EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Brussels, 4 June 2019

COST 023/19

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action "Glioma MR Imaging 2.0" (GliMR) CA18206**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action Glioma MR Imaging 2.0 approved by the Committee of Senior Officials through written procedure on 4 June 2019.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA18206
GLIOMA MR IMAGING 2.0 (GliMR)

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

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

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

The main aim and objective of the Action is to build a pan-European network of experts in glioma research, patient organisations, data scientists, and MRI scientists by uniting the glioma imaging community within Europe and progressing development and application of advanced MRI for improved decision making in diagnosis, patient monitoring, and assessment of treatment response in clinical trials and practice. 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 84 million in 2018.

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

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

OVERVIEW

Summary

In Europe, 50,000 new cases of primary glioma occur each year, and this number is expected to rise with the aging population. Well-established international consortia are putting tremendous research efforts into a better understanding of glioma pathology and improved treatment strategies. Magnetic resonance imaging (MRI) only has a minor role in these research efforts, despite being a widely available medical imaging modality and whilst advanced MRI techniques are emerging with great potential for improved characterisation of glioma. To exploit advanced MRI to the fullest, two issues need to be solved: (1) The scattered research landscape in which advanced MRI is being developed for glioma imaging. (2) The limited presence of advanced MRI research in established consortia for clinical work and research in glioma.

This COST Action aims to build a pan-European and multidisciplinary network of international experts in glioma research, patient organisations, data scientists, and MR imaging scientists by uniting the glioma imaging community within Europe and progressing the development and application of advanced MR imaging for improved decision making in diagnosis, patient monitoring, and assessment of treatment response in clinical trials and clinical practice.

This COST Action will bring Europe to the global forefront on glioma imaging research, by providing recommendations and open-access software tools that will accelerate the bench-to-bedside translation of advanced MRI techniques. These scientific developments will further the understanding of glioma pathophysiology facilitating scientific breakthroughs in novel therapies and improve personalised patient management ultimately increasing the quality of life of glioma patients.

Areas of Expertise Relevant for the Action	Keywords
● Medical engineering: Diagnostic tools (e.g. genetic, imaging) ● Medical engineering: Databases, data mining, data curation, computational modelling ● Clinical medicine: Oncology ● Clinical medicine: Clinical trials	● Glioma ● Magnetic resonance imaging ● Biomarkers ● Multi-site data integration ● Neuro-oncology

Specific Objectives

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

Research Coordination

● Coordinate the identification and quantification of advanced MRI biomarkers for the application in the field of glioma, via harmonisation of imaging protocols and standardisation of open-access data analysis tools.
● Coordinate multi-site date integration and enable the creation of large datasets in glioma diagnostics by combining heterogeneous data sets from sites across Europe.
● Disseminate the Action's goals and results in tailored manners to all relevant stakeholders, including the scientific and clinical communities, patient organisations, industry, and the general public.

Capacity Building

● Foster cross-border information and knowledge exchange about past and current clinical trials and studies of glioma in order to develop multi-site, multidisciplinary, pan-European clinical studies while increasing the involvement of Inclusiveness Target Countries (ITCs).
● Act as a pan-European network for advancing glioma MRI and translating advanced MRI biomarkers from bench to bedside, bridging between MR imaging scientists and stakeholders from key international and multidisciplinary organisations on glioma research, industry collaborators, clinical practice and patient

organisations.

TECHNICAL ANNEX

1 S&T EXCELLENCE

1.1 SOUNDNESS OF THE CHALLENGE

1.1.1 DESCRIPTION OF THE STATE-OF-THE-ART

In Europe, approximately 50,000 new cases of primary glioma (brain tumours originating from glial cells) occur each year[1]. As the incidence rate increases with age, this number is rising with the aging European population. Overall survival rates range from >10 years for lower grade glioma to only 10 months for the most aggressive forms of glioma (glioblastoma)[2]. The optimal treatment strategy depends on the type and grade of glioma and can consist of a 'watch-and-wait' period, surgery for maximum safe resection, chemo- and radiotherapy. Accurate diagnosis of glioma and optimal patient monitoring are of utmost importance for timely treatment decision making and adequate therapy planning. Moreover, with no existing cure tremendous research efforts are being made into a better understanding of glioma biological behaviour to improve current and develop new treatment strategies. As a widely available, non-invasive and applied medical imaging modality for investigating the structure and physiology of brain tissue, magnetic resonance imaging (MRI) is the diagnostic modality of choice to direct patient-centred management in clinical practice, and has a key role to fulfill in research into the mechanisms of glioma pathophysiology and novel treatments.

