enterprises (SMEs) working in the fields of epidemiology and disease control that would benefit most from the use of BLCMs

To ensure the involvement of all relevant stakeholders there will be a subgroup within the coordination working group (WG1) dealing with this task for the first year of the Action. The leader of this group will be the Action's dedicated stakeholder coordinator (SC) who will supervise the critical element of attracting stakeholders. Specifically:

1. WG1 and the SC will identify and contact the most appropriate stakeholders starting as early as the beginning of the Action, based on existing as well as new contacts obtained from the tasks of the other WGs,
2. The MC, via WG1 and the SC, will establish communication with members of selected stakeholders and invite them to participate in the Action.
3. An open access online platform disseminating HARMONY activities will further facilitate the involvement of further relevant stakeholders.
4. Stakeholders will be invited to participate in the knowledge sharing activities and, in particular, the international conference at the final year of the action.
5. Dedicated sessions on sharing expertise, identifying mutual challenges and needs, and familiarising stakeholders with BLCMs will take place at the early stages of the action. Stakeholders will cooperate in the Action via interactive workshops and training schools.

Importantly, stakeholders will be treated as peers in terms of knowledge and expertise, rather than mere "end-users." This unique interactivity between individuals developing BLCMs and those needing to use these methods is key to this Action.

2.2.3 MUTUAL BENEFITS OF THE INVOLVEMENT OF SECONDARY PROPOSERS FROM NEAR NEIGHBOUR OR INTERNATIONAL PARTNER COUNTRIES OR INTERNATIONAL ORGANISATIONS

HARMONY is proudly backed by a broad network of secondary proposers, including one from NNC (Kosovo) and six from IPCs (Australia, Canada, India, New Zealand, Qatar and U.S.A.). These proposers are internationally acknowledged experts in the field of BLCMs with vast experience in the development and application of such models. Their experience and input will be extremely useful to

this Action. They will also serve as a linking point to international organizations and stakeholders relevant to this Action. In return, enrolled IPCs and NNCs will gain a better understanding of the needs and specific requirements for harmonization of disease data across Europe. Involvement of international experts and stakeholders in this Action is key for the development of coordinated control and disease eradication efforts internationally through harmonized reporting of disease prevalence.

3 IMPACT

3.1 IMPACT TO SCIENCE, SOCIETY AND COMPETITIVENESS, AND POTENTIAL FOR INNOVATION/BREAK-THROUGHS

3.1.1 SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS (INCLUDING POTENTIAL INNOVATIONS AND/OR BREAKTHROUGHS)

HARMONY will establish a strong link between (i) European and international researchers working with BLCMs and (ii) policy makers whose organizations will benefit most from the use of BLCMs.

The Action is expected to generate the following short-term scientific impacts:

1. set up and strengthen the theoretical and methodological framework for BLCMs.
2. a series of BLCMs tailored to current global needs of diagnostic test evaluation and prevalence estimation.
3. guidelines for the sound application of BLCMs within various settings.
4. enhance the visibility and ease of access to BLCMs.
5. promote the application of BLCMs in practice.

The long-term scientific impacts of HARMONY are:

1. a unified research agenda on BLCMs and a user-friendly framework for their implementation.
2. a creation of an international society, which will be strongly interdisciplinary and will integrate research on BLCMs from the different fields of life sciences.
3. the capacity to guide future innovative research towards the fit-for-purpose evaluation of diagnostics and the harmonization of reported disease prevalence.
4. the global leadership of the European Research Area in the field of BLCMs.

Above all, the long-term socio-economic impact of HARMONY is emphasised. That is, the improved and more efficient disease and control eradication efforts and increased efficiency in terms of allocation of the limited resources for these efforts. This will be obtained through the field deployment of BLCMs, which are cost-effective methods for the evaluation of diagnostic tests, harmonization of disease prevalence estimates and certification of disease freedom.

