Brussels, 24 October 2016

COST 123/16

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action "Brillouin Light Scattering Microspectroscopy for Biological and Biomedical Research and Applications" (BioBrillouin) CA16124**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action Brillouin Light Scattering Microspectroscopy for Biological and Biomedical Research and Applications 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 CA16124
BRILLOUIN LIGHT SCATTERING MICROSPECTROSCOPY FOR BIOLOGICAL AND BIOMEDICAL RESEARCH AND APPLICATIONS (BioBrillouin)

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 BioBrillouin aims to bring together the community working in the field to stimulate collaboration, promote technological advancement and life science/biomedical applications. Stimulate the coordination of studies to asses the feasibility for medical diagnostics. Promote the translation of ideas from academia to industry, and nurture the next generation of scientists.. This will be achieved through the specific objectives detailed in the Technical Annex.

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

COST is supported by the EU Framework Programme Horizon 2020

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OVERVIEW

Summary
This *BioBrillouin* Action will establish a collaborative network of European researchers and instrument developers working in the field of Brillouin Light Scattering Spectroscopy (BLSS) applied to life sciences and health related problems. BLSS uses visible or infrared light from a laser source to probe the mechanics of a material through light scattering from thermally induced acoustic modes. It can give access to the viscoelasticity and structure of matter in a non-destructive contactless way, and when coupled to optical (confocal) microscopy, has proven to be particularly well suited for biomedical applications. Though an established tool in condensed matter physics, only more recently has BLSS seen promising applications in the life sciences and medical diagnostics. This can largely be attributed to advances in instrument (spectrometer) design coupled with increasing interest in the biomechanics of cells and tissues and their relation to disease, underlying genetics and biochemistry. There are now a significant and increasing number of researchers actively working in BLSS for biomedical research in Europe. It is the aim of the BioBrillouin Action to for the first time bring together the diverse community working in the field, which includes instrument developers, physicists, chemists, biologists and clinicians, with the core aim of stimulating collaboration, promoting technological advancement and paving the way towards routine life science research and clinical applications of BLSS.

Areas of Expertise Relevant for the Action	**Keywords**
● Physical Sciences: Biophysics ● Biological sciences: Biophysics ● Physical Sciences: Lasers, ultra-short lasers and laser physics ● Physical Sciences: Optics, non-linear optics (theory) ● Biological sciences: Morphology and functional imaging of cells	● Brillouin Light Scattering Spectroscopy ● Optical microscopy ● viscoelasticity ● Biomechanics ● mechanobiology

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

Research Coordination
● To create a close knit pan-European network, and central platform, for Brillouin Light Scattering Spectroscopy users and instrument developers as well as interested users working in the life sciences and medicine.
● To develop Brillouin Light Scattering Spectroscopy and facilitate its recognition as a powerful analytical tool for biomedical research and explore and novel biomedical applications. To fully understand the physical origin of experimental results.
● To establish standardized characterization, analysis and interpretation protocols for Brillouin Light Scattering Spectroscopy
● To facilitate interactions between Brillouin Light Scattering Spectroscopy researchers, researchers and clinicians, and researchers and industry. In particular to provide a forum for collectively working towards the establishment of diagnostic protocols, to initiate further grant applications, and promote the development of marketable products and routine biomedical/diagnostic applications.
● To bring Brillouin Light Scattering Spectroscopy and the potentials it offers to the wider attention of both the scientific research community and the general public via open days, and hands-on workshops for identified target groups.

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Capacity Building

● Set up a user friendly website with a porthole (Sample and Personnel Exchange (SAPE) Porthole) to arrange Short Term Scientific Missions (STSMs) and sample/personnel exchange.

● Support Early Career European researchers (ECER) by provision of STSMs and organization of scientific meetings, Workshops, Conferences and Training Schools aimed at training a new generation of young scientists in an interdisciplinary setting.

● Establish long-term collaborations between researchers already involved in Brillouin Light Scattering Spectroscopy, researchers in areas of microrheology and biomechanics,aswell as industrial partners and clinicians.

● Facilitate knowledge transfer among European members as well as with leading researchers and industrial participants outside Europe to further promote the role of Europe in Brillouin Light Scattering Spectroscopy.

● Develop a vision of EU-wide advancement of biomedical Brillouin Light Scattering Spectroscopy, and seek a consensus on experimental and analytical approaches in the field.

● Bring Brillouin Light Scattering Spectroscopy for biology/biomedical applications to the wider attention of the scientific research community and the general public, via special journal editions, articles, conferences and satellite-meetings.

● Establish a multidisciplinary network that will lead to a cooperative action for preparing and submitting proposals for Horizon2020 and other collaborative international and EC initiatives. Promote grant applications such as Marie Curie Actions to fund research projects connected to this network and to train the next generation researchers.

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TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. Challenge

1.1.1. Description of the Challenge (Main Aim)

The action “Brillouin Light Scattering Microspectroscopy for Biological and Biomedical Research & Applications” (BioBrillouin), will establish a collaborative network of leading researchers and instrument developers working in the field of Brillouin Light Scattering Spectroscopy (BLSS) applied to the life sciences and health related problems. BLSS uses visible or infrared light from a laser source(s) to probe the mechanics of a material through light scattering from thermally induced acoustic modes, or phonons. It gives access to the viscoelasticity and structure of matter in a non-destructive contactless way. When coupled to optical (confocal) microscopy, it has proven to be particularly well suited for biomedical applications. Though an established tool in condensed matter physics, only more recently has BLSS seen promising applications in the life sciences and medical diagnostics. This can largely be attributed to advances in instrument (spectrometer) design coupled with increasing interest in the biomechanics of cells and tissues and their relation to disease, underlying genetics and biochemistry. Unlike other mechanical and rheological measurement techniques, BLSS probes mechanical properties in the GHz frequency range, and thus offers a new ‘window’ for the investigation of microscopic scale biomechanical information. There are now a significant and increasing number of researchers actively working in BLSS for biomedical research in Europe. It is **the aim of this COST action to bring together, for the first time, the diverse community working in the field, which includes instrument developers, physicists, chemists, biologists and clinicians, with the core aim to stimulate collaboration, promote technological advancement and pave the way towards routine life science research and clinical applications.** The current state of BLSS brings several challenges which need to be tackled: **(1)** There is much interest in potential clinical applications, and the proposed network, which also involves clinical partners, is expected **to stimulate the coordination of distributed and parallel studies on pathological samples to asses the practical feasibility and reproducibility of BLSS for effective diagnosis of diverse medical conditions.** Similarly it is crucial that at this stage the exact origin of the Brillouin spectrum of biomaterials be clarified which is an underlying basis for the current proposal, and the need for a network. A longer term goal is to establish BLSS as a routine tool in diagnostics and theranostics for medical conditions associated with changes in the cellular or tissue level mechanical properties (e.g. diabetes, atherosclerosis, osteoporosis, etc.) as well as to investigate its potential for non-invasive early diagnosis of various cancers, neurodegenerative diseases such as Alzheimer’s, cardiovascular diseases, and bone diseases which are known to be associated with changes in mechanical properties. **(2)** There is also strong commercial interest, given the general absence of dedicated commercial BLSS instruments, and the proposed meetings/workshops are in this regard also expected **to facilitate the translation of ideas from academia to industry and vice versa, thereby promoting the development of marketable products.** Dedicated workshops and satellite meetings will serve to foster potentially novel biomedical research and diagnostic applications, promoting instrument development and optimization that will eventually lead to patents, commercializable products and diagnostic capabilities. **(3) Attracting and nurturing the next generation of scientists**; thereby enabling new prospects for research and industrial growth at the European level and beyond.