While conventional MRI techniques mostly assess 'static' information about structure of brain tissue and vasculature, advanced MRI techniques measure physiology of brain tissue, including dynamic processes such as: perfusion, metabolism, and oxygen extraction. These advanced techniques give valuable MRI *biomarkers* for glioma, as they are (semi)quantitative and aid in detection, diagnosis, prognosis, treatment planning, and assessment of treatment response.

Advanced MRI is the diagnostic modality of choice to detect and diagnose gliomas. These tumours are known to have a heterogeneous microenvironment: different types of pathological tissue of varying levels of aggressiveness are present within each tumour. Accurate diagnosis of glioma according to the 2016 World Health Organisation (WHO) Brain Tumour Classification[3] requires molecular analyses of tissue obtained from the most aggressive part of the tumours. There is a growing body of research highlighting that (a combination of) physiological biomarkers resulting from advanced MRI techniques are able to map the heterogeneous microenvironment of brain tumours non-invasively (Figure 1)[4,5]. This means that for the individual patient, not only more accurate tumour delineation can now be done than the current standard based on conventional MRI alone, the most aggressive parts of the tumour can be more reliably identified and targeted to obtain the most accurate and relevant diagnosis of glioma.

Advanced MR imaging has a vital role in the development of *radiomics* for glioma: the extraction of large numbers of features from imaging, genetics (radiogenomics), and clinical assessments that jointly analysed via machine learning algorithms are used to aid diagnosis and predict treatment response for the individual patient[5,6]. The WHO 2016 reclassification of gliomas underlines that genomic and proteomic analyses, rather than histopathological analyses are the key prognostic determinants in glioma. Out of the 70,000 active genes in the human genome, some were identified to influence glioma response to therapy and malignancy such as *IDH mutation* status, *ATRX*, p53, 1p/19q-co-deletion, and *MGMT* status. To further the field of *radiomics* and find non-invasive markers for diagnosis and prognosis of glioma, big data sets are required that included advanced MR imaging data.

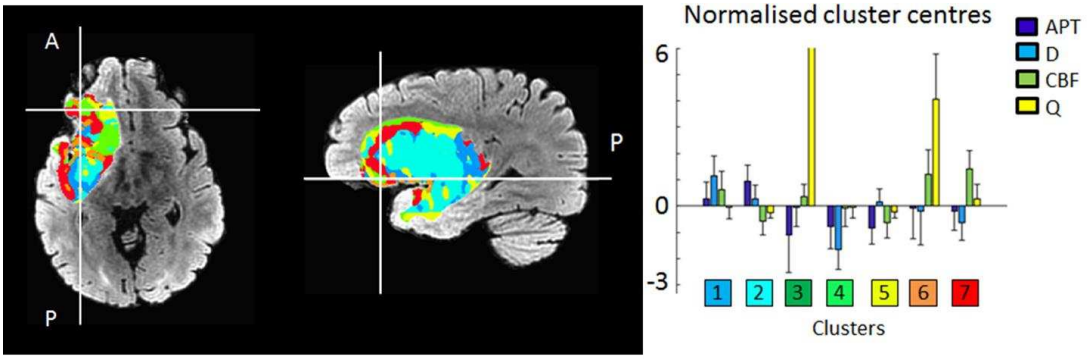

Figure 1. Example of using advanced MRI biomarkers to map the heterogeneous microenvironment of non-enhancing glioma. **Left**: Overlay of 7 different types of tissue within the tumour on axial and sagittal cross-sections of a T_2-weighted FLAIR image. Tissue types are determined based on a clustering algorithm with advanced MRI biomarkers as input and are characterised on the **right**. *APT: Amide proton transfer ratio, D: Diffusion coefficient, CBF: Cerebral blood flow, Q: Vessel density, A: anterior, P: posterior.*

