Brussels, 24 October 2016

COST 112/16

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action "CliniMARK: 'good biomarker practice' to increase the number of clinically validated biomarkers." (CliniMARK) CA16113**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action CliniMARK: 'good biomarker practice' to increase the number of clinically validated biomarkers. approved by the Committee of Senior Officials through written procedure on 24 October 2016.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA16113
CLINIMARK: 'GOOD BIOMARKER PRACTICE' TO INCREASE THE NUMBER OF CLINICALLY VALIDATED BIOMARKERS. (CliniMARK)

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);
b. "COST Action Proposal Submission, Evaluation, Selection and Approval" (COST 133/14);
c. "COST Action Management, Monitoring and Final Assessment" (COST 134/14);
d. "COST International Cooperation and Specific Organisations Participation" (COST 135/14).

The main aim and objective of the Action is to The challenge of the CliniMARK network is to establish a 'Best Biomarker Practice' (BBP) community to significantly increase the number of biomarkers with reproducibly demonstrated feasibility.. 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 56 million in 2016.

The MoU will enter into force once at least five (5) 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.

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.

OVERVIEW

Summary
Thousands of circulating proteins have been shown to be hallmarks of emerging disease, response to treatment, or a patients' prognosis. The identification of these small molecule biomarkers holds a great promise for significant improvement of personalized medicine based on simple blood tests. For instance, diagnosis and prognosis with biomarkers (e.g. carcinoembryonic antigen (CEA)) has significantly improved patient survival and decreased healthcare costs in colorectal cancer patients. Unfortunately, despite significant investments to increase the number of biomarker studies, only ~150 out of thousands of identified biomarkers have currently been implemented in clinical practice. This is mainly caused by the time-consuming process of reliably detecting biomarkers, the irreproducibility of studies that determine a biomarkers' clinical value, and by a mismatch in studies that are performed by academia and what is required for regulatory and market approval. To increase the number of clinically validated biomarkers, rather than further increasing the number of biomarker discovery studies, CliniMARK will improve the quality and reproducibility of studies and establish a coherent biomarker development pipeline from discovery to market introduction.

CliniMARK aims to achieve said goal by creating a **Best Biomarker Practice (BBP) community,** which will provide guidance to:

1. Classify biomarkers according to their characteristics, anticipated clinical use, and their phase of development,
2. Select and validate appropriate research-grade biomarker detection tests,
3. Select appropriately designed studies and biological samples to reliably and reproducibly validate biomarkers clinically, and
4. Select and report on appropriate clinical data storage, biomarker data storage, data analysis protocols, privacy concerns, ethical issues, and statistical analysis methods.

Areas of Expertise Relevant for the Action	**Keywords**
● Basic medicine: Proteomics	● biomarkers ● guidelines ● technologies ● clinical translation ● validation

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

Research Coordination
● To establish a BBP guideline for selection and validation of biomarker detection techniques
● To establish a BBP guideline for clinical validation study design
● To implement BBP to the biomarker research field with a focus on Chronic Obstructive Pulmonary Disease (COPD) as demonstrator

Capacity Building

COST is supported by the EU Framework Programme Horizon 2020
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- To connect the European research infrastructure for biomarker research

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TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. Challenge

1.1.1. Description of the Challenge (Main Aim)

The **aim** of the **CliniMARK** network is **to establish** a **'Best Biomarker Practice'** community to significantly increase the number of biomarkers with reproducibly demonstrated feasibility.

Thousands of circulating proteins and metabolites have been shown to be hallmarks of emerging diseases, response to treatments, or a patients' prognosis. The identification of these biomarkers holds a great promise for significant improvement of personalized medicine based on simple blood tests. For instance, diagnosis and prognosis with biomarkers (carcinoembryonic antigen (CEA)) has significantly improved patient survival in colorectal cancer patients. Unfortunately, despite significant investments in biomarker discovery studies, only ~150 out of thousands of identified biomarkers have currently been regulatory accepted implemented in clinical practice. This is mainly caused by an incoherent pipeline from biomarker research to market introduction.

A lack of accurately validated protein biomarkers - The process from discovery of a biomarker to clinical implementation consists of 3 phases (Figure 1.1): (1) **Research:** discovery studies to identify potential biomarkers for a given indication, (2) **Development:** determining the feasibility of the biomarker through analytical development and validation of a prototype biomarker test, and validation in clinical studies, (3) **Market:** further development and extensive validation of a clinical-grade biomarker assay fulfilling diagnostic and regulatory criteria towards clinical use of the biomarker. Significant hurdles lie within the transitions of phase 1 to 2 and phase 2 to 3, yielding two large biomarker innovation gaps (Figure 1.1). **Therefore, the CliniMARK network will focus on the analytical and clinical validation of biomarkers to improve the transition of biomarkers from the Research to the Market phase.**

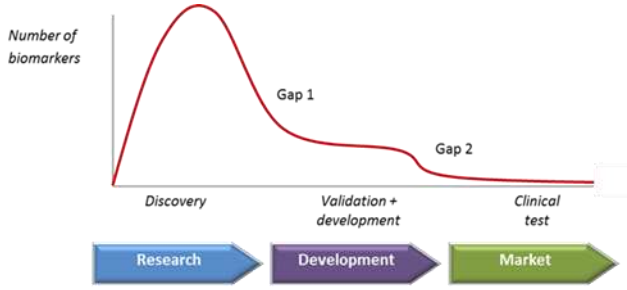

Figure 1.1: The number of biomarkers in the phases 1-3 of the pipeline from biomarker discovery to clinical use.

Improving the pipeline from biomarker Research to Market - The large biomarker innovation gaps are caused by two main problem. **First**, due to lack of standardisation and harmonisation, biomarker data can hardly be reproduced. Efforts to combine and standardize approaches in biobanks and databases at the (inter)national level exist (e.g. the EATRIS, BBMRI, and ELIXIR initiatives), but mostly aim at establishing larger databases and more analytical capacity by standardizing data collection, while as of yet not standardizing study designs with regard to reporting on meta- and raw-data acquisition, description of data analysis protocols and statistical methods. As a result, when a biomarker reaches phase 3, different research groups have studied the biomarker using different detection, calibration, and validation methods, using poorly described data analysis protocols, study designs established ad hoc and different statistical methods [1]. This results in different outcomes on measured biomarker levels in 80% of the cases [1]. In addition, only about 20% of published data is available according to the FAIR data principles (Findable, Accessible, Interoperable, Reusable), leading to a total percentage of reproducible and reliable biomarker studies of 4% [2]. Thus, in the vast majority of cases, clinical diagnostic laboratories and companies need to repeat the studies already performed in order to acquire reliable data before investing significant amounts of money