1.1.2. Relevance and timeliness

Over the last few years, there has been a boom in the implementation of BLSS in the life sciences as well as the appreciation of mechanical features of biological systems, ranging from optometry

and cardiovascular disease diagnostics, to the mechanobiology of cells subjected to different perturbations or genetic factors. Despite the established capabilities of BLSS in micromechanical testing, the interpretation of the viscoelastic parameters – especially in regards to their biological relevance - extracted from BLSS measurements is still to some extent debated. Given the inherently complex structure of most biological matter, this can lead to ambiguities in the interpretation of the data, as well as a lack of consensus on the potential applications and limitations of the method. To address these points a concerted effort by the community as a whole is required, especially towards the eventual implementation in clinical settings. Although the latter is beyond the scope of the present proposal, it is expected to be the subject of collaborative interdisciplinary grant applications promoted by networking activities resulting from this Action. Over the last few years numerous potentially useful biomedical applications of BLSS have been reported by independent research groups, and there exists a clear need to coordinate research efforts (e.g. via distributed parallel studies to test the reproducibility and statistical reliability of results) in order to take BLSS (as a biomedical research technique) to the next level of routine implementation and where relevant also to clinical trials. In light of all this, a coordinated effort and synergy of leaders in BLSS to form a network that can bring together the active scientific, industrial and medical community is urgently needed. To our knowledge there currently exists no dedicated community or forum on BLSS in biomedical research, and this is one of the main motivations for this proposal. The relevance of establishing such a community for sharing and discussing experimental approaches and analytical methods as well as building collaborations and links between researchers with different areas of expertise as well as industry is thus both extremely relevant and timely, and will allow Europe to be at the forefront in the biomedical implementations of BLSS. Such a network will provide the much-needed stimulus for advances in the field, both from the perspective of fundamental research and in the long term for the investigation of novel diagnostic methodologies/devices that yield economic, social and health benefits.

1.2. Specific Objectives

1.2.1. Research Coordination Objectives

The primary goal of the Action is to create a platform that facilitates exchange of knowledge and information and promote communication and partnership between experts in the field of biomedical BLSS, the exchange of personnel and biological/clinical samples between researchers, and generally provide an open forum for the exchange of ideas, advances and protocols. It should also serve as a platform for organizing and reporting on coordinated efforts performing parallel or serial measurements on samples in different labs to establish a basic consensus and benchmarks for the reliability and robustness of measurements for biomedical research and diagnostic applications. To facilitate all the above objectives a key aspect will be setting up a user friendly and easy to navigate website and database with a porthole to arrange Short Terms Scientific Missions (STSMs) and sample/personnel exchange in a minimally bureaucratic manner. While there are well defined and annually updated specific objectives within each working group (WG), there are several global Action objectives which are as follows: **(1)** To create a close knit pan-European network, and central platform, for BLSS users and instrument developers as well as interested users working in the life sciences and medicine. The network would serve as a go-to information hub, for people not yet involved but interested in the field, contributing samples, networking with the active research community, etc. **(2)** To develop BLSS and facilitate its recognition as a powerful analytical tool for biomedical research and explore and expand on novel biomedical applications. To fully understand the physical origin of experimental results. The network involves all the principal leaders in the field. **(3)** To establish standardized characterization, analysis and interpretation protocols. **(4)** To facilitate interactions between BLSS researchers, researchers and clinicians, and researchers and industry. In particular to provide a forum collectively working towards the establishment of diagnostic protocols, to initiate further grant applications, and promote the development of marketable products or routine biomedical/diagnostic applications. **(5)** To bring BLSS and the potentials it offers to the

wider attention of both the scientific research community and the general public via open days, and hands-on workshops for identified target groups, as described below.

1.2.2. Capacity-building Objectives

The main objective of this action is to boost European research efficiency and competitiveness in the field of biomedical BLSS. Since this is an emerging and promising area of research and technological development with potential for disease diagnostics, the opportunity to take a lead in this area at a European level is crucial, if the currently existing independent efforts can be integrated into joint activities that combine complementary skills and approaches. Currently BLSS set-ups suitable for studying biological samples exist at selected locations in Europe, which will initially serve as "hubs" (see 1.3.3) where samples provided by biologists and clinicians can be investigated. These will also serve as meeting points for networking and training activities. The participants of this Action have already received numerous competitive funds to develop BLSS into more viable biological and clinically relevant methods, however this has been at the level of single research groups (at most involving clinical links) and countries. This Action should prove to be central in bringing together and coordinating the forthcoming advances in biomedical BLSS.
(1) Months 1 – 6: Setting up a user friendly website with a porthole (Sample and Personnel Exchange (SAPE) Porthole) to arrange STSMs and sample/personnel exchange. The SAPE porthole will also offer an online forum for posting and discussing technical and practical issues, troubleshooting recommendations, etc. **(2)** Months 6 – 48: Support of Early Career European researchers (ECER) by provision of STSMs and organization of scientific meetings, Workshops, Conferences and Training Schools aimed at training a new generation of young scientists in an interdisciplinary setting. ECERs will benefit from joint mentorship by leading experts in BLSS and have access to premier facilities throught the COST member countries. Moreover, the Action will promote gender balance at all levels of its organization. **(3)** Months 6 - 48: Establish a long-term collaboration between researchers already involved in Brillouin microspectroscopy, researchers in areas of microrheology and biomechanics,aswell as industrial partners and clinicians. It is expected that over the course of the first years an increasing number of clinicians will join the action as a result of targeted publicity and invitations to workshop meetings where relevant. **(4)** Months 13 – 48: Facilitate knowledge transfer among European players as well as between leading groups outside Europe and the Action members in order to promote the role of Europe in Brillouin Microspectroscopy development. **(5)** Months 19 – 48: Develop a vision of EU-wide advancement of biomedical BLSS with all countries involved at various levels. Seek a consensus on experimental and analytical approaches based on BLSS. **(6)** Months 25 – 48: Bring Brillouin Microspectroscopy to the wider attention of the scientific research community and the general public. Aside from the scientific outputs from peer-reviewed publications and associated press releases, this will also be achieved through special journal editions, conferences and satellite-meetings with associated proceedings, and the publication of a compendium in the last year of the action (to be funded by institutional means). **(7)** Months 37 – 48: Establish a multidisciplinary research network that will lead to a cooperative action for developing, preparing and submitting proposals for Horizon2020 and other collaborative international and EC joint initiatives. Promote grant applications such as Marie Curie Actions to fund research projects connected to this network and to train the next generation of BLSS researchers.