Advanced MRI is the diagnostic modality of choice to monitor patients diagnosed with glioma before, during, and after treatment[7]. MRI offers the ability to do non-invasive, repeated examinations with minimum risk for the patient. Firstly, treatment monitoring is important for patients diagnosed with low grade glioma, for whom early and aggressive treatments do not necessarily lead to improved overall survival[8]. Novel physiological parameters, resulting from advanced MRI techniques can serve as early markers for progression from low to high grade glioma[9]. Secondly, advanced MRI is optimal for treatment planning; novel MRI biomarkers lead to improved localisation and determination of the extent of the tumour. Moreover, MRI-only treatment planning for photon/proton radiotherapy is emerging, including ultra-short echo time sequences to create maps of bone tissue (*synthetic computed tomography*) which reduces the pre-treatment radiation dose to the patient. Lastly, accurate determination of treatment response to distinguish tumour progression from radiation necrosis and pseudoprogression is vital for decision making after treatment[7]. In contrast to conventional MRI, advanced MRI techniques have shown the potential to distinguish treatment response from tumour progression and thus greatly improve timely decision making[10,11].

Advanced MRI is the diagnostic modality of choice for research into improved and novel treatment strategies for glioma. Advanced MRI techniques are currently used in research studies into *in vivo* glioma pathophysiology[12], have the potential to identify novel targets for treatment strategies[13], and are used to investigate mechanisms of treatment, both on pathological and healthy tissue[14,15]. As an example, non-invasive physiological biomarkers are being developed for early identification of adverse effects on healthy tissues, allowing for timely adaptation of therapy for the individual patient (Figure 2). Furthermore, advanced MRI is essential in clinical trials. Not only is the excellent sensitivity to the heterogeneous microenvironment of glioma important for optimal patient selection, but the capability of differentiating response to treatment from tumour progression make advanced MRI ideal for assessment of treatment efficacy of novel therapeutics.

Europe has the potential to become world-leading in glioma imaging diagnostics and thus further advance glioma treatment. European clinical centres already are international leaders in clinical trials and research for improved treatment strategies of glioma. Across Europe there are world-leading research groups developing advanced MRI biomarkers in health and disease. Moreover, the combined capacity of academic and general clinical centres in Europe, with 24 operational proton therapy centres[16] (and several more under construction), approximately 4000 radiotherapy units, and 10.000 MRI units[17] on which more and more advanced MRI data is being collected every day, enables Europe to pioneer the field of glioma MRI diagnostics.

1.1.2 DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Despite its clear potential, advanced MRI is barely used in clinical practice and research for non-invasive characterisation of tumour physiology and metabolism in glioma diagnostics. The application of advanced MRI is hampered by:

1. The scattered research landscape in which advanced MRI is being developed for glioma imaging.
2. The limited presence of advanced MRI research in established consortia for clinical work and research in glioma.

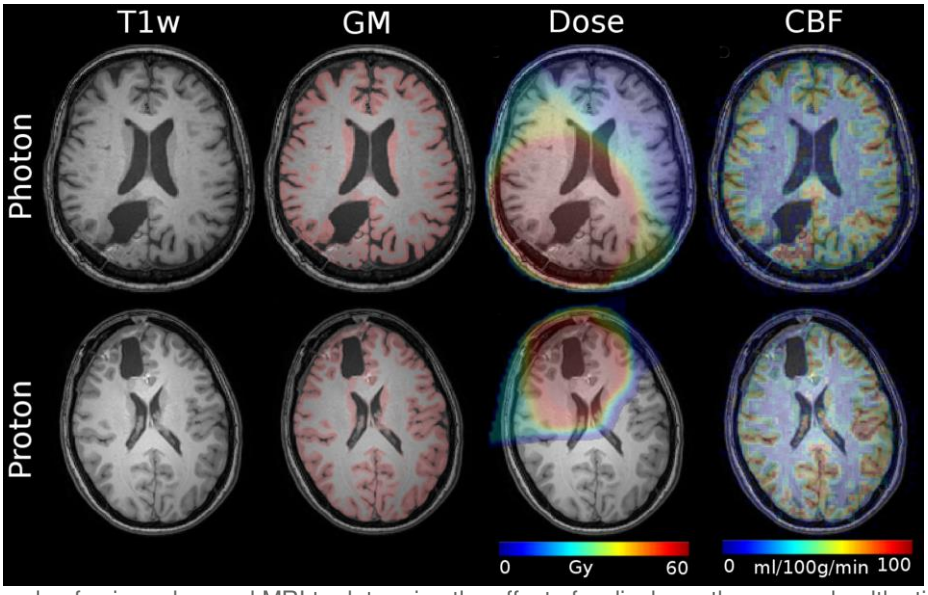

Figure 2. Example of using advanced MRI to determine the effect of radiochemotherapy on healthy tissue. *From left to right*: T1-weighted structural images, T1-weighted overlaid with a segmentation of the grey matter (GM) in red, calculated total radiation-dose, and cerebral blood flow (CBF) maps acquired using arterial spin labeling MRI. Images from patients treated with photon therapy (top row) and proton beam therapy (bottom row).