into the development of a clinical-grade diagnostic assay. **Second,** the different phases in biomarker development are not well connected. Guidelines exist on biosample isolation and storage [3], analytical assay validation in general [4, 5], specific technologies as clinical mass spectrometry [6] and next generation sequencing [7], and for data stewardship [2]. In addition, development of clinical-grade assays is guided by FDA regulations such as the ICH E16. However, there has been no combination of existing guidelines into one comprehensive agnostic guideline on biomarker discovery, validation and development to streamline and connect the different phases, that takes considerations for market approval into account from the start. As a result, when a biomarker reaches phase 3, companies cannot rely on available data and are forced to repeat most of the work from phases 1-2 to fill in the gaps and regain confidence in the specific biomarker. Phase 3, guided by FDA and EMA regulations, itself is receiving significant interest at the global level, and new guidelines on regulatory requirements will be generated during the WRIB (Workshop on Recent Issues in Bioanalysis) meeting in Orlando in April 2016. **To maximize the efficiency of transitioning biomarkers from phase 1 to 3 and provide companies with convincing biomarker for development in phase 3, European guidelines to standardize biomarker research and connect the separate phases must be developed.**
In addition, with scientific journals dictating what is published and what is not, thereby driving the activities of scientists, adherence to existing guidelines is low. For scientists, no direct incentive exist to adhere to best practices and/or whitepapers and even the journals publishing these guidelines do not adhere to them. **For new guidelines to be effective, new strategies to improve adherence to guidelines are essential and their acceptance must be measurable.**

1.1.2. Relevance and timeliness

Protein and metabolite biomarkers have been used for diagnosis and prognosis for decades. With the exponential progress in development of high-throughput and comprehensive detection techniques like mass spectrometry, next generation sequencing, imaging, and multi-plex immuno-assays, biomarkers hold great promise for personalized medicine. As a result, biomarker research has received significant attention worldwide. This is exemplified by recent initiatives for extensive public and private funding, such as the biomarker focused HORIZON2020 calls (and specifically the PHC12 calls in 2014 and 2015; € 110 million [8] and SME instrument calls in 2017; € 45 million [9]), president Obama's precision medicine initiative ($215 million) [10]), IMI 2 program (€ 3.2 billion) and national programs such as CTMM (Netherlands, € 321 million). In addition, regulatory and other authorities recognize the need to regulate and standardize biomarker development, as explained in several meetings and reports by the FDA [11], the European Science Foundation [12], and the Organisation for Economic Co-operation and Development [13]. Efforts are also being made to connect biobanks and laboratories throughout Europe (BBMRI, EATRIS), and to coordinate biomarker validation studies for specific diseases (e.g. Alzheimer's association 'Global Biomarker Standardization Consortium' [14]).
Despite these efforts, only few newly developed diagnostic and prognostic biomarker assays enter the clinic. The significant investments to increase the number of studies on biomarkers and to connect existing biobanking infrastructures, are unfortunately not matched by similar efforts in standardization.

1.2. Specific Objectives

1.2.1. Research Coordination Objectives

Objectives 1 and 2: Best Biomarker Practice Guidelines to (1) select and validate biomarker detection tests and (2) select and design studies to for clinical biomarker feasibility studies - To increase the number of clinically used biomarkers, CliniMARK will, in collaboration with biomarker initiatives throughout Europe, improve the quality and reproducibility of clinical biomarker feasibility studies, rather than further increasing the number of biomarker discovery studies.

CliniMARK aims to achieve this goal by creating **Best Biomarker Practice (BBP) Guidelines,** which will provide guidance for:

1. Discovery of biomarkers,
2. Classification of biomarkers according to their characteristics, anticipated clinical use, and their phase of development,
3. Selection, development and validation of appropriate research-grade biomarker detection tests,
4. Selection of appropriately designed studies and biological samples to reliably and reproducibly determine the feasibility of biomarkers clinically,
5. Selection and reporting on appropriate clinical database structure and vocabularies, biomarker data storage, data analysis protocols, privacy concerns, ethical issues, and statistical methods, and
6. Connection of the separate phases by keeping the eventual goal of market introduction in mind.

Objective 3: Implementation of the CliniMARK approach: Demonstrator project in Chronic Obstructive Pulmonary Disease (COPD) - To demonstrate the value of the generated BBP guidelines, COPD will be chosen as a demonstrator project. The CliniMARK network will gather and classify all known COPD biomarkers and select the appropriate research-grade detection tests. Furthermore, the CliniMARK network will design technical validation studies, and design clinical multi-centre feasibility studies.

Objective 4: Capacity building: New channels for BBP dissemination - CliniMARK aims to develop novel strategies to improve adherence to guidelines. Implementation of BBP guidelines throughout Europe will greatly improve the biomarker research capacity. Therefore CliniMARK will disseminate the results through channels such as publication of guidelines in scientific journals, LinkedIn groups, conferences, flyers, and publication of reports. However, these channels have proven insufficient to promote strong adherence to guidelines. One new example that will be investigated is an online platform where the expertise of all network members will be compiled and classified. Scientists who aim to study a biomarker can enter this biomarker in the online tool, classify the biomarker according to the BBP guidelines and receive an overview of which studies must be performed for each phase and of experts or existing platforms (like the EATRIS Biomarker and BBMRI Biobanking platforms) that can provide the necessary expertise, samples and tools for each phase. In addition, the network will seek collaboration with scientific journals on biomarkers to develop a publication policy to stimulate adherence to the BBP. The relationship between the CliniMARK aim, objectives, Action challenge and the multidisciplinary Action network is represented in Figure 1.2.

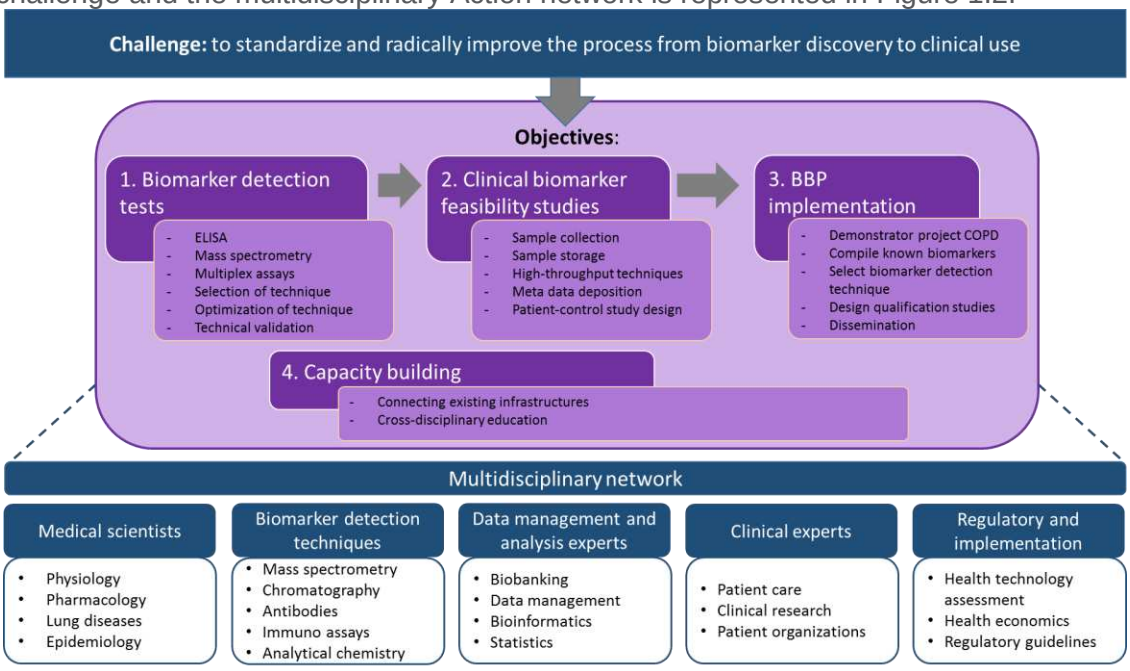

Figure 1.2 The relation between CliniMARK aim, objectives and COST challenge

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Table 1.2.1 Research coordination objectives