1.3. Progress beyond the state-of-the-art and Innovation Potential

1.3.1. Description of the state-of-the-art

BLSS is a non-destructive, contact-free technique which probes the elastic properties of materials at the microscopic scale via the the scattering of light from thermally induced acoustic waves or phonons. By probing a sample with visible or near-infrared monochromatic (laser) light and measuring the change in frequency (GHz) of the scattered light due to photon-phonon interactions, one can deduce parameters pertaining the viscoelastic properties of the sample – such as the elastic

storage and loss moduli. By scanning or rotating the sample under a microscope objective coupled to a BLSS spectrometer, one can generate diffraction limited 3D spatial maps, of the viscoelastic properties and gain information about the stiffness tensor of the material respectively. Traditionally, techniques for obtaining viscoelastic properties involve inducing physical perturbations and mechanical stress to a sample, or dynamically tracking labelled/scattering constituents. BLSS on the other hand offers a powerful non-invasive label-free means of studying mechanical properties of materials. Typically, the spontaneous Brillouin scattering signal is weak, which has in the past required the use of high laser powers and long acquisition times, which proved challenging for studying biological samples and processes with statistical relevance. Recently, the implementation of alternative spectrometer designs – employing e.g. Virtually Imaged Phase Arrays, has opened up new avenues for in vitro and in vivo studies. Also recently the implementation of Stimulated Brillouin scattering for mapping the mechanical properties of biological samples has shown to be promising for speeding up acquisition times. One setback has been that the Brillouin scattering spectra can be complex, and extracting the relevant parameters from measured spectra (especially in the case of opaque materials) is not always trivial. Furthermore, the interpretation of results in light of other mechanical measurements is still subject of controversy, partly due to the often unknown local densities and refractive indecies of samples.

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

Progress will follow along several distinct yet connected directions as outlined in the WGs. On the one hand, there is a broad interest from a fundamental research perspective in measuring non-invasively the mechanical properties of tissues at a subcellular level in order to better understand and model biological processes. Furthermore, the ability to correlate these with the underlying biochemistry, genetics and structural biology can provide a deep and far reaching insight into the interplay between molecular processes inherent to life and a living systems environment (nature). BLSS's **innovation potential** can be recognized in several areas. From a **biomedical perspective** many pathological conditions (various cancers, neurodegenerative diseases such as Alzheimer's, cardiovascular diseases, ophthalmological conditions, and bone diseases) are known to be closely associated with mechanical changes at the cellular and molecular level. Though having great diagnostic potential, due to the absence of suitable, reliable, and clinically approved methodologies, routine diagnoses based on mechanical properties are still largely absent. Identifying BLSS "signatures" for particular conditions or the onset thereof could lead to faster, reliable, cheaper and less invasive diagnostics and thereby provide benefits for human health. Correlative chemo-mechanical studies (as have been recently demonstrated using BLSS and sponataneous Raman spectroscopy) may lead to the identification of genetic/biochemical precursors and thus to novel therapeutic routes. BLSS also offers much potential for plant research, since the measurement of mechanical properties in soft tissue such as live roots is currently not possible using common perturbation based techniques, yet essential for understanding developmental processes. There is a growing interest in BLSS within the agricultural industry, for instance in the realization of robust and environment optimized crops. The potential to characterize the structural integrity and health of crops/ forests (which can be tied to their sustainability and commercial viability) in a non-invasive manner could save billions of dollars to the agricultural industry in addition to providing environmental benefits, if such measurements could e.g. be performed in an automated fashion at discrete locations in a field or forest. All these applications would also greatly benefit from more robust and compact BLSS set-ups and standardized analysis protocols, the creation, organization and infrastructure for which are key topics in this Action. **The anticipated progress beyond the state-of-the-art can be summarized as follows**: **(1)** exploring and unlocking the medical/diagnostic potential of BLSS by standardizing and optimizing data analysis and interpretation, and envisaging prospects for clinical tests. This includes investigating the potential for correlating observed spectral signatures with different diseases and conditions not yet investigated. For this task close collaboration with clinician partners providing pathological samples is envisioned; **(2)** Development of BLSS for phenotyping in life sciences. This involves more research effort being focused onto cellular analysis at the level of

single cell imaging, e.g. through microfluidic devices (participants are actively involved in this research area with funded projects on live cell sorting); **(3)** Instrument development specifically for BLSS applied to biological samples. This includes novel instruments/set-ups beyond the state of the art in terms of efficiency, stability, and multi-functionality. In this respect, great potential can be foreseen in multi-modal devices (e.g. micro-Brillouin/Raman and micro-Brillouin/Fluorescence set-ups) which can give both mechanical and molecular (chemical) characterization of the sample simultaneously, as already demonstrated by the applicants; **(4)** Investigating areas for application of BLSS within life sciences which have so far not been fully anticipated, e.g. stimulated Brillouin light scattering spectroscopy. All in all the work of the COST action is aimed at leading the way to transforming BLSS from a technique available in a few scattered optics/physics laboratories to a routine, robust and versatile analytical tool, opening the door for the wider implementation of BLSS in life science research, and paving the way for its implementation in clinical diagnostics to improve future healthcare and yield societal and economic benefits within Europe.

1.3.3. Innovation in tackling the challenge

Application of BLSS to life sciences holds far-reaching innovation potential which has not yet been fully realized. To exploit this potential, mutual interaction between separate groups working on BLSS technology development and scientists performing BLSS or other mechanical studies on different biological systems is crucial, the realization and promotion of which the proposed Action offers a perfect tool for. The main expected innovations resulting from the proposed Action are: **(1)** Development of standardized methodologies for the use of BLSS in the life sciences and investigation of its uses for non-invasive recognition of pathological changes in cells caused by the above mentioned diseases. **(2)** Development of strategies for real time assesment of therapies that alter tissue stiffness for clinical purposes. **(3)** Optimization and development of instrumentation specifically for BLSS of diverse biological samples. These proposed innovations can be achieved only through interaction of Action participants coming from distinct academic backgrounds. To this end the custom designed SAmple and Personnel Exchange (SAPE) Porthole, will be a key part of the Action website. In addition to arranging STSMs, this will also allow for the organization and documentation of sample exchanges and offer an open communication/discussion forum for all members of the Action.

1.4. Added value of networking

1.4.1. In relation to the Challenge

Currently different research groups use distinct (typically home built or modified) spectrometers and custom-developed acquisition and analysis protocols, aspects of which may not always be optimal for the system they are interested in studying. **An open exchange of information in this regard will prove greatly beneficial.** Another significant benefit that will naturally emerge from networking is the sharing of information on the use of optimal data analysis approaches and the establishment of acceptable quality standards for interpreting significant changes in viscoelasticity. Bioinformatician collaborators will be involved in the development of open source software for data analysis, in collaboration with members of all WGs. **Interaction of BLSS developers and users with private companies will allow for the potential integration of the latest discoveries into marketable BLSS based products.** The intended platform will enable their mutual meetings, staff exchange, and direct collaboration. All of this will further **stimulate more wide spread studies on pathological samples to asses the use of BLSS for diagnostics**. The other aspect of networking involves **training the next generation of scientists in BLSS.** A number of the WG leaders of this action are themselves early career researchers demonstrating that much attention is given to promote the career development of young scientists in the field. All efforts and enthusiasm put into this newly emerging technology together make a valuable knowledge base which will be systematically transferred to the interested scientific community. Special emphasis will be given to young

researchers who will be preferentially chosen for STSMs. Similarly, great attention will be paid to equal participation of both genders. This will present a unique opportunity for a broad multidisciplinary training covering biology, soft matter physics and biophysics, chemistry, engineering, material science, optics, medical research, and biomechanics.