Despite tens of thousands new cases of glioma each year in Europe, the local incidence is low. This leads to the current landscape of small, often underpowered, research studies at individual sites across Europe, running in parallel and generally without coordinating their approaches for imaging diagnostics and inclusion of advanced MRI methods. In addition, a multitude of advanced MRI techniques exists with even less consistency between sites in their approach to subsequent image analysis. This is especially problematic because evidence is emerging that optimal in vivo characterisation of glioma should be done via a *combination* of advanced MRI parameters[18]. There is limited harmonisation of the advanced MRI techniques to be used, there are no recommendations of the optimal combination of these biomarkers, nor is there standardised open source data analysis software for post-processing. This scattered landscape additionally hampers the formation of big data sets, which complicates the development of *radiomics* for glioma diagnostics.

There are well established consortia with a focus on glioma research, particularly into improved and new treatment strategies. However, despite the presence of imaging subcommittees, the research community on advanced MR imaging has only limited representation in these consortia. This means that the required critical mass of multidisciplinary experts in the fields of glioma research and advanced MRI does not currently exist, and the use of advanced MRI for glioma diagnostics remains limited.

As a consequence of not using advanced MRI to its full potential for glioma diagnostics, developments towards *personalised medicine* in glioma are stagnant. Accurate and detailed characterisation of glioma physiology and metabolism *in vivo* is required to be able to tailor treatment strategies to the individual patient, ensuring minimal burden to the patient and hereby ensure the highest quality of life. Moreover, through the failure to exploit the potential of advanced MRI to identify novel targets for therapy and assess treatment efficacy, scientific breakthroughs for developing novel treatment strategies are hampered by the lack of advanced MRI in glioma research.

This COST Action aims to build a pan-European and multidisciplinary network of international experts in glioma research, patient organisations, data scientists, and MR imaging scientists by uniting the glioma imaging community within Europe and progressing the development and application of advanced MR imaging for improved decision making in diagnosis, patient monitoring, and assessment of treatment response in clinical trials and clinical practice.

1.2 PROGRESS BEYOND THE STATE-OF-THE-ART

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

This COST Action will bring Europe to the forefront of glioma imaging diagnostics by coordinating the development of advanced MRI biomarkers and the collection and combination of datasets across

Europe, as well as the stimulation of their use in clinical research and practice, by uniting researchers, clinicians, patients, industry, and society.

To tackle the scattered landscape of research studies on advanced MRI for glioma imaging this COST Action will focus on harmonising these efforts across Europe. Via multidisciplinary networking clear, open-access guidelines and recommendations on data acquisition and open-source analysis tools for advanced MRI biomarkers for glioma characterisation will be created. As a consequence, the current necessity of in-house expertise and experience for application of advanced MRI biomarkers for glioma diagnostics in both research and clinical settings will fade. This in turn will stimulate the development and application of emerging imaging biomarkers for glioma characterisation, such as non-invasive measurement of tissue oxygenation and real-time metabolic flux imaging, and will bring Europe to the global forefront of glioma imaging research.

This COST Action will initiate a multi-site data integration approach to tackle the issue of small local datasets on glioma imaging, which are a result of the scattered landscape of research in combination with the low local incidence of glioma. These small studies currently impede the impact of advanced MRI in glioma research, due to the limited statistical power and low repeatability of the results. This COST Action will make an inventory of European glioma research studies by building lasting bridges between existing, international consortia on glioma research, MRI imaging scientists, clinicians, patient organisations and other relevant stakeholders. This interdisciplinary network will progress glioma research as it allows for identifying the clinical needs and assisting clinical application of advanced MRI. Furthermore, this network will stimulate multi-site and international research studies in which existing data is given added value via careful evaluation of the current use of advanced imaging biomarkers, as well as studies in which novel, structured acquisition approaches to investigate the application of advanced MRI in glioma are designed.