Specific	Measurable	Achievable	Relevant	Timely
Objective 1: To establish a BBP guideline for selection and validation of biomarker detection techniques				
What: BBP guideline **Why:** To standardize biomarker detection **Who:** Researchers and companies **Where:** In Europe	**How many?** One Guideline **When accomplished?** When whitepaper of guideline is published.	**How to be achieved?** By involving multi-disciplinary team of experts, defining biomarker classes and evaluation existing detection techniques., and reaching consensus on best practice.	**Is it relevant?** A BBP for selection and validation of biomarker detection will decrease the time needed to develop a reliable biomarker detection test.	41 months
Objective 2: To establish a BBP guideline for clinical validation study design				
What: BBP guideline **Why:** To standardize clinical feasibility study design **Who:** Researchers and clinicians **Where:** In Europe	**How many?** One Guideline **When accomplished?** When whitepaper of guideline is published	**How to be achieved?** By involving multi-disciplinary team, defining biomarker classes, feasibility study designs and out-read parameters, and reaching consensus on best practice.	**Is it relevant?** A BBP for clinical feasibility study design will make these studies more reproducible. As a result, the clinical value of biomarkers can more reliably be determined in multi-centre studies.	41 months
Objective 3: To implement BBP to the biomarker research field with a focus on COPD as demonstrator				
What: Applying BBP guideline in COPD research **Why:** To demonstrate value of the BBP approach **Who:** Researchers and companies **Where:** In Europe	**How many?** The BBP will be applied to study one (pattern) of biomarker(s) **When accomplished?** When reproducible studies on clinical value of biomarkers are published.	**How to be achieved?** By applying the BBP guidelines to running studies on biomarkers in COPD.	**Is it relevant?** To achieve successful implementation of BBP guidelines, their value must be demonstrated.	48 months

1.2.2. Capacity-building Objectives

Table 1.2.2 Capacity-building objectives

Specific	Measurable	Achievable	Relevant	Timely
Objective 4: To connect the European research infrastructure for biomarker research				
What: New concepts for dissemination of guidelines (e.g. online tool) **Why:** To connect existing infrastructure and facilitate the use of BBP guidelines. **Who:** Researchers and companies **Where:** In Europe	**How many?** Pilot project for one new concept for dissemination. **When accomplished?** When new pilot project has been developed and tested.	**How to be achieved?** First by developing an online system according to the BBP guidelines, then by adding the data from CliniMARK network members.	**Is it relevant?** This online tool will greatly improve the capacity to establish research collaborators with all necessary expertise according to the BBP guidelines.	41 months

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 technologies to measure protein biomarkers include:
Within CliniMARK, the focus will be on protein biomarkers using two key technologies:
(1) mass spectrometry based methods like Matrix-Assisted Laser Desorption/Ionization (MALDI), Liquid Chromatography coupled to tandem mass spectrometry (LC-MS/MS) and Selective Reaction Monitoring (SRM)/Multiple Reaction Monitoring (MRM)/Parallel Reaction Monitoring (PRM),

(2) immuno-assay based methods include immunocyto/histochemistry, western blotting, the enzyme-linked immunosorbent assay (ELISA), multiplex assays (e.g. Luminex or affimer/aptamer-based technologies), and plasmon resonance imaging.
Continuous development of these analytical techniques improves their reliability, detection limits, and high-throughput potential. However, since in guidelines for early development no attention is payed to eventual market introduction, different research groups use methods that cannot be used in later phases (e.g. for market introduction).
State-of-the-art clinical biomarker feasibility studies. Case-control studies to determine sensitivity, and specificity of biomarkers are mostly performed on human samples from biobanks. The use of biobank materials has significant issues such as low sample amounts, non-standardized sample collection, handling and storage, and lack of uniformity of concomitant clinical data. Several efforts have been made to provide standardized guidelines on biobanking, and to extend sample cohorts by connecting existing biobanks throughout Europe (e.g. BBMRI). Only limited efforts, however, exist to standardize clinical validation study designs. As a result, the sensitivity and specificity of biomarkers are often reported based on ill-designed studies that lack critical information (e.g. health status, confounding factors like BMI or medication, health care costs, technical details on the used biomarker detection technique). This makes it very difficult to reproduce and compare biomarker validation studies.

1.3.2. Progress beyond the state-of-the-art

This COST Action is the first pan-European initiative to deliver guidelines for 'Best Biomarker Practice' that cover the design of biomarker development studies to establish clinical feasibility of the biomarker and connect the different phases in biomarker research. These will include sample handling, detection techniques, laboratory reproducibility assessments, clinical validation designs, and extensive diagnostic assay development of biomarkers. To establish the BBP, the network will focus on one disease: COPD, with the objective to define a general framework that is applicable to more technologies, disease indications, and other biomarker use.
CliniMARK will rank known COPD protein biomarkers based on physico-chemical characteristics (e.g. size, charge, concentration), and evaluate all research-grade detection techniques and their shortcomings that are available for each biomarker, related to their clinical use. For each biomarker, CliniMARK will then select the most appropriate detection technique per biomarker with regards to expected analytical sensitivity and specificity, with-in run and between run reproducibility, expected optimization and analytical validation duration, and feasibility to further develop the research-grade test into a clinical-grade test. Subsequently, CliniMARK will define the requirements for analytical validation for the selected test for each biomarker (e.g. what sample material to use, and limits for variability, and reproducibility). Furthermore, the network will compile and use existing guidelines on biobanking for biobanks in COPD. CliniMARK will classify COPD biomarker classes according to their prospective use (e.g. diagnosis, companion diagnostic, prognosis) and evaluate optimal clinical validation study designs (e.g. sensitivity, specificity, clinical impact, economic impact). For each protein biomarker, a development plan for appropriate feasibility study designs will be developed. In addition, in parallel to the specific development plans for COPD biomarkers, a BBP will be designed, based on the thorough evaluation of available biomarker measurement techniques, clinical feasibility study design and existing guidelines.
This process will result in two documents: First, a standardized development plan, (outlining intended use, analytical specificiations, and clinical feasibility study design) for selected COPD biomarkers to efficiently enter into phase 3. And second, during development of the plan for specific biomarkers, all decisions and considerations for these decisions will be documented and integrated to develop a standardized BBP whitepaper on selection and analytical validation of research-grade detection techniques and clinical feasibility studies for biomarkers in general. Furthermore, the CliniMARK network will identify current technological hurdles of detection techniques (e.g. sample preparation,

sensitivity, high-throughput potential, sample preparation methods), and establish development plans to overcome these hurdles.
The development plans to pass COPD biomarkers through phase 2 will subsequently be carried out by the CliniMARK network members. For each task in the development, the network member with appropriate expertise will be selected. This will result in the standardized development of 1 selected biomarker from phase 1 into phase 3.
In addition, the CliniMARK network will develop a pilot online tool to establish research networks for biomarker feasibility research and development. This tool will be designed according to the BBP and be loaded with information on the CliniMARK network with regards to expertise on biomarker detection, biobanking, medical expertise, data analysis, study design, statistical analysis, and health technology. Members can subsequently enter a biomarker in this tool, provide its class and will subsequently receive a biomarker study plan according to the BBP with suggestions of CliniMARK network members that can provide the necessary expertise and data.