3.2 MEASURES TO MAXIMISE IMPACT

3.2.1 KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

The promotion of BLCM methods implicitly assumes the efficient transfer of knowledge between experts and interested stakeholders. To this end, emphasis is placed on the following COST networking tools that facilitate knowledge sharing:

1. Knowledge transfer:
 - a. between scholars at different career stages (especially ECIs and PhDs)
 - b. among COST countries, IPCs and especially towards ITCs
2. Eleven widely advertised workshops
3. Eight training schools at different levels of difficulty and for different target audience
4. STSMs especially focused to ECIs and ITCs.
5. Establishment of the BLCM society and
6. Organization of the first international conference of the BLCM society

Special emphasis will be given to researches from ITCs and ECIs for all training activities. Furthermore, to promote expansion in the use of BLCMs we will encourage participation of researchers and stakeholders who have never used before BLCMs to exceed at least 20%, in all the Action's opportunities.

3.2.2 PLAN FOR DISSEMINATION AND/OR EXPLOITATION AND DIALOGUE WITH THE GENERAL PUBLIC OR POLICY

HARMONY will disseminate its outputs through several channels to maximize the impact among interested researchers, relevant stakeholders and policy makers.

The strongest dissemination tools will be the interactive HARMONY website and its associated social and scientific media, where all BLCMs, training materials and resources will be freely available. The website will be constantly updated and will remain active beyond the end of the Action by the main proposer's host institution. There will be free access training tutorials/videos, a mailing list and a newsletter that will be published several times a year.

A central achievement of this Action will be the creation of the BLCM society and its biennial conference.

4 IMPLEMENTATION

4.1 COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

4.1.1 DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

Working group 1: Coordination

WG1 has the critical role of coordinating the work of the other WGs and ensuring that effective interaction among them occurs. WG1 will promote coordination primarily at the partner meetings and electronically via e-mail or web meetings. To ensure effective communication at least one member of each WG should participate in WG1 to serve as liaison officer between WG1 and their WGs. A crucial task of WG1 would be to attract the interest and the involvement of new relevant stakeholders in addition to those that were already backing this Action as secondary proposers. Within WG1, a subgroup of members will be assigned to this role and will be headed by the dedicated Stakeholder Coordinator (SC) of this Action. Last but not least, WG1 in connection with WG5 will coordinate the efforts to set up the International BLCM Society.

Tasks

T1.1: Set up collaboration and coordination of this Action activities

T1.2: Collect information on the potential stakeholders to involve on the Action in due course.

T1.3: Establish the International Society for the application of BLCMs in Life Sciences.

Associated deliverables: All

Working group 2: Evaluation of diagnostic tests with BLCMs

Initially, WG2 will summarize the existing BLCM methodology for the estimation of the Se and Sp of the diagnostic tests. Subsequently, WG2 will identify existing gaps and propose modifications to the available methods to cover these gaps. Consequently, WG2 will also be responsible for the creation of open-source software tools for implementing the new methods and making more straightforward the application of existing. WG2 will also be in charge of issuing guidelines for the sound application of BMLCs in routine diagnostics in the field. Training and the development of available online material for

BLCMs on the evaluation of diagnostic tests will also be the responsibility of WG2 in conjunction with WG5.

Tasks

T2.1 Perform systematic review and evaluation of existing BLCMs for the estimation of the Se and Sp of the diagnostic tests.

T2.2 Prepare a white paper on the sound application of BLCMs for Se/Sp estimation in Life Sciences.

T2.3 Develop training material for domain-expert scientists as well as methodologists in BMLCs.

Associated deliverables: D1, D2, D3, D4, D5, D6, D20

Working group 3: Estimation of true disease prevalence with BLCMs

WG3 will focus on BLCM methods for estimating the true prevalence of disease by accounting for the imperfect Se and Sp of the diagnostic process. These methods will capture the hierarchical structure of the data (i.e. they will estimate the prevalence at each level of data organisation). In line with the work carried out in WG2 a review of existing BLCMs methods for true prevalence estimation will be followed by the identification of outstanding needs and the necessary modification to existing methods that is required to address these needs. Training and dissemination activities of the updated BLCMs for true prevalence estimation will be carried out by WG3 in connection with WG5.