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

There are currently no existing European or International networking efforts dedicated exclusively to BLSS in Biological Systems. The main motivation of this Action is to establish the first network of scientific collaborators in the field of BLSS, to promote advances in biological and health related applications and to become a leading community in "BioBrillouin". In addition to the organization of an annual (BioBrillouin) Meeting, focus groups, summer schools, workshops and events will be organised also as satellite meetings in conjunction with international events related to the study of biomechanics such as the Biophysical Society and mechanobiology subgroup meetings, the Plant Biomechanics International Conference; or other microscopy /optics events (e.g. Focus on Microscopy, SPIE, and European Light Microscopy Initiative meetings). Emphasis will also be placed on establishing links with other funded COST Actions such as Raman4Clinics (collaborations between WG leads are already in place).

2. IMPACT

2.1. Expected Impact

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

Short-term Science & Technology impact: (1) The Action will allow all participating researchers to compare and contrast, discuss and better understand the requirements and potential of their respective methodologies and protocols and to be on the "same page" regarding out-look and practical expectations and possibilities offered by the technology. **(2)** Networking will **minimize ineffective experimental duplications and time losses**, while coordinated efforts will yield **accelerated development of BLSS instrumentation and applications**. **(3) Development and implementation of standardized definitions and protocols for BLSS** beneficial for future users as well as for the technique developers including private manufacturers. This **will facilitate and speed up their efforts**. **(4)** Networking between instrument developers, biophysicists/biologists and clinicians to identify key application and diagnostic possibilities which will become the focus of further grant applications. (**5**) Coordinating distributed and parallel studies between different labs to statistically validate results and diagnostic potential **(6)** Undergraduate, PhD and postdoctoral positions will be generated via joint grant applications stimulated by this Action, which will introduce the technology to young scientists and allow for the infusion of fresh ideas.
Short-term Socio-economic impact: Although the impact is primarily on advancing new knowledge and sharing/exchanging ideas and good practices on the development of BioBrillouin, the short-term impacts will include **(1)** enabling a new generation of scientists to come together and get training/career development in BLSS. **(2)** creating a platform where clinical partners can be directly involved, generating opportunities for growth through e.g. in vivo studies and stimulating further grant proposals to support validation and clinical applications. **(3)** A platform giving industrial partners access to scientific discoveries and clinical partners will lead to expediated development of marketable products and filing of patent applications.
Long-term Science & Technology impact: (1) Bringing together all the players in this emerging field will greatly stimulate its long term **evolution towards an accessible, reliable and routine biomedical technique**, stimulate its advancement, and help introduce international standards and norms. This will lead to a **boost for the research in the field**. **(2)** The Action will have an overall **impact on the European scientific community** in terms of becoming the main source of knowledge on BLSS in biological samples and the latest developments. It will also **improve visibility** of the involved parties worldwide. **(3)** Support of Early Stage Researchers (ESRs) will yield **the next**

generation of BLSS experts who will continue working on the development of BLSS for life sciences applications, clinical applications, and beyond. **(4)** Longterm collaboration among all involved players will be generated, which will maximize coordinated development of BLSS and will pave the way for leveraging European funds in joint European research and development projects. **(5)** Knowledge transfer from overseas countries to Europe will ensure **Europe can stay at the forefront of BLSS research** and its biomedical and clinical applications.

Long-term Socio-economic impact: **(1)** Development of BLSS towards routine clinical use in the future will have a general impact on improving **public health through novel diagnostics and therapies of diverse medical conditions.** BLSS also has potential applications in cell-based therapies, since transplanted cells may need to be placed in tissue regions with a specific stiffness (or else tissue stiffness has to be altered before cell transplantation). **(2)** Development of BLSS for minimally invasive, fast and low-cost early diagnosis of diseases such as cardiovascular diseases, osteoarthytis, osteoporosis, keratoconus, etc. will in the long term contribute to a significant **decrease of treatment costs** by allowing timely implementations of optimum therapies/treatments and shorter hospital stays for patients. **(3) Realization of spin off companies** for the development of research- and diagnostic-grade BLSS instrumentation, as well as service orientated companies offering biomedical diagnostics. **(4) Involvement of European countries on a pathway to mutual development and concerted growth**.

2.2. Measures to Maximise Impact

2.2.1. Plan for involving the most relevant stakeholders

To the best of our knowledge all research groups actively working on BLSS for life science applications in Europe have been offered to be part of this Action. The feedback has been overwhelmingly positive, and includes also members from different disciplines and complementary fields. Applicants include also important overseas leaders in BLSS for biomedical applications. Medical doctors are also involved as Action proposers, who will enable access to pathological samples, and spread awareness of the Action in their communities to attract more clinicians to the field. In particular concerted efforts will be made to increase the number of medical doctors, expert pathologists, surgeons, and ESRs in the Action throughout its course by targeted advertisement and invitations to meetings/workshops. The main stakeholders in this Action are as follows:

- **Scientists working on BLSS instrumentation**. Unlike other spectroscopy and microscopy techniques there is currently no coordinated network or forum for discussing the advancement and optimization of BLSS specific instrumentation in regards to novel, routine or field applications.
- **ESRs** (including externally funded undergraduate and postgraduate researchers). BLSS in biological systems is by definition an extremely interdisciplinary field, requiring a solid understanding of optics, material science, phyisics and biology, and thus provides a broad, comprehensive training and fruitful research area for students and ESRs.The network can be considered essential to make possible such interdisciplinary research (by supporting e.g. student exchanges between labs with different areas of expertise/complementary approaches), while also stimulating future cross-disciplinary applications for funding students, industrial placements, and attracting ESRs to the field.
- **Biologists** (interested in understanding mechanical properties associated with fundamental biological processes using BLSS). In order for this to be possible a platform allowing access to both instrumentation (via instrument developers), as well as access to a network that includes researchers with expertise in biophysics/mechanobiology/material science (to assist with interpretation of results in the context of relevant material properties and other known or to be determined mechanical properties) are essential, and one of the key goals of the Action. The participants have already established links with genetists and neurophysiologists and these can be involved in the network as BLSS will develop into a powerful and validated tool in analytical research.
- **Clinicians** (physiologists, pathologists and surgeons). In the early stages of the Action clinicians will be invaluable for proving expertise on current challenges encountered in clinical settings (and thereby steering general research directions). This can be expected to indirectly enhance the