1.3.3. Innovation in tackling the challenge

Significant investments have been made in biomarker discovery studies, clinical biomarker feasibility studies, and development of diagnostic tests to increase the amount of validated biomarkers and clinically implemented diagnostic tests. These investments have resulted in the discovery of thousands of new potential biomarkers, but not in reproducible outcomes of clinical biomarker feasibility studies, nor in a significant increase in clinically implemented diagnostics tests. Therefore, CliniMARK will not focus on discovery or on full diagnostic development but on the intermediate analytical and clinical biomarker development phase (Figure 1.1). CliniMARK intends to improve the quality and reproducibility of discovered biomarkers through a unique European network that will standardise and connect methods to clinically validate biomarkers.

1.4. Added value of networking

1.4.1. In relation to the Challenge

The main aim of CliniMARK is to develop a European network of analytical, clinical, and industrial biomarker experts that define consensus on selection and validation of biomarker detection techniques and clinical feasibility study designs. Separated networks at the national level exist but significant efforts by these networks often lead to non-reproducible results. To develop a BBP guideline to increase the number of thoroughly validated, reliable biomarkers, a pan-European academic-industrial network is not only valuable, but an absolute necessity [15].

1.4.2. In relation to existing efforts at the European and/or international level

The CliniMARK Action is complementary to existing efforts. To achieve its long term goal of increasing the number of reproducibly studied biomarkers, the developed BBP guidelines must be implemented in running projects. To achieve such implementation, CliniMARK follows a 3-phased approach. **First**, CliniMARK will invite members from current biomarker initiatives throughout Europe to join the CliniMARK Action from the start to help establish BBP. Identified initiatives include ESFRI landmark infrastructures such as EATRIS, BBMRI, and ELIXIR, the FP7 projects IMPROvED, E-PREDICE and DIPROMON, the Horizon 2020 PHC-12 projects, and other projects such as BIOAIR, BIOFINDER. **Second**, to demonstrate the value of the BBP approach, CliniMARK will implement these guidelines in running projects on COPD as a demonstrator project. COPD has been selected as multiple members of the CliniMARK network are involved in COPD biomarker projects and actual implementation of the BBP guidelines in these projects is feasible. **Third**, since members of existing European biomarker initiatives have been invited to CliniMARK network at the start, the network to implement the demonstrated CliniMARK BBP approach can be directly transferred to biomarker validation projects for other medical conditions through the CliniMARK network. In addition, the

CliniMARK network will establish close contacts with EMA and FDA initiatives on regulatory guidelines for biomarkers (such as the WRIB meetings and EBF (European Bioanalysis Forum) meetings).

2.1. Expected Impact

2.1.1. Short-term and long-term scientific, technological, and/or socioeconomic impacts

Scientific impact - **Short-term**, CliniMARK will develop BBP guidelines that will speed-up development of research-grade biomarker detection tests, and increase the reproducibility of clinical feasibility studies. During the COST Action runtime, the network will apply these guidelines to 2 technologies and 1 disease area (COPD), and determine its clinical feasibility before the project end. **On the long-term**, the developed BBP guidelines can serve as a template in biomarker development for a multitude of medical indications (cardiovascular, cancer, etc.). As a results, development of research-grade tests, and clinical feasibility studies of biomarkers will be achieved faster and with less resources. Ultimately, this will lead to an increase in the number of thoroughly and reproducibly studied biomarkers as targets for new diagnostic assays.
Technological impact - To develop the BBP guidelines, relevant existing methods for biomarker detection, validation and assay development will be evaluated. This allows the identification of critical hurdles in sensitivity and reproducibility of mass spectrometry, sample preparation methods, immuno-assays, clinical information storage in databases, data storage and analysis protocols, and user-friendliness of protocols and training of personnel for platform techniques in clinical chemistry laboratories. By identifying these critical hurdles, new Europe-wide studies can be established to significantly improve existing technologies and assist in novel technology development for biomarker validation and clinical implementation. The CliniMARK network will design those studies, establish new consortia from its network, and apply for European funding programmes (e.g. Horizon 2020) for the required financial resources.
Societal/economic impact - **Life science companies:** The increased quality of clinical biomarker feasibility studies will provide life science companies in Europe with more accurately validated biomarkers. This will lead to an increased confidence in published biomarkers and adoption for successful commercial development of diagnostic tests. Since the return on investment for European life sciences companies will increase, they will be more competitive in the worldwide biomarker diagnostic market. **Physicians:** The increased number of biomarkers with established reproducible feasibility and new diagnostic tests for these biomarkers will aid physicians to diagnose patients in more detail, allowing personalized treatments and better chances of survival and/or quality of life. This will first be achieved for the demonstrator project of COPD, but later also for other disease indications. **Patients**: The availability of better biomarkers will improve diagnosis, prognosis, and predict response to treatment of patients at a personal level. As a result, patients will receive personalized treatments, greatly improving their survival and quality of life. **European healthcare system**: Through improved diagnosis, prognosis, and prediction of response to treatment, patients will receive more effective treatments. This will decrease health cost expenditures. Ultimately, the correct use of reliable biomarkers will both improve healthy outcome throughout Europe and decrease health care expenses.

2.2. Measures to Maximise Impact

2.2.1. Plan for involving the most relevant stakeholders

CliniMARK will impact on several stakeholders (Figure 2.2.1). During the first half year of CliniMARK, representatives for all these stakeholders will be actively approached through the personal network of the network of proposers, LinkedIn, Facebook, Twitter, Google adds, adds in Biomarker journals (e.g. Clinical Chemistry, Bioanalysis, J. Chromatography B, Molecular Cellular Proteomics), flyers at conferences (e.g. ASMS, AACR, MSACL), and a specific search and personal invitation of

individuals. Representatives of regulatory authorities, and European Union (EU) will be invited to join meetings as independent guests and will be approached for consultation meetings. Members that apply to the CliniMARK Action will be assigned to the Working Group of their choice. Members that occupy a senior position at their respective institute will be encouraged to actively take the lead in Working Group discussions to design the guidelines, while junior members will be encouraged to participate in Working Group discussions, and participate in short-term-scientific exchanges, work-shops, and training schools.