Tasks

T3.1: Perform systematic review and evaluation of existing BLCMs for the estimation of the true disease prevalence. There will also be, wherever required, specific overview within distinct life-science domains.

T3.2: Write up of technical reports/white papers about suitable methods for sound application of BLCMs for Se/Sp estimates in life sciences.

T3.3: Develop training material for domain-expert scientists as well as methodologists in BMLCs.

Associated deliverables: D7, D8, D9, D13, D14, D20

Working group 4: Certification of disease freedom BLCMs

The work of WG4 is strongly linked to WG3. The updated BLCMs methods of WG3 will be modified under WG4 to be used for calculating the probability of disease freedom, as well as the probability of not exceeding pre-specified critical thresholds of true prevalence at each compartmental level (e.g. the probability that less than 10% of households or other regional divisions within a country are infected). As with WG2 and WG3, training and dissemination on disease freedom calculations will be the responsibility of WG4 and WG5 members.

Tasks

T4.1: Review and update existing methods for calculating the probability of disease freedom.

T4.3: Prepare of a white paper reporting sound and case-specific methods for calculating the probability of disease freedom.

T4.3: Develop training material for domain-expert scientists as well as methodologists in BMLCs.

Associated deliverables: D10, D11, D12, D13, D14, D20

Working group 5: Networking and knowledge sharing

WG5 has the critical task of maintaining communications with all relevant stakeholders and policy makers. WG5 will also ensure that the methods developed under WG2, WG3 and WG4 are effectively disseminated to the broader scientific community. To this end, WG5 is responsible for (i) attracting all relevant stakeholders and policymakers to participate in the action, (ii) the creation and maintenance of the action's website in which all deliverables will be deposited and freely available to the scientific community and (iii) the maintenance of a network/ mailing list for scientists and stakeholders/policy makers interested in these methods. Most importantly, WG5 (in connection with WG1) will be responsible for setting up the International BLCM Society and lead the preparations for the first conference of this Society.

Tasks

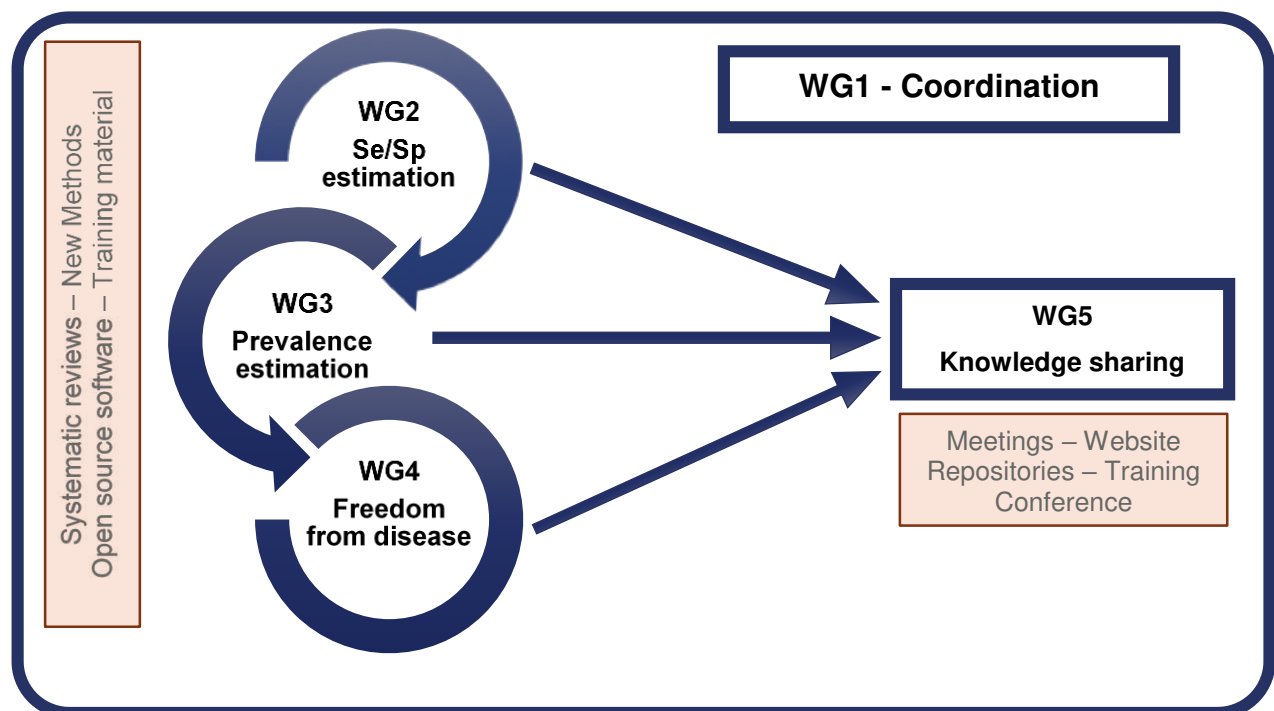
T5.1: Disseminate, in an effective way, the outputs of WG2, WG3 and WG4.