By bringing together experts in data sharing governance, reviewing existing data sharing facilities, and creating guidelines for best practices in data sharing, this COST Action will facilitate the generation of large data sets for glioma research. This approach will allow for ground-breaking progress in the development of MRI biomarkers for glioma, as well as the application of *radiomics*, in which quantitative imaging data is combined with genetics and clinical assessments. This COST Action will focus on tackling two major problems that come with multi-site data integration; (i) Pooling existing datasets from multiple imaging sites is complex, due to the heterogeneity of the data caused by factors such as varying imaging instruments, machine-specific artefacts, and differences in MRI-sequences; but also from subtle variations in the performed procedures within the clinical setting. This COST Action will facilitate data exchange within Europe, while stimulating the use of methods that can deal with this unwanted heterogeneity. In addition, this COST Action will define best practices to inform participants and collect their consent for data sharing, identify and advertise existing infrastructures, and standardise how metadata are shared. (ii) The development of recommended cross-discipline approaches for streamlining the application of advanced MRI in glioma research requires input of specialists in all glioma-related clinical domains, including neuro-oncology, neurology, radiotherapy, neurosurgery, neuropsychology, molecular biology, genetics, and pathology. This COST Action will generate the interdisciplinary network with the needed critical mass to develop guidelines on the combination of imaging data with non-imaging related metadata such as psychological assessments, genetics, and histological data. These guidelines should be feasible within a standard clinical setting, both academic as general, therefore requiring the input of involved staff members of the daily clinical practice, such as nurses and radiographers. Finally, patient comfort should always be guaranteed, which make patient organisations an important part of this COST Action, as they will represent the interests of patients diagnosed with glioma.

This COST Action will progress beyond the state-of-the-art in glioma imaging by accelerating the use of advanced MRI for tumour characterisation, the identification of regions at risk of progression, the assessment of disease progression, and the evaluation of treatment-related adverse effects. For example, a more precise identification of infiltrative tumour regions and a better differentiation between progression and pseudo-progression during treatment can be achieved by using multiple advanced MRI biomarkers, which together evaluate the heterogeneity of both the structure ***and*** physiology of the glioma and surrounding tissue, rather than a single parameter such as the maximum perfusion within the tumour. As another example, glioma treatment is associated with brain damage, located within the environment of, as well as in regions remote from the primary target region of treatment. Studies are emerging, investigating the side-effects of different treatment strategies (e.g. radiation, chemotherapy, or both) and varying doses on brain damage and clinical complications, leading to a reduced quality of life. Large, longitudinal studies are key to finding

associations between glioma treatment, MRI biomarkers, as well as patient outcomes, such as the long-term quality of life and cognitive capacity. Such findings might lead to successful tools for patient monitoring and early prediction of patient outcomes. **This COST Action will use these new insights to stimulate innovation in *personalised* strategies, aiming at the refinement of diagnosis and the assessment of disease progression, the minimisation of adverse effects, and eventually the improvement of the long-term quality of life of the patient.**

1.2.2 OBJECTIVES

1.2.2.1 Research Coordination Objectives

This COST Action will focus on uniting the know-how of advanced MRI in glioma research and demonstrating how combining data acquired across European centres of excellence can aid in the use of advanced MRI biomarkers in the diagnosis, the assessment of the disease progression and evaluating the treatment of glioma. Therefore, this COST Action aims to:

- Coordinate the identification and quantification of advanced MRI biomarkers for the application in the field of glioma, via harmonisation of imaging protocols and standardisation of open-access data analysis tools; *[Working Group (WG) 1]*
- Coordinate multi-site date integration and enable the creation of large datasets in glioma diagnostics by combining heterogeneous data sets from sites across Europe; *[WG2]*
- Disseminate the Action's goals and results in tailored manners to all relevant stakeholders, including the scientific and clinical communities, patient organisations, industry, and the general public. *[WG5]*

1.2.2.2 Capacity-building Objectives

To generate the required critical mass of experts and stakeholders to promote the use of advanced MRI biomarkers in glioma imaging in research and clinical practice this COST Action aims to:

- Foster cross-border information and knowledge exchange about past and current clinical trials and studies of glioma in order to develop multi-site, multidisciplinary, pan-European clinical studies while increasing the involvement of Inclusiveness Target Countries (ITCs); *[WG3]*
- Act as a pan-European network for advancing glioma MRI and translating advanced MRI biomarkers from bench to bedside, bridging between MR imaging scientists and stakeholders from key international and multidisciplinary organisations on glioma research, industry collaborators, clinical practice and patient organisations. *[WG4]*

2 NETWORKING EXCELLENCE

2.1 ADDED VALUE OF NETWORKING IN S&T EXCELLENCE

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

As this COST Action aims to bridge the gap between imaging scientists and the wider (clinical) research community, collaborations with existing efforts and networks with a focus on glioma (imaging) research are foreseen throughout the duration of the Action.