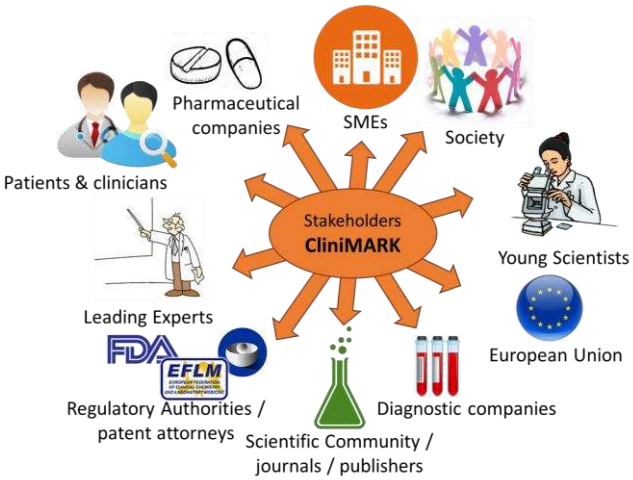

Figure 2.2.1 Stakeholders of CliniMARK

2.2.2. Dissemination and/or Exploitation Plan

For dissemination of the CliniMARK results, specific target groups have been identified: (1) Scientific community/journals/publishers, (2) Young scientists, (3) Patients, (4) Clinicians, (5) Leading experts from industry, (6) Regulatory authorities/patent attorneys, (7) EU, (8) SMEs, (9) Big diagnostic and pharmaceutical companies, and (10) General public. CliniMARK will actively approach professional networks, patient organizations, and key opinion leaders for dissemination through classic dissemination channels. This is coordinated by the Core Group, which contains the grant holder and the Working Group Chairs. In addition, Working Group 4 will investigate new channels for dissemination (e.g. through an online platform). Specific dissemination activities are listed in Table

Table 2.2.2 Specific dissemination activities

What?	Who?	How?
General CliniMARK dissemination material		
CliniMARK recruitment material	1, 2, 3, 4, 5, 6, 8, 9	Flyer, website, LinkedIn, Twitter, Facebook, google adds, adds in journals (e.g. Clinical Chemistry, Bioanalysis, J. Chromatogr. A and B, and Bioanalytical Chemistry), conferences (MSACL), personal invitations.
CliniMARK results promotion material	1, 2, 3, 4, 5, 6, 7, 8, 9, 10	YouTube (e.g. BDC YouTube channel), flyer, website, LinkedIn, Twitter, Facebook, conferences, publication of integrated whitepapers.
Objective 1: To establish a 'Best Biomarker Practice' guideline for choice and validation of biomarker detection techniques		
Overview of existing detection techniques, validation methods, and suggestions for improvement.	1, 2, 5	Scientific publication, conference, CliniMARK website.
	6, 8, 9	Information leaflet, CliniMARK website, Facebook, Twitter.
Whitepaper on BBP for biomarker detection techniques.	1, 2, 5	Scientific publication, conference, website.
	1, 6, 8, 9	Information leaflet, website, Facebook, Twitter, policy plan for journals/publishers as guideline for publications.
Objective 2: To establish a 'Best Biomarker Practice' guideline for study design and read-out parameters for clinical feasibility studies on biomarkers		
Overview of existing infrastructure, feasibility study designs, and suggestions for improvement.	1, 2, 5	Scientific publication, conference, website.
	6, 8, 9	Information leaflet, website, Facebook, Twitter.
Whitepaper on BBP for clinical feasibility studies.	1, 2, 5	Scientific publication, conference, website.
	1, 6, 8, 9	Information leaflet, website, Facebook, Twitter, policy plan for journals/publishers as guideline for publications.
Objective 3: To implement 'Best Biomarker Practice' into the biomarker research field, with a special focus on the COPD networks		
Report on practical issues for implementation of BBP guidelines.	1, 2, 5	Scientific publication, flyer distributed on scientific conferences and through CliniMARK website, Facebook, and Twitter.
	1, 2, 3, 4, 5	Scientific publication, YouTube video, and online report distributed via CliniMARK Website, Facebook, and Twitter.

What?	Who?	How?
Report on success of implementation of BBP guidelines.	6, 7, 8, 9, 10	Advisory report via CliniMARK website, Facebook, Twitter, and e-mailing.
Objective 4: To connect the European research infrastructure for clinical validation of biomarkers		
Investigate new dissemination channels	1, 2, 5, 8, 9	E.g. online platform to connect biobanks, detection techniques, and biomarker clinical validation studies for classes of biomarkers.
Short-Term Scientific Missions (STSMs)	2	Website announcement, email invitation, Twitter, Facebook.
Summer school	2	Website announcement, email invitation, Twitter, Facebook.

2.3. Potential for Innovation versus Risk Level

2.3.1. Potential for scientific, technological and/or socioeconomic innovation breakthroughs

The potential for innovation of this Action include:

At the scientific level, CliniMARK will support the significant existing efforts in biomarker research. The standardized BBP approaches of CliniMARK will lead to more time-efficient biomarker detection studies and clinical feasibility studies. The proposals to improve existing methodologies, standardize data deposition, and make accessible repositories will further increase the effectiveness and comparability of current research efforts. In summary, CliniMARK will enable existing biomarker efforts to be more successful.

At the technological level, CliniMARK will analyse the shortcomings of existing technologies in a multi-disciplinary manner. In addition, a research plan will be designed to improve existing mass spectrometry, immuno-assay, and multiplex approaches. Through the pan-European, multi-disciplinary CliniMARK network approach, a focused development plan will be designed, including research proposals and timelines for technological innovations throughout the process from biomarker discovery to clinical validation. This integrative approach forms a focused and efficient framework for Europe to become the technological centre of excellence in biomarker research.

At the level of the society, CliniMARK will have several important contributions.

- Through improved diagnosis, prognosis, and prediction of response to treatment, patients will receive more effective treatments. This will decrease health cost expenditures. Ultimately, the correct use of reliable biomarkers will both improve the health status throughout Europe and decrease health care expenses.
- Increased public awareness on the exciting field of biomarkers and its potential clinical applications.

The risk level: BBP will only have effect if adherence to the guidelines is high. Currently, with journals not adhering to guidelines themselves, no incentive exists for scientists to adhere to guidelines. To improve adherence, CliniMARK follows an approach with 3 foci: (1) Including major initiative in biomarker and biobanking research (BBMRI, EATRIS, ELIXIR), (2) Development of a new online tool for capacity building with hard-coded BBP, and (3) Collaboration with scientific journals to develop a policy that encourages publications using the BBP. Another risk is the heterogeneity of the network of experts from different disciplines, all with their own preferred techniques and methods, who will have to reach consensus on a BBP guideline. By including experts on standardization and regulation, the Action can draw from experience on successful implementation of guidelines in other areas of bioanalysis. For example, the diagnostics and the pharmaceutical industries adhere to such guidelines as do the clinical chemistry laboratories. CliniMARK thus does not have to "reinvent the wheel" but can learn from good practices elsewhere.