potential societal and economic impact of work carried out by Action members. Clinicians with related research interests will assist in facilitating routine access to pathological samples and assessing the significance and real-world feasibility of BLSS measurements as well as the relevance of the results in contrast to or as a means of complementing other approaches. Clinicians stand to benefit most significantly in the long term (beyond the scope of the current Action), whereby they can help facilitate larger scale clinical applications based on laboratory findings (of e.g. viscoelastic signatures associated with the onset of specific medical conditions), which may lead to routine use of BLSS in clinics for diagnostics and therapy.
- **Companies** (manufacturing optical and biomedical diagnostic equipment and pharmaceutical industries). These stand to benefit most significantly in the medium and long term. The action can be expected to stimulate collaborations with scientists working on BLSS instrumentation, for developing novel, optimized and robust BLSS setups, the potential market for which would include initially the biologists/biophysicists and clinicians listed above. Networking with researchers in academia can in the short term already be expected to stimulate co-applications for Academia-industry collaborative national and EU grants (e.g. FET Open), which will accelerate advances beyond the state-of-the-art and the realization of market ready products. In a similar way, pharma companies will be involved to test e.g. in vitro the effectiveness of their products towards recovery of elasticity in tissues. This could lead to improvements in treatment, such as in relation to ageing and diseases connected with collagen and elastin components of tissues losing their function.

2.2.2. Dissemination and/or Exploitation Plan

Dissemination is an essential part of the proposed Action. In order to ensure that all proposed activities will be carried out in a timely and effective manner, one of the MC members will be appointed as Dissimination Coordinator. Her/his first task will be to set up a dissemination plan with a set of guidelines where duties of the Action partners are listed. These will include the following:
- Creation of the Action logo and templates to be used for all BioBrillouin Action outputs.
- Creation of the Action web page including the SAPE porthole (described below).
- Preparation of online material, videos, photos and short descriptions for the web page.
- Exchange of the generated knowledge among Action members at regular BioBrillouin Meetings.
- Orchestration of exchange of ESRs between Action member laboratories.
- Publication of press releases to reach interested lay science audiences (1 per year).
- Organizing the publication of scientific reviews in journals describing the status/outlook of the field.
- Publication of popular-science articles aimed at lay audiences.
- Organizing Open-days, Open-days for Clinicians, Hands-on Workshops, and final Action conference.
- Additional dissemination activities (events in collaboration with research councils, societies, industries, and city councils) involving other funding bodies, charities, schools and media.

An additional task of the Dissemination Coordinator will be reaching out to members of specific target groups not yet aware of the action (industries focused on specific technologies, e.g. tissue engineering and pharmaceuticals, and clinicians working on particular diseases) in line with current and forseen progress/developments/popular-topics in the Action, and inviting these to general meetings and/or to join the Action. This will assure that access to relevant expertise is maintained among Action members, and that the Action network evolves and maintains its leading position in the field.
Web page: The Action's web page will be the central point where all information on the activities, open positions at member/partner institutions, as well as achievements and events within and related to the network will be posted. Confidential information (sensitive material e.g. when IP is to be protected) will be stored in a section accessible via login and password. Regular updates of the web page with the latest news and opening posts will be managed by an appointed Web Coordinator (an already employed IT specialist of one of the MC members' organisations). A part of the web page will be setup to facilitate arrangements for STSMs with minimum bureaurocracy – the Sample and

Personnel Exchange (SAPE) Porthole. This will also allow for the organization and documentation of sample exchange and offer an open communication/discussion forum for Action members. The locations of BLSS setups will be listed as hubs, with their availability for collaborative studies as well as details of the existing instruments. Over the course of the Action new members can list their set-ups with all specifications in this porthole. In an analogous manner, the porthole will also have a section where biophysicists, biologists and clinicians may list their profiles, scientific interests and offered resources, such that they can also be approached by instrument developers. This will include early career researchers so they can obtain support also for career development. This is expected to organically give rise to additional collaborations, shared students/postdoctoral researchers, and national and international grant applications. The full details and protocols for this SAPE porthole will be discussed during the first MC meeting, presented and further refined at the 1st BioBrillouin Meeting, and implemented shortly thereafter (see GANTT chart). In this way we expect to bridge and combine the diverse research expertise of the different members of the Action. A section of the webpage will also be dedicated to collecting and sharing data acquired from initiatives involving parallel or comparative studies by WG's. This would include raw spectra of materials, particularly standards for validation studies in the beginning, experimental protocols, and any relevant pathology or complementary non-BLSS studies. Presentations of the Action achievements at conferences: All conference contribution will acknowledge support from the Action and this will help disseminating the achieved outputs. Filing patent(s): Coordinated efforts of all involved parties are expected to yield patent applications supported in part by companies manufacturing relevant instrumentation. The framework for management of intellectual property resulting from joint Action projects will follow the rules set up in the **Intellectual Property Guidelines (IPG)** to be formulated and approved by the Management Committee in the first month of the Action. The IPG will be based upon the principle that for joint projects, unless agreed otherwise by all involved parties, each partner is entitled to use and license the knowledge independently.

BioBrillouin Hands-on Workshops: Two events will take place during the course of the Action. The workshops will focus on practical training in BLSS for various biomedical applications at one of the BLSS hubs. Educational material in the form of an electronic brochure will be produced as guidelines for Hands-on Workshop attendees, and later also available through the Action website. Demonstrators including the applicants themselves will provide training for the attendees.

BioBrillouin Meetings will be held annually with the participation of all WGs. These are intended as an occasion for presentation of each WG's achievements, knowledge transfer, discussions, general networking and idea exchanges.

BioBrillouin Open-days and **BioBrilloiuin Open-days for Clinicians** will be organized by the Outreach & Dissemination Work Group. These events will be aimed at students with diverse backgrounds and clinicians, respectively. Open days will be organized in connection to other Bio-Brillouin networking events to leverage funds in the most effective way.

STSMs as a tool for ESR exchange will be organized in the form of an open call for applications. 10 – 15 STSMs per year are expected to be organized, depending on the length of the stays. Strong preference will be given to young scientists and realizing equality between female and male scientists. If more that 60 % of the expected STSMs are assigned to one gender, applications by the opposite gender will be prioritized. All target groups will be taken into account for STSMs in order to maximize the Action impact.

A **BioBrillouin Conference** will be organized as the closing event for the Action. This will be open to external participants and prospective partners for further grant proposals. Internal as well as external speakers will be invited, a special section for involved ESRs will be organized, and future plans for financing the BioBrillouin community will be presented.