The EORTC Brain Tumour Group initiates and conducts academic clinical trials in patients diagnosed with brain tumour, as well as designs and completes translational research associated with these trials in collaboration with the EORTC Imaging Group (http://www.eortc.org/research_field/imaging/). It has a strong track-record in past and present projects in glioma (http://www.eortc.org/research_field/brain/) and a subcommittee dedicated to imaging. The European Association for Neuro-Oncology (EANO) is an international and multidisciplinary organisation with a particular focus on neuro-oncology. It also has the EANO Youngsters, which is a platform of young scientists with a special interest in neuro-oncology. The Glioma Longitudinal AnalySiS Consortium (GLASS) is a global initiative that aims to systemically catalogue the longitudinal changes in glioma, by generating a longitudinal genomic/molecular dataset representing a large cohort of patients diagnosed with glioma across the three specified diffuse glioma genomic subtypes: IDH wild-type, IDH-mutant, and IDH-mutant 1p/19q co-deletion. However, neither of the above consortia currently has reached a critical mass of MRI researchers within their ranks to move advanced MRI forwards, partly because funding to bring

imaging experts together is limited. This COST Action will collaborate with the EORTC and GLASS, and will align if possible some of the Action events with those organised by GLASS and the EORTC. This will allow exchange of imaging and non-imaging expertise to the mutual benefit of this COST Action and GLASS and EORTC.

This COST Action will collaborate with the European Imaging Biomarkers Alliance (EIBALL), an alliance that finds its origin in a collaboration of the EORTC and the European Society of Radiology (ESR), and focuses on the advancement of imaging biomarkers in general. Another initiative for quantitation of MRI biomarkers is the Quantitative Imaging Network (QIN), a USA-based network within the Cancer Imaging Group of the National Institutes of Health (see Section 2.2.3).

PanCare Society is an EU network of professionals, cancer survivors and their caregivers aiming at improving the long-term health and quality of life in childhood and adolescent cancer survivors. While many clinical and neuropsychological parameters are studied, there is no strong emphasis on the application of imaging. Advanced quantitative MRI has a large potential for the monitoring and early detection of the adverse effect of radiochemotherapy, and can serve as a proxy for the prediction of quality of life and neurocognitive outcome. This COST Action will collaborate with the PanCare Society, and will align if possible with their activities and expertise to promote the use of MRI in long-term cancer patient monitoring.

This COST Action will take part in international standardisation initiatives including: Brain Imaging Data Structure (BIDS) to set up the structure for sharing the imaging data and 'open brain consent' to exchange existing consent forms enabling data sharing. This COST Action will collaborate with the European Network for Brain Imaging of Tumours (ENBIT) and the International Neuroinformatics Coordinating Facility (INCF). ENBIT is a network of imaging scientists specialised in tumour imaging which has as a primary objective data sharing via their web portal. The International Neuroinformatics Coordinating Facility is internationally recognised for its work in the definition of standards and best practices in neuroscience. This COST Action will collaborate with both ENBIT and INCF and will align if possible some of the Action events with INCF/ENBIT meetings.

2.2 ADDED VALUE OF NETWORKING IN IMPACT

2.2.1 SECURING THE CRITICAL MASS AND EXPERTISE

The critical mass required for reaching the first two Research Coordination Objectives, in which identification and harmonisation of advanced MRI biomarkers and multi-site data integration are the main aims, is present within the network of proposers of this COST Action. This network includes experts in the fields of advanced MRI biomarker development, radiomics, and big data sharing, in addition to clinical specialists in the fields of neuro-oncology and neuroradiology. Within the network there are experts with experience of working in international and multidisciplinary consortia focused on harmonisation of data acquisition and analysis to obtain quantitative MRI biomarkers. These experts will collaborate in interdisciplinary WGs, in which supply and demand will be carefully matched, such that the Research Coordination Objectives will be met with the highest standard of advanced MRI techniques tailored to the clinical need for glioma imaging.