The innovation potential versus Risk level of CliniMARK: When taking into account EU investments in biomarker research, which adds up to over €200 million over the years 2014-2017, the potential of the CliniMARK COST Action to benefit all these efforts, and the relatively modest investment that is needed to set up this Action, the return on investment for this project is expected to be very good.

3.1. Description of the Work Plan

3.1.1. Description of Working Groups

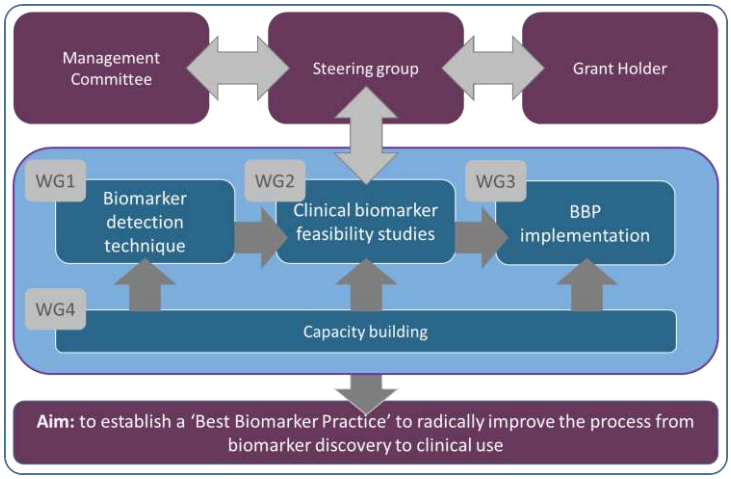

Figure 3.1.1: Workflow of CliniMARK.

The Working Groups - One Working Group for each objective will be established (Figure 3.1.1):

1. Biomarker detection technique
2. Clinical biomarker feasibility studies
3. Implementation of BBP in COPD biomarker research
4. Capacity building

Each Working Group will consist of a multi-disciplinary team of medical scientists, biomarker detection technique experts, data storage and analysis experts, clinical experts and regulatory and implementation experts. Working groups will be interconnected through inter-Working Group discussions at annual meetings of the entire network.

Working group 1: Selection and analytical validation of biomarker detection technique(s) - Working group 1 will develop a consensus on what biomarker detection technique should be used for specific biomarkers in COPD and biomarkers in general. In addition, it will develop a consensus on how detection techniques should be validated to achieve reproducible detection of biomarkers. Ultimately, Working Group 1 will produce a development plan for biomarkers in COPD and a BBP whitepaper on the selection and analytical validation of biomarker detection techniques to ensure standardized and reproducible biomarker detections for each class of biomarker throughout Europe.

Objectives:

- To establish a development plan for biomarkers in COPD.
- To establish a BBP whitepaper for selection and analytical validation of detection techniques.

Tasks:

1. **To evaluate and select types** of mass spectrometry techniques, protein multiplex techniques and high-throughput immune-based techniques that are used to **measure protein biomarkers**, and of different **types of source material** that are used for analytical validation of the detection techniques, including evaluation of existing guidelines.
2. **To evaluate and select read-out parameters** used as criteria **for analytical validation** of detection techniques for each ranked biomarker (e.g. detection limit, variability, duration of test, high-throughput potential, cost), including evaluation of existing guidelines.
3. To **integrate considerations**, including FDA and EMA guidelines for eventual market approval, and identified hurdles and solutions for biomarker detection tests and technical validation **to define a BBP guideline** for:
   3.1. Selection of detection technique and source material for each class of protein biomarker
   3.2. Selection and analytical validation of biomarker detection techniques for each class of protein biomarker.
4. **To develop a whitepaper** for BBP for selection and analytical validation of biomarker detection techniques.
5. **To identify technical bottlenecks** in the methods that will be included in the BBP whitepaper.
6. **To set up new research proposals** to develop solutions for the technical bottlenecks in the BBP.

Activities:

These tasks will be organized through video conferences (Tasks 1-8), WG meetings (Tasks 1-8), Short-Term Scientific Missions (STSM) (Tasks 2, and 3), a scientific symposium (Tasks 4, and 6), development of dissemination material and scientific publications (Tasks 4, and 6).

Major deliverables:
1. BBP guidelines on biomarker detection techniques.
2. New research proposals to develop solutions for technical bottlenecks.

Milestones:
1. Publication of BBP white paper on biomarker detection techniques.

Working group 2: Biomarker clinical feasibility study design - Working group 2 will develop a consensus on how clinical feasibility studies on biomarkers will be performed in three phases. First, the Working Group will establish a consensus plan on the use of biobanks for clinical feasibility studies of COPD biomarkers. Second, the working group will establish a consensus on clinical feasibility study design and readout parameters for COPD biomarkers. Ultimately, Working Group 2 will write a whitepaper on BBP in biobanking and clinical feasibility studies by integrating considerations made in establishing the development plan for COPD. This will ensure that multiple studies on the same biomarkers make use of tissue samples of comparable quality, and report on the same outcome parameters. As a result, the outcomes of clinical feasibility studies can be compared between multiple sites, which will increase the confidence in biomarkers.

Objective:
- To establish a BBP whitepaper for clinical validation of reliable biomarkers.

Tasks:
1. **To take inventory of existing** sample collection **methods**, sample storage methods, data collection, processing and storage methods, data analysis methods, data reporting methods, and existing guidelines **for biobanking** for COPD biomarker studies.
2. **To evaluate existing clinical feasibility studies** of biomarkers to identify 'best practice in study design (e.g. sample size, type of control vs patient group, necessary meta-data, necessary raw data, age and gender matching, statistical methods, etc.), relevant read-out parameters (e.g. sensitivity, specificity, clinical impact, economic impact, etc.), and statistical models for each biomarker class defined in WG2, task 1.
3. **To evaluate the identified methods for biobanking** under task 2 and the identified clinical feasibility studies under task 3, for each of the classified COPD biomarkers under task 1.
4. **To integrate considerations**, and identified hurdles and solutions for clinical feasibility study of COPD biomarkers **into a BBP guideline**.
5. To develop a **whitepaper for BBP** for clinical feasibility studies:
   5.1. On biobank building and maintenance and
   5.2. Clinical feasibility study design and read-out parameters.
6. To set up **new research lines** to improve the **methods included in the BBP** (e.g. sample handling, storage, data processing, meta-data deposition).

Activities:
These tasks will be organized through video conferences (Tasks 1-8), WG meetings (Tasks 1-8), Short-Term Scientific Missions (STSM, Tasks 2-4), a scientific symposium (Tasks 5, 7, and 8), development of dissemination material and scientific publications (Tasks 5, and 7).

Major deliverables:
1. BBP guidelines for clinical feasibility studies on biomarkers.
2. New research proposal to develop solutions to improve methods in the BBP guidelines.

Milestones:
1. Publication of BBP white paper on clinical feasibility studies on biomarkers.