2.3. Potential for Innovation versus Risk Level

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

The field of Brillouin scattering spectroscopy in biological systems is starting to find applications in several diverse fields, but has yet to be accepted as a standard tool in biomedical research. This can be attributed to several factors, including **(1)** Stability and efficiency of current instruments, **(2)** Awareness within the scientific community, especially among biomedical researchers, and **(3)** Standardized and meaningful interpretation of results in relation to other techniques. This Action attempts to address all of these points so that they can reinforce and complement each other. It is very likely that advances in these key areas will enable a much wider range of applications for BLSS in biomedical research as well as clinical diagnostics. The potential of being able to map the high-frequency viscoelasticity in a non-invasive, safe manner with high-resolution spatial and temporal resolution is appealing in many life science applications. Furthermore, it can be expected that collectively, the combined progress of the defined WGs in this Action will eventually provide a fertile ground for the realization of commercial Brillouin Microspectroscopy solutions, either in the form of instruments developed by spin-off companies, in collaboration with established companies, or in the form of service orientated solutions for sample analysis/diagnostics. In particular, the long term potential of Brillouin microscopy finding routine uses in clinical research and diagnostics/therapy is an important outlook and motivation for this Action. The clinical usefulness of BLSS has been demonstrated in ophthalmology, and there already exists concrete evidence of the ability for the detection of cardiovascular diseases and cancer using BLSS. The organization of more comprehensive and comparitive studies (with other methodologies as well as BLSS measurements in different labs) is however necessary to help establish its validity and usefulness for diagnostic purposes. In this regard the network provides a “spring board” for initiating such comparative investigations as well as coordinated exploratory approaches to early diagnostics of other conditions, and establishing new and sustainable funding strategies for further studies. Given the continuing global rise in persons affected by major diseases such as cancer and dementia, the realization of novel complementary early diagnostic techniques is a societal priority, with the potential of enormous social and economic impact.

3. IMPLEMENTATION

3.1. Description of the Work Plan

3.1.1. Description of Working Groups

WG1: Medical and Clinical Applications

While certain medical conditions and diseases can be seen as being a direct consequence of changes in the mechanical properties of associated tissues (e.g. osteoarthritis, keratoconus, cardiovascular diseases), other diseases have also been found to be accompanied by less trivial changes in local stiffness. For example, certain cancers are known to be associated with or precluded by changes in mechanical properties, and there is mounting evidence that changes in the viscoelasticity may be connected with a host of other medical conditions including neuropathological disorders such as Alzheimer's disease. Furthermore, mechanotransduction and the effect of tissue substrate stiffness on stem cell differentiation has important implications in the rapidly developing field of cell-based therapy. The objectives of this WG consist of gathering and creating databases of spectral datasets, setting clinical standards, analysis of results in relation to routine pathological analysis, and optimization/development of instruments and protocols for clinical applications. Focus points: **T1.1** Intra/inter cellular and high spatial resolution BLSS mapping. Including mechanics at the tissue prosthesis interface (e.g. bone implants and dentistry), and in situ measurments of prosthesis aging. **T1.2** Tissue level BLSS mapping. **T1.3** In vivo BLSS applications. **T1.4** BLSS Biosensors and Endoscopy. **T1.5** Protocols, data interpretation, safety and quality control standardization. **T1.6** Establishing an online database of characteristic spectra/spectral signatures. **T1.7** Joint grant applications, and coordination of parallel, comparative and distributed studies on different pathology samples. Deliverables: Collating and reporting on individual and joint publications by action members pertaining to: **D1.1:** Studies of intracellular BSS mapping of pathological cells.

Month 13, 25, 37; **D1.2:** Studies of large area/volume BLSS tissue mapping of pathological cells. Month 13, 25, 37; **D1.3:** In vivo BLSS studies and progress towards BLSS endoscopy and biosensors. Month 25, 37**; D1.5:** publication of joint reports on the standardization of data analysis protocols, data interpretation for medical diagnostics and safety and quality procedures. Month 13, 37; **D1.6** Online open source spectra database for a range of different pathological samples. Month 37. Milestones: **M1.1:** Joint grant applications, collaborations and publications. Month 13, 25, 37**; M1.2:** Yearly WG meeting. Month 1, 13, 25, 37.

WG2: Phenotyping and Novel Applications in the Life Sciences

Detailed quantitative studies of the molecular/genetic origin as well as any associated morphological and behavioural characteristis of cellular and tissue scale high-frequency viscoelastic properties remain largely unexplored. This WG will work towards correlating how genetic/biochemical variations are correlated to viscoelastic properties as measured by BLSS (BLSS phenotyping), as well as on studies of changes in the viscoelasticity that may occur throughout the developmental cycle, are brought about by induced/environmental perturbations and their correlation to different phenotypes. Due to significant sample-to-sample variation in the mechanical properties and the sensitivity of BLSS to experimental and environmental conditions, as with WG1, a focus will be on collating results between labs to achieve statistically significant conclusions. While currently active use of BLSS in research/diagnostics is limited to several specific research areas, one can expect this WG to grow over the course of the Action, as BLSS becomes relevant in addressing diverse questions in biology. This WG is thus intended to also provide a platform for exploring such applications with collaborators working on disease diagnostics in collaboration with WG1. Focus points : **T2.1** Phenotyping (genetic, developmental, behavioural). **T2.2** Novel applications of BLSS in the life sciences. **T2.3** Protocol, data/result standardardization and interpretation. **T2.4** Establishment of an online database of Brillouin spectra. **T2.5** Joint grant applications. Deliverables: Collating and reporting on individual and joint publications by action members pertaining to: **D2.1:** BLSS Phenotyping studies. Month 1, 13, 25, 37**; D2.2:** Novel applications of BLSS in the life sciences. Month 1, 13, 25, 37; **D2.3:** publication of joint reports on standardized analysis protocols and norms for different phenotyping studies and emergent applications as relevant. Month 13, 37**; D2.4:** Online open source Spectra database, Month 37. Milestones: **M2.1:** Joint grant applications, collaborations and publications. Month 13, 25, 37, **M2.2:** Defining new biological applications. Month 13, 25, 37, **M2.3:** Annual WG meetings. Month 1, 13, 25, 37.

WG3: Instrument Design and Data Analysis

A large amount of effort is being dedicated to improving measurement techniques (primarily spectrometer design) in BLSS, since a major challenge in BLSS is due to the relatively weak scattering signal, which can require extensive acquisition times for high quality spectral data. For non-transparent materials such as biomedical samples, the elastic scattering can become overwhelming and needs to be sufficiently suppressed by high contrast interferometers for accurate BLSS analysis. Current spectrometer designs are often extremely sensitive to component alignment and can at times be quite expansive (taking up half of a large optical table). For routine use, fieldwork, clinical applications and commercialization, miniaturization and improvement of the robustness of BLSS spectrometers is highly desirable. Finally, since BLSS probes the stiffness tensor, measurements at different scattering angles and polarizations can be used to extract information on the stiffness tensor components in anisotropic samples, which can prove important for modelling mechanical properties, as well as for diagnostic purposes. Focus points : **T3.1** Improvement of instrument efficiency and novel spectrometer designs (including miniaturization, stabilization, and parallelization) **T3.2** Data Analysis: Data Clean Up / Information extraction / Data interpretation. **T3.3** Measurement of stiffness tensor (and other elastic moduli). **T3.4** Optimization of the sample environment and mounting for measuring highly anisotropic samples. **T3.5** Joint grant applications. Deliverables: Collating and reporting on individual and joint publications by action members pertaining to: **D3.1:** Advancements in BLSS instrumentation efficiency and speed. Month 1, 13, 25,

37; **D3.2:** Advancements in miniaturization/stabilization of BLSS instrumentation. Month 1, 13, 25, 37**; D3.3:** Progress towards measurement of anisotropic and complex samples. Month 1, 13, 25, 37**; D3.4:** Progress in optimizing sample environments for BLSS studies. Month 1, 13, 25, 37, and **D3.5** Standardized protocols for data processing, extraction, and interpretation. Month 13, 25, 37. Milestones: **M3.1:** Joint grant applications, collaborations and publications. Month 13, 25, 37**; M3.2:** Yearly WG meeting. Month 1, 13, 25, 37.