T5.2 Create and maintain the necessary networking tools for participants, stakeholders, public bodies and general audience.

T5.3 Create and maintain the necessary media for the dissemination of the training activities of this Action.

Associated deliverables: D15, D16, D17, D18, D19, D20

Figure 1. Graphical Representation of the Working groups and their interactions



4.1.2 DESCRIPTION OF DELIVERABLES AND TIMEFRAME

The expected deliverables are:

WG2

1. Two workshops, involving expert scientists and relevant stakeholders/policy makers, on existing BLCMs and update/modification of these methods for Se/Sp estimation (D1 – month 6 & 12)
2. A report/guide summarizing the updated/modified BLCMS methods for Se/Sp estimation that will be made available online (D2 – month 14)
3. Making algorithms and code for Se/Sp estimation freely available with step-by-step instructions and explanations (D3 – month 18)
4. Two training schools at the basic level for ECI and interested researchers on Se/Sp estimation with BLCMs (D4 – month 12 & 18)
5. One training school at the advanced level for ECI and interested researchers on Se/Sp estimation with BLCMs (D5 – month 18)
6. STSMs for ECI/researchers interested in Se/Sp estimation (D6 – month 11 & 17)

WG3

7. Two workshops, involving expert scientists and relevant stakeholders/policy makers, on existing BLCMs and update/modification of these methods for true prevalence estimation (D7 – month 18 & 24)
8. Overview and update/modification of existing BLCMS methods for true prevalence estimation (D8 – month 26)
9. Making algorithms and code for estimation of true prevalence freely available with step-by-step instructions and explanations (D9 – month 28).

WG4

10. One workshop, involving expert scientists and relevant stakeholders/policy makers, on existing BLCMs and update/modification of methods for disease freedom surveys (D10 – month 30)
11. A guide on the updated/modified existing BLCM methods for disease freedom surveys that will be available online (D11 – month 34)
12. Making algorithms and code for establishing freedom from disease freely available with step-by-step instructions and explanations (D12 – month 36)

WG3 & WG4

13. Two training schools for true prevalence estimation and certification of disease freedom (D13 – month 26 & 32)
14. STSMs for researchers interested in true prevalence estimation and certification of disease freedom (D14 – month 36)