To unite the current European clinical expertise on glioma research, this COST Action already has proposers from 23 clinical centres, of which 13 are in ITC, Near-Neighbouring Countries (NNCs), and International Partner Countries (IPC). Although this basis is already well on the way to European-wide application of advanced MRI techniques in clinical research and trials, there is a specific capacity-building objective to ensure to continuously grow and foster this basis within the timeframe of this COST Action. A dedicated WG will ensure that multidisciplinary and cross-border collaborations are formed and fostered, such that they remain strong beyond the duration of this COST Action, for instance via the design of multi-centre and international research studies.

This COSTAction already includes at the proposal stage both Early Career Investigators (ECIs) and Senior Investigators, whose networks span a wide range of (inter)national industrial partners, clinical advisory boards, professional associations, and patient organisations. This together with foreseen future collaboration with impactful European and international networks on glioma research and industrial partners relevant in glioma imaging, this forms the basis to create the critical mass required for translating the advanced MRI biomarkers from the research domain to clinical application. To continuously grow and foster this basis, a specific capacity-building objective is put in place for building lasting bridges with all relevant stakeholders. A designated WG within this COST Action will ensure that this strong multi-disciplinary expertise and critical mass is harboured and will act as a lobbying and liaising platform throughout the course of this COST Action.

2.2.2 INVOLVEMENT OF STAKEHOLDERS

The most relevant stakeholders within this COST Action include MRI research scientists, clinical specialists with a special focus on glioma (neurologists, neuroradiologists, oncologists, radiation oncologists, molecular biologists, neuropsychologists, radiographers, and pathologists), (inter)national organisations for glioma research and clinical practice, industrial partners with an interest in the results of this COST Action (MRI vendors, software developers, SMEs), and patient organisations. Involvement of all stakeholders will be ensured via invitations to partake and/or help organise networking and dissemination activities planned throughout the Action.

A dedicated WG will focus on disseminating the Action's plans, activities, and results in tailored manners to all stakeholders. To ensure involvement of all stakeholders across the continent and beyond, particular focus of this WG will be to ensure multilingual promotion and dissemination will take place for making the network inviting to national (local) stakeholders as well. This will happen by instating a Science Communication Officer who will hold the responsibility of ensuring that this dissemination occurs.

To generate tools for the application of advanced MRI biomarkers, this COST Action will work with SMEs that develop phantoms for reproducibility measurements of novel biomarkers (Gold Standard Phantoms) and develop open-access software tools for data analysis (i.e. Medical Software Solutions GmbH, Quantib, and mediri GmbH). In addition, this COST Action will work with Specific Organisations for imaging data integration (INCF, ENBIT). Furthermore, through the open network involvement of new SMEs and Specific Organisations will be encouraged via invitations to representatives of these entities to the Action's meetings and events, wherever appropriate.

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

Two secondary proposers are based in North-America (one in the USA, one in Canada). One of them is linked with the Quantitative Imaging Network (QIN), which is a subdivision of the Cancer Imaging Program of the National Institutes of Health in the USA. Within QIN, experience exists to develop and validate both standard and novel perfusion-weighted MRI and diffusion-weighted MRI biomarkers for evaluation of brain tumours and their response to therapies. The second North-American proposer has extensive experience in the development and validation of advanced MRI biomarkers. This COST Action will greatly benefit from the experience and expertise on harmonisation and standardisation of advanced MRI biomarkers of these proposers, which will happen via one of the Training Schools organised by the Action. Their involvement is also highly beneficial for the global outreach of the results of this COST Action. In return, the network of this COST Action connects these proposers with European experts in the field of glioma research and collaborations will be stimulated via as well as encouraging STSMs to their institutions.

One secondary proposer is based in a NNC (Morroco), a team of neurosurgeons from the Mohammed V University of Rabat (Morocco). This site is one of the most important sites of neuroscience research in North Africa, and is currently the only site in Africa that applies focal treatment. Moreover, the Rabat Reference Center for Training Young African Neurosurgeons is the only Full Program Training Center for the entire North African region certified by the World Federation of Neurosurgical Societies. As such, it presents a crucial and influential point of contact to disseminate knowledge and information to a vast geographical region. This COST Action will greatly benefit from these influential key players in building a network of contacts and collaborations with a large neighbouring region that currently lacks strong ties to EU research institutes. With a quickly aging population, incidence of glioma is on a steep rise in North Africa. Rapid economic development in these countries with strong economic ties to the EU allows growing investment to research and clinical infrastructure, including modern MRI devices. This COST Action can provide the much desired assistance in strengthening the knowledge and experience by encouraging STSMs from Morocco. As such this COST Action will be of benefit to quickly put the collaborating institutes on the map of global research. Validating the use of advanced MRI methods that do not use contrast agents is a key priority in the region due to the cost burden associated with the use of contrast-agents in this geographical area and can positively influence care for the North-African patients diagnosed with glioma in the long term.