Working group 3: Implementation of BBP guidelines: demonstrator project COPD - Working group 3 will apply the developed BBP guidelines in ongoing biomarker studies on COPD. A number of CliniMARK network members are currently involved in projects that focus on clinical feasibility studies on biomarkers in COPD. To demonstrate the value of the BBP, the development plan for one COPD biomarker, developed in WG 3, tasks 3 and 4, will be executed in running projects on COPD biomarkers. This will result in new study designs on specific biomarkers in COPD. In addition,

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two reports will be produced, one to describe the practical issues encountered during implementation of the guidelines, and one to describe the success of implementing BBP.
Objective:
- To implement BBP guidelines in ongoing biomarker studies on COPD

Tasks:
1. **To rank COPD biomarkers** according to physico-chemical properties (e.g. size, charge, concentration) and their phase of development.
2. **To classify COPD biomarkers** according to clinical use (e.g. diagnostic, prognostic, companion diagnostic, etc.)
3. **To define a BBP analytical development plan for each COPD biomarker**, defining the chosen research-grade biomarker detection technique and analytical validation plan, and identifying the necessary expertise to execute the development plan.
4. **To define a BBP development plan for clinical feasibility studies** for each classified COPD biomarker, defining the biological samples, the data processing tools, data reporting methods, study design and read-out parameters, and statistical models that are needed for each biomarker, and timelines for all separate parts of the development plan.
5. To **identify** the most suitable **CliniMARK members** for **execution** of the COPD biomarker development plan for **analytical validation** of biomarker detection test.
6. To **identify** the most suitable **CliniMARK members** for **execution** of the development plan for COPD biomarker **clinical feasibility** studies.
7. To **establish** and **document the pipeline** for the **clinical feasibility studies on COPD** biomarkers describing what will be performed, who will perform it, and when it will be finished.
8. To **manage** the established **research network and timelines**.
9. To **document hurdles and successes**.
10. To hold an **interdisciplinary scientific symposium** after completion of the development plan for COPD biomarker clinical validation to discuss encountered hurdles and successes.
11. To develop a **publication** on practical **issues** and **solutions**, and **successes** while implementing the **BBP guidelines** on COPD biomarker clinical feasibility studies.

Activities:
These tasks will be organized through WG meetings (Tasks 1-7), STSM (Tasks 3, 4, and 5) video conferences (Tasks 1-7), a scientific symposium (Task 6), development of dissemination material and scientific publications (Task 7).
Major deliverables:
1. BBP development plan for COPD biomarkers.
2. Publication of report on practical issues while implementing the BBP guidelines
3. Publication of report on success of implementing BBP guidelines
4. Interdisciplinary scientific symposium, meeting minutes available on website

Milestones:
1. Established BPP development plans for select COPD biomarkers.
2. Start of execution of development plan for one COPD biomarker.
3. Successful completion of development plan for on COPD biomarker.

Working group 4: Capacity building - Working groups 4 will design a website, attract new network members to expand the CliniMARK network within the first 6 months of its running time, integrate the whitepapers from WGs 1-3, coordinate the dissemination of CliniMARK results through 'classic' channels and investigate the establishment of new dissemination channels, and coordinate the CliniMARK education curriculum.
Objectives:
- To furnish the European research infrastructure for clinical validation of biomarkers
- To implement the whitepapers from WGs 1-3 into the biomarker research field with a special focus on the COPD networks.

Tasks:

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1. To **design a website** and **expand the CliniMARK network**. A website for CliniMARK will be created with sections on project objectives, member information, education curriculum, how to join, publications, stakeholders, a password protected user-section, section for the general public, and an agenda with CliniMARK activities. In addition, to extend the network, recruitment material in the form of a flyer, LinkedIn page, Facebook account, and Twitter account will be created and actively used to expand the network during the first 6 months of the COST Action runtime.
2. To **recruit network members** as described in section 2.2.1.
3. **To integrate separate white papers** from WGs 1-3 into one for the process from biomarker discovery to clinical implementation.
4. To **disseminate the CliniMARK results**, including the whitepapers for BBP outside of the Action network through 'classic' dissemination channels as explained in section 2.2.2. 'Dissemination and/or Exploitation Plan' and to design a publication policy strategy in collaboration with scientific journals to improve adherence to BBP guidelines.
5. To investigate **new dissemination channels** in three steps:
    5.1. Analysis of the success of existing dissemination channels (e.g. mailing lists, publications, conferences, LinkedIn groups, Twitter, Youtube, website)
    5.2. Development of new concepts for dissemination e.g. a 'clinical validation of biomarkers' online platform. This platform would compile all expertise of network members, classified according to the developed whitepapers. To this platform, network members will provide the class of biomarker that needs to be clinically validated, and the type of sample that is needed and will then be provided with a list of biobanks that hold the necessary tissue samples, a list of proteomic research labs that can perform the detection of biomarkers, and a list of research groups that can design and perform the clinical feasibility study. The platform will be furnished to automatically comply to the developed guidelines of BBP.
    5.3. Piloting of the new concepts for dissemination. Success and hurdles will be analysed for further development.
6. To **establish a CliniMARK education curriculum**. The education curriculum of CliniMARK will consist of yearly training schools, workshops and STSM. The education curriculum will combine parts of existing curricula to both ensure attainability and quality. This education curriculum will have a dedicated part on the CliniMARK website and will be free for Action participants. All education activities will be bundled into a BBP education curriculum. After the end of CliniMARK this curriculum can still be provided throughout Europe.

Activities:

These tasks will be organized through WG meetings, Short-Term Scientific Missions (STSM), video conferences, a scientific symposium, development of dissemination material and scientific publications.

Major deliverables:

1. CliniMARK website
2. Integrated whitepaper on BBP guidelines
3. Dissemination materials for the BBP guidelines
4. New concepts for dissemination of guidelines
5. A CliniMARK education curriculum

Milestones:

1. Website for the CliniMARK Action online
2. Integration of whitepaper on BBP from WGs 1-3
3. Novel dissemination channel pilot online

3.1.2. GANTT Diagram

The duration for CliniMARK is 4 years (See also Figure 3.1.2a). The Kick-off meeting will be the starting point of the Action where the Chair, vice-Chair(s), Working Group (WG) co-ordinators, website coordinator, WG meetings' coordinator and STSMs and other teaching activities' coordinator will be selected. Details about the frequency and the timing of networking activities are indicated in Figure 3.1.2b.