WG5

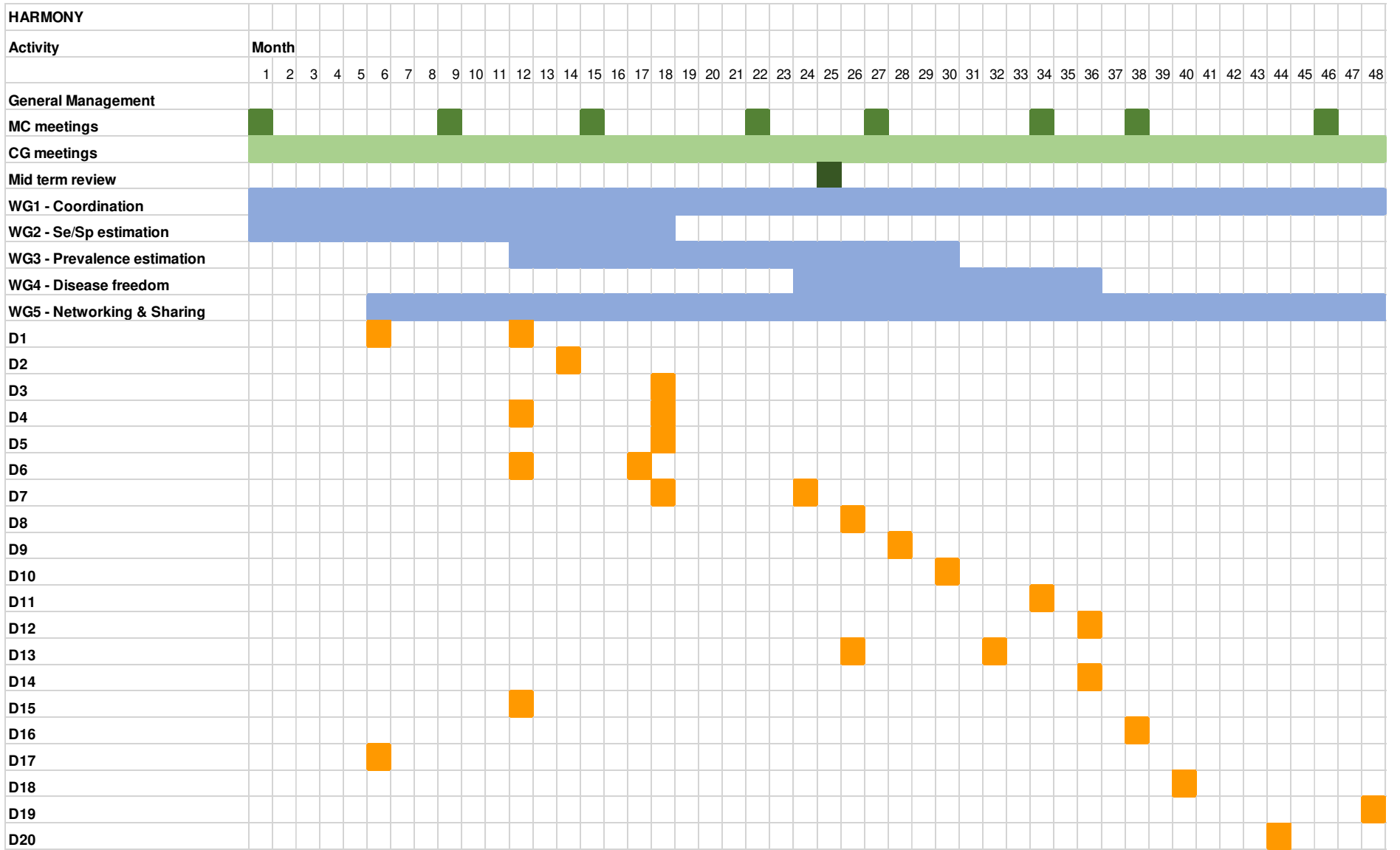
15. A website with the developed guides and BLCM methods (D15 – month 12)
16. An interactive web application for these methods (D16 – month 38)
17. A network/mailling list for scientists and stakeholders interested in these methods (D17 – month 6)
18. Creation of an International BLCMs society (D18 – month 40)
19. Organisation of the first BLCMs society meeting (D19 – month 48)
20. A GitHub repository for BLCM software codes, examples and any other training and research relevant software (D20 – month 48)