WG4: Correlative & Comparative Methods

While BLSS yields information on the viscoelasticity, it provides no direct information on the underlying molecular constituents and limited direct information on the morphological structure. It is thus desirable, especially for research applications, to combine the technique with other imaging/detection modalities to be able to understand the underlying origin of the measured mechanical properties. Furthermore, to calculate viscoelastic moduli, knowledge of the refractive index and the density in the probed volume is required, which may be inferred from parallel or sequential measurements using e.g. phase contrast techniques or fluorescence lifetime measurements. Finally, since BLSS measures viscoelastic parameters in the high-frequency regime, direct comparisons to techniques which measure the low-frequency elastic properties is nontrivial and material dependent (an inherent problem of viscoelastic materials). Comparative studies of the frequency scaling of viscoelasticity can thus prove insightful for understanding how materials behave accross different frequency regimes. Focus points: **T4.1** Combined or correlative measurements with other optical technqiues (Raman, CARS, Fluorescence, SHG, etc.), other functional imaging modalities, as well as approaches for improving signal-to-noise in BLSS measurements using e.g. surface/cavity enhancement effects, etc. **T4.2** Comparative studies with other mechanical measurement techniques (AFM, micro-rheology, etc.), as well as experimental and theoretical work on the frequency scaling of mechanical parameters in different samples. **T4.3** Joint applications for national and international grants. Deliverables: Collating and reporting on individual and joint publications by action members pertaining to: **D4.1:** Correlative studies with other functional imaging modalities. Month 1, 13, 25, 37**. D4.2:** Comparative studies with other methods measuring mechanical properties. Month 1, 13, 25, 37. Milestones: **M4.1:** Joint grant applications, collaborations and publications. Month 13, 25, 37**; M4.2:** Annual WG meetings. Month 1, 13, 25, 37.

WG5: Outreach and Dissemination

Though a number of studies using BLSS on biological samples have been documented, there is a lack of awareness of the technique among the general public, the biomedical research community, and even the microscopy/bioimaging community at large. Part of this Action will thus be dedicated to public outreach. A focus will also be offering assistance to researchers for the development and installation of set-ups in their laboratories and at bioimaging/biooptics facilities. Researchers affiliated with this group will present the potential of BLSS to, e.g., the “Winter School on Biotechnology” in Perugia and other similar schools for graduate students in the EU. In the last year of the Action, an online open access book will be published (funded by external sources: participants’ grant, donations from different societies/Universities) written for biomedical researchers and authored by the partners of the Action cataloguing the principles, results and latest developments in BLSS as applied to biomedical applications. Publications will be accompanied by public outreach activities including press releases, also through social media outlets. Tasks of the WG will also involve maintenance of regular news and event updates on the website relating to activities of action members as well as other relevant research results, maintenance of the online spectra databases in collaboration with other WGs, and editing and organizing meeting proceedings. Deliverables: **D5.1:** Organizing/editing proceedings of WG meetings. Month 1, 13, 25, 37; **D5.2:** Organizing and reporting on Open days. Month 9, 33**; D5.3:** Organization of Hands-on Workshops. Milestones: **M5.1:** Reaching out to the general public, scientists, clinicians, industry and other groups described in the dissemination plan.

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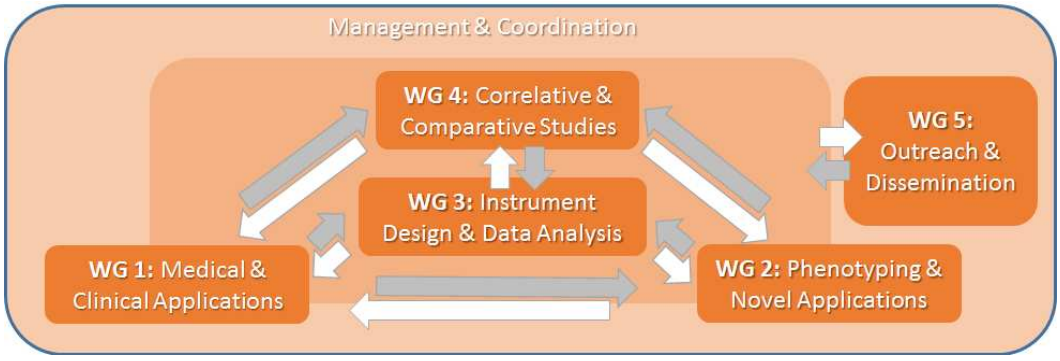
3.1.2. GANTT Diagram

GANTT CHART		Duration (months 1–48)
WP1	**Medical & Clinical Applications**	48 months
T1.1	Intra/inter cellular mapping	
T1.2	Tissue level BLSS mapping	
T1.3	*In vivo* BLSS applications	
T1.4	Biosensors and Endoscopy	
T1.5	Protocols/safety/quality	
T1.6	Online Database	
T1.7	Joint Grant applications	
WP2	**Phenotyping & Novel Applications**	48 months
T2.1	Phenotyping	
T2.2	Novel Applications	
T2.3	Protocols/data/standardization	
T2.4	Online Database	
T2.5	Joint Grant applications	
WG3	**Instrument Design & Data Analysis**	48 months
T3.1	Instrument/spectrometer design	
T3.2	Data analysis/interpretation	
T3.3	Stiffness Tensor & other moduli	
T3.4	Sample environment/mounting	
T3.5	Joint Grant applications	
WG4	**Correlative & Comparative**	48 months
T4.1	Correlative	
T4.2	Compartive/frequency scaling	
T4.3	Joint Grant applications	
WG5	**Outreach & Dissemination**	48 months
T5.1	Website	
T5.2	Open day	
T5.3	Open day (for clinicians)	
T5.4	Hands on w orkshop/training schools	
T5.5	Publication of book	
T5.6	Publication of meeting proceedings	

3.1.3. PERT Chart



3.1.4. Risk and Contingency Plans

WG	Risks	Contingency plan
WG1 Medical and Clinical Applications	1) Obtaining approval to work with pathological/animal samples. 2) Adverse affects of high laser powers / extended exposure times / prolonged alignment times, leading to unreliable data or negatively affecting samples.	- Close collaborations with clinicians. Preparing & submitting applications for working with samples in a timely fashion. - Optimize instruments and methodologies (collaboration with WG3 & WG2) to preserve relevant properties (e.g. reduced spectral or spatial resolution mapping)