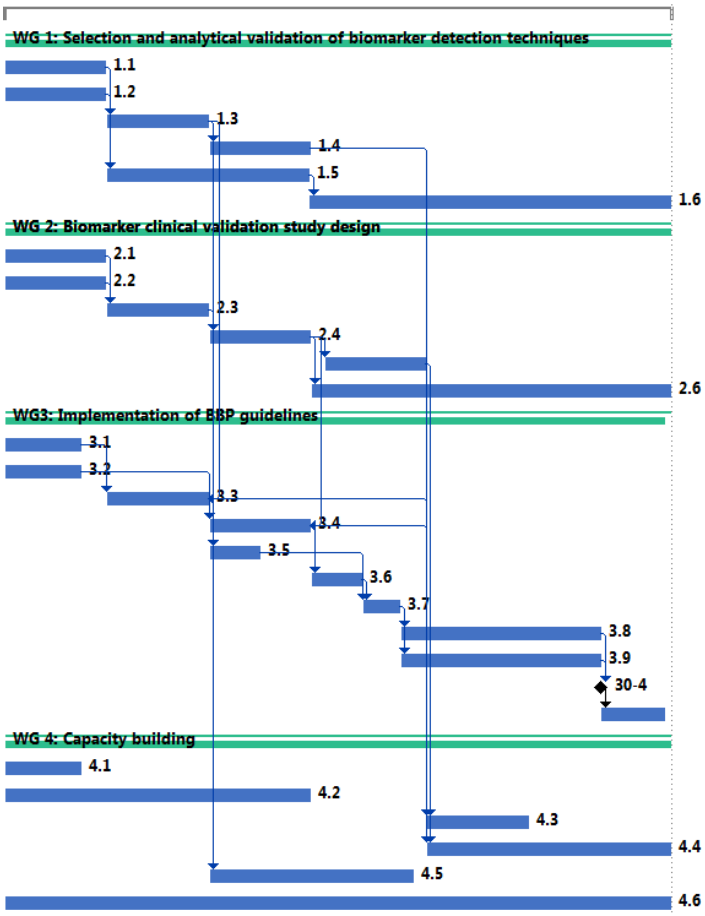

Figure 3.1.2a: GANTT chart of the CliniMARK Working Groups.

3.1.3. Risk and Contingency Plans

The main risks of CliniMARK are difficulties to reach consensus on BBP and not including phase 4 in the scope of CliniMARK.

Reaching consensus on BBP: In the time plan of CliniMARK, significant time is taken to reach consensus on a BBP as CliniMARK will deal with a multi-disciplinary team. If differences of opinions do arise that cannot be solved by majority vote within Working Groups by stringent guidance of the Working Group leader, an on-line voting system for the entire network is used and majority vote there is binding.

Not including phase 4 in CliniMARK: Phase 3 is not included in CliniMARK and poses a risk for clinical implementation of biomarkers. However, phase 3 is already addressed by the WRID and ESB forums, and CliniMARK will not duplicate efforts. Therefore, close relations will be established with representatives of WRID and ESB to ensure a strong connection of the CliniMARK results (end of phase 3) and the WRID and ESB efforts (begin of phase 4).

3.2. Management structures and procedures

CliniMARK will be coordinated by the Management Committee (MC), according to the published rules and procedures and with the support of the Scientific Secretariat in Brussels. To better organize and promote interactions between the multidisciplinary teams of scientists participating in the Action, 4 Working Groups will be established as described above (Figure 3.1 a).

The **Management Committee (MC)** will have as main responsibilities:

1. Appointment of Chair, vice-Chair(s), WG coordinators during the kick-off meeting, and a partner responsible for generating and coordination of the CliniMARK website.
2. Decision-making on the distribution of funds to the various activities of the Action.
3. Planning and coordination of several types of meetings and teaching activities, detailed below.
4. Evaluation of these meetings and other activities necessary to meet the set objectives.
5. Evaluation and (annually) report of the progress of the different WGs and the Action as a whole.
6. Promotion of collaboration between the different WG members, members of other related Actions and Scientific programs in Europe and world-wide.
7. Improvement of CliniMARK visibility and promote interactions with stakeholders.

A **Core Group (CG)** consisting of the Chair, vice-Chair(s), web-site coordinator and the WG coordinators will be established. Members of this group will be in frequent (at least once every two-months) communication to discuss on the progress. The Chair will be contacting members of the MC during inter-meeting periods to inform them about CG discussions as needed, and to recruit the necessary elements for achieving the milestones. Besides these checkpoints, the MC/WG meetings will also play a very crucial role in evaluating the progress of CliniMARK (see below).

Activities	Year														
	2016		2017			2018				2019				2020	
Management and Reporting	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3
Coordination	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Progress report				×				×				×				×
Meetings																
Kick-off meeting	×															
MC meetings			×				×				×				×	
WG meetings			×				×				×				×	
Education																
Workshops / Training schools		×		×		×		×		×		×		×		×
Webinars			×		×		×		×		×		×		×	
Short-term scientific missions			×	×	×	×	×	×	×	×	×	×	×	×	×	
Dissemination																
Brochure	×															
Website & Updates			×	×	×	×	×	×	×	×	×	×	×	×	×	×
Training materials on website				×			×				×					×
Publication of proceedings				×			×				×					×
Conference																×

Figure 3.1.2b: Timeline of the CliniMARK networking activities.

MC/WG meetings

The MC will convene yearly twice to ensure efficient coordination, evaluate the progress and make specific plans for future activities. These meetings with the exception of the first one (kick-off meeting) will coincide with the WG meetings. In addition, an MC/WG meetings coordinator will be appointed during the kick-off meeting. Efforts will be made so that the MC/WG meetings coincide with larger meetings in the field (for example, the Human Proteome Organization (HUPO), Biomarkers & diagnostics world congress) so as to increase the visibility of the Action and attract more participants. To ensure efficiency in meeting the WG-specific needs and to promote the exchange of information among different WGs, the meetings will include 1-2 day WG-specific sessions and at least 1-day plenary sessions (involving the WG representatives).

Short Term Scientific Missions (STSMs) and other teaching activities

An STSM and teaching activity coordinator will be appointed during the CliniMARK kick-off meeting. The STSMs are a major tool for the dissemination of “know-how” to young investigators and the promotion of collaborations between different research teams. Candidates to participate in these activities will be selected following an application process and assessment by the MC members. In addition, the organization of about 5-day long summer schools and workshops for young investigators will be conducted. For these training activities special efforts will be made to utilize available e-learning infrastructures, such as EMBER (European Multimedia Bioinformatics Educational Resource), developed under EU Framework programs. These teaching activities provide the unique opportunity to disseminate this knowledge to young researchers in Europe, promoting scientific Excellence in the field of biomarker translation studies.

3.3. Network as a whole

The CliniMARK consortium consists of a multidisciplinary consortium and is geographically balanced with 25 partners from 15 COST member countries. CliniMARK comprises a number of female scientists, young early stage investigators and experienced researchers from 5 COST inclusiveness target countries. CliniMARK has three world leading experts in biomarker research from international partner countries (IPCs) as their multidisciplinary expertise is necessary for the positive outcome of CliniMARK. In addition, clinical scientists and physicians are involved to develop BBP guidelines for biomarker studies that deliver clinically relevant data.

Gender balance and involvement of early-stage researchers

This Action will have an appropriate gender balance in all its activities and the Management Committee will place this as a standard item on all its MC agendas. This Action will also be committed to considerably involve early-stage researchers. It is worth noting that early stage female scientists have already played a major role in the conception and delineation of the objectives of CliniMARK. It is therefore expected that young female scientists will also play leading roles in the Management

of the Action. Moreover, early-stage investigators will be pursued to actively participate in the networking activities of this Action. As described above, gender balance will be observed in the Workshops, Teaching Activities and Short-Term Scientific Missions, in which early stage researchers are expected to form the majority of participants.

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