4.1.3 RISK ANALYSIS AND CONTINGENCY PLANS

Risk Identification	Likelihood	Contingency plan
Partners unable to fulfil commitments	Likely	The Core Group will regularly review the contributions of all partners. If any partners should start failing to meet their objectives, then corrective action will be taken to identify potential barriers and establish a clear follow-up plan that will ensure achievement to future assigned tasks.
Lack of coordination between WGs	Unlikely	This Action has a strong coordination plan. In the unlikely event that the participant(s) in each WG responsible for interaction between WGs will not fulfil their role, they will be changed.
Inadequate representation from stakeholders/policy makers	Unlikely	The dedicated stakeholder coordinator of the Action will be first assisted, and if still incapable of fulfilling the role, she/he will be changed. The Action will utilize a wide variety of communication channels, with the most important being a wide network of proposers with links to relevant institutions.
Inability to produce freeware code	Very Unlikely	Very unlikely but in case it occurs expert code developers will be asked to assist. We note that several members of the network of proposers have a history of producing such code.
Too few enrolled in the Training Schools and/or Workshops	Unlikely	The calls for participation in the Training Schools and workshops will take place 9 months before the planned date of the activity. Failure to attract the participation of the desired number of participants will necessitate an extension of the call and re-evaluation of the publicity/dissemination strategy
Too few (less than 50) enrol for the BLCM conference	Unlikely	The calls for the conference will take place 18 months before the planned date. Failure to attract the participation of the desired number will necessitate re-evaluation and strengthening of the publicity/dissemination strategy
Failure of adequate meeting attendance:	Likely	The likely difficulty in attending physical meetings will be mitigated by using teleconferences or similar remote means of communication.

4.1.4 GANTT DIAGRAM

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REFERENCES

1. Branscum, A. J., Gardner, I. A., & Johnson, W. O. (2005). Estimation of diagnostic-test sensitivity and specificity through Bayesian modeling. *Preventive veterinary medicine*, 68(2-4), 145-163.
2. Collins, J., & Huynh, M. (2014). Estimation of diagnostic test accuracy without full verification: a review of latent class methods. *Statistics in medicine*, 33(24), 4141-4169.
3. Denwood, M. J. (2016). runjags: An R Package Providing Interface Utilities, Model Templates, Parallel Computing Methods and Additional Distributions for MCMC Models in JAGS. *Journal of Statistical Software*, 71(9). <https://doi.org/10.18637/jss.v071.i09>
4. Hui, S. L., & Walter, S. D. (1980). Estimating the error rates of diagnostic tests. *Biometrics*, 167-171.
5. Johnson, W. O., Gastwirth, J. L., & Pearson, L. M. (2001). Screening without a “gold standard”: the Hui-Walter paradigm revisited. *American Journal of Epidemiology*, 153(9), 921-924.
6. Joseph, L., Gyorkos, T. W., & Coupal, L. (1995). Bayesian estimation of disease prevalence and the parameters of diagnostic tests in the absence of a gold standard. *American journal of epidemiology*, 141(3), 263-272.
7. Kostoulas, P., Nielsen, S. S., Branscum, A. J., Johnson, W. O., Dendukuri, N., Dhand, N. K., & Gardner, I. A. (2017). STARD-BLCM: standards for the reporting of diagnostic accuracy studies that use Bayesian latent class models. *Preventive veterinary medicine*, 138, 37-47.
8. Mata, D. A., Ramos, M. A., Bansal, N., Khan, R., Guille, C., Di Angelantonio, E., & Sen, S. (2015). Prevalence of depression and depressive symptoms among resident physicians: a systematic review and meta-analysis. *Jama*, 314(22), 2373-2383.
9. Plummer, M. (2003). JAGS: A Program for Analysis of Bayesian Graphical Models Using Gibbs Sampling JAGS : Just Another Gibbs Sampler. In *Proceedings of the 3rd International Workshop on Distributed Statistical Computing (DSC 2003)* (p. March 20–22, Vienna, Austria. ISSN 1609-395X.). <https://doi.org/10.1.1.13.3406>
10. R Core Team. (2018). R: A Language and Environment for Statistical Computing. Vienna, Austria. Retrieved from <http://www.r-project.org/>
11. Walter, S. D., & Irwig, L. M. (1988). Estimation of test error rates, disease prevalence and relative risk from misclassified data: a review. *Journal of clinical epidemiology*, 41(9), 923-937.