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WG2 Phenotyping and Novel Applications	1) Large variability between similar samples and measurements at different labs (high sensitivity to experimental / sample conditions). 2) No clear correlation to biochemistry/genetics/phenotype.	- Collaborate with WG3 to develop optimized instruments and experimental standards. - Refer to the established standards for phenotyping studies. - Perform measurements at different labs. - Explore other viscoelastic parameters (e.g. Shear Modulus)
WG3 Instrument Design and Data Analysis	1) Limitations on efficiency and versatility of miniaturized instruments. 2) Disagreement on standards/figures of merit for assessing instrument/design performance, reliability and stability.	- Establish collaborations with experts in academia and industry to develop focus groups that address bottlenecks in instrument design. - Open discussions between members to draft a consesus on experimental standards early on in Action. Referring to this document when disagreements arise.
WG4 Correlative Methods	1) Adverse affects of high laser powers on correlated imaging modality measurements. 2) “Bleed through” on detected Brillouin spectra from parallel correlated imaging modality. 3) Labeling required for correlative measurement technique affects elastic properties obtained by BLSS.	- Optimize setup to reduce spatial and/or spectral resolution such that conditions are favorable for correlative technique (work with WG3 & WG2). - Do sequential as opposed to parallel correlative studies. Perform second imaging mode on a different sample and map correlations on sample template. - Focus on studying specified regions of interest as opposed to large areas
WG5 Outreach and Dissemination	1) Delays in publishing/distributing reports. 2) Limited attendance at hands-on workshops.	- Closely follow the agreed workplan. - Promote meetings through journals, conference websites, mailing lists, other relevant consortia.

3.2. Management structures and procedures

BioBrillouin’s management will follow the COST Action Management rules, as specified in the COST Vademecum and will work in agreement with the Action Science Officer. Therefore no detailed description of these procedures are presented here. The action will be initiated by the 1st **MC Meeting** which will be held together with a Kick-off meeting in the 1st month of the Action. MC meetings will be organized and will take place annually, and back-to-back with annual WG meetings (**BioBrillouin meetings**) to minimize travel costs. All Action decisions are taken by the MC, the Chair with the support of the core group will propose decisions which may then be taken by the MC. Scientific goals of each WG will be discussed and assessed annually. Throughout the course of the Action, 2 day MC and BioBrillouin meetings will take place at different locations, reflecting the geographical distribution of the current Action members.

The Action will establish a **Core Group (CG)** as an operative body in order to facilitate the day-to-day management, communication, and decision-making. The CG will be composed of Chair, Vice Chair, web coordinator, grant manager, dissemination coordinator, STSM coordinator and the WG leaders, and serve to ensure overall effective implementation of management, monitoring, and networking procedures. Key tasks with approval of the MC will include **(1)** To ensure transparent and efficient project administration, including management of financial issues. **(2)** To organize and

coordinate all networking activities in collaboration with WG5. **(3)** To maintain the Action website including the SAPE porthole. **(4)** To implement procedures for efficient coordination, monitoring and evaluation of project activities. **(5)** To monitor, evaluate and mitigate potential risks that might arise during the project in accordance with the risk management plan. Deliverables will include: **(1)** Kick-off meeting minutes (month 1); **(2)** Dissemination plan. Month 2; **(3)** Website publication (month 3); **(4)** Action handbook as approved by MC (month 3); **(5):** Documenting Minutes of MC meetings (month 1, 13, 25, 37, 47); **(6):** Project progress reports (month 12, 24, 36, 48). Milestones will include **(1)** Kick-off meeting (month 1); **(2)** Realization of first STSMs (month 12); **(3)** BioBrillouin meetings (month 1, 13, 25, 37). CG meetings, held monthly in the form of Skype conferences, will discuss the coordination of the next steps in the Action plan. The CG's initial responsibility will be to produce a simple set of Action rules (**Action handbook**) in accordance with the COST rules, that will be approved by the MC. The handbook will contain protocols on how to accept new Action members, communication rules, contact details of all MC and CG members, quality assurance rules, internal evaluation forms, the dissemination plan, an outline of all Action activities, and application format for STSMs. Besides Chair, Vice Chair, and Grant Manager, whose roles are given by the COST rules, a **Web Coordinator**, **Dissemination Coordinator and STSM Coordinator** will be appointed. The Web Coordinator (a currently employed IT specialist of one of the participating organisations) will be responsible for the creation of the Action website and SAPE porthole, as well as regular updates and maintenance thereof. The Dissemination Coordinator (a voted MC member) will be responsible for elaboration of a Dissemination Plan, and its proper implementation and execution. The STSM Coordinator (a voted MC member) will be responsible for forming an STSM Committee and defining transparent criteria for STSM evaluation, the evaluation of STSMs, and reporting to the MC. A COST Action **Website** (e.g. www.BioBrillouin.eu) along with a mailing list will keep Action members up to date with current events and developments related to the Action. Delays resulting from disagreements between partners or coordination/availability problems will be solved by initiating open discussiona among involved parties and closely following the agreed upon work plan and deliverables.

Hands-on Workshops (~1 week duration) will be organized two times during the Action. These will be located in two of the "hubs" and make use of the accessible facilities/infrastructure. Shorter hands-on workshop/open-days specifically for clinicians will be organized by one of the hubs once a year (see also GANTT chart). **BioBrillouin Open days** will be organized twice during the Action (1st and 3rd year), and focus on attracting undergraduate and PhD students with backgrounds in the life and physical sciences, and held at two other Action hubs back-to-back with another Action event (Hands-On trainings or similar). A number of **STSMs** will be financed each year for exchange of knowledge and training between partners in different COST member states. These will be organized via the SAPE porthole on the Action website where a call for STSMs will be regularly published. After each call the CG will evaluate the applications and decide which to finance. The final decision will be approved by the MC, who bears the right to overide the CG's decision. The CG will favour the mobility and training of young researchers and promote gender equality and balance.

3.3. Network as a whole

Over the last several years a clear need has arisen for increased mutual interaction between groups developing and using BLSS on biological samples as well as interested biologists and clinicians. While there have been some collaborative exchanges between instrument developers, there exists no dedicated network, forum or meeting, which has stunted the wider application, popularity and refinement of the use of BLSS for biological research and its development towards clinical use. In this regard, the COST Action is ideally suited for boosting the technological development and implementation of BLSS in the life sciences. The network of proposers have a diverse set of expertise, ranging from theoretical and experimental optics and physics, to material science, physical chemistry, clinical research and molecular biology. They hold positions ranging from acclaimed independent researchers at universities/research Institutes and managers of advanced optical

microscopy facilities/centers, to medical researchers at hospitals and scientists at European companies. Additional International proposers are leaders in the field and compliment the existing expertise, assuring that all major players are involved. Cross fertilization of ideas can be expected to not only lead to innovative applications and implementations of BLSS, but also to strongly promote and guide the development of novel BLSS instrument designs for routine and specific life science applications. The critical mass for the proposed Action is evident in the participation of nearly all researchers actively publishing on BLSS as applied to biomedical research. The action will continuously seek out new academic and industry members as well as clinicians during the first three years to continously maximize the impact of the network and assure that it always remains relevant to current research trends.

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