3 IMPACT

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

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

The short-term impacts of this COST Action include the following:

- **Accessible advanced MRI biomarkers of glioma.** This COST Action will lead to the possibility of global clinical implementation of advanced MRI biomarkers for glioma, via the open-access publication of recommendations on the use of advanced MRI biomarkers for glioma characterisation, planning, and monitoring. In addition, via existing code sharing platforms (e.g. GitHub), this COST Action will stimulate the development of software tools to analyse imaging data and obtain the relevant biomarkers. These tools will facilitate implementation in clinical research and practice. This has the potential to also reach non-academic MRI centres, as it overcomes the necessity for in-house expertise to use advanced MRI.
- **Boost the value of existing glioma imaging and non-imaging data.** This COST Action will result in an inventory of data sets on glioma in Europe. The direct economic impact of this process is that value will be added to existing data by making them accessible for further exploitation within international research projects resulting from this COST Action.

After the duration of the Action, the long term impacts include the following:

- **Advance the understanding of glioma pathophysiology via the use of advanced MRI methodologies.** This COST Action will lead to an improved understanding of the pathophysiology of glioma and its response to treatment, which will occur via multidisciplinary collaborations. A deeper understanding of glioma pathophysiology will be feasible via in vivo monitoring of physiology with advanced MRI. This in turn will accelerate the advancement of glioma diagnostics and facilitate scientific breakthroughs in novel treatments.
- **Improve personalised treatment planning and treatment efficacy in glioma.** Advanced MRI biomarkers will improve characterisation of glioma tissue, which will greatly benefit personalised surgical and radiotherapy planning due to the improved localisation and delineation of the extent of the tumour. In addition, the MR imaging tools developed in studies resulting from this COST Action will allow for the more timely and precise differentiation of progression versus pseudoprogression and for early and non-invasive detection of detrimental side effects in healthy brain tissue. This will lead to improved treatment efficacy, because timely decisions can be made on treatment strategy. Moreover, this advancement in mapping glioma pathophysiology will improve the efficacy of clinical trials, for which an accurate patient selection for enrolment and early and accurate detection of treatment response (or lack thereof) is invaluable.
- **Improve the quality of life of patients diagnosed with glioma and their caregivers**. The combined efforts of this COST Action include working towards non-invasive diagnosis and treatment response assessment/prediction of glioma, reduce the need for gadolinium based contrast agent, and linking imaging biomarkers to other clinical and neurocognitive parameters during the course of treatment and disease progression. All of these efforts aim to reduce the burden to patients diagnosed with glioma and their caregivers throughout the course of the disease, by improving the selection of appropriate treatment and limiting adverse effects of treatment and diagnostic procedures.
- **Raise the public understanding of the role of MRI in glioma diagnosis.** Advanced MRI requires patient compliance as minimum head motion is a must, and advanced MRI scans may add to the scan time. Clear explanation of the benefits of the imaging procedures will increase patient understanding and compliance during the imaging, to the mutual benefit of the patients and clinicians/researchers evaluating the images.
- **Provide a lasting network of mutual knowledge exchange in glioma imaging.** By the end of this COST Action a multilateral and interdisciplinary network for glioma imaging will be established, dynamically outliving the generation of its original stakeholders, and continuing to provide and develop cutting-edge imaging technology to benefit patients, but also to build the careers of young glioma imaging scientists all over Europe and associated countries beyond.

3.2 MEASURES TO MAXIMISE IMPACT

3.2.1 KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

Each of the WGs of this COST Action will focus on reaching one of the Objectives of this COST Action, which means that every member of the network will be working towards knowledge creation, transfer of knowledge. ECIs will be furthering their careers via their participation in the Action, which includes the mentorship of Senior Investigators within the Action.

Knowledge creation will happen via:

- **Multidisciplinary WGs**. In reaching the Objectives of this COST Action, multidisciplinary collaborations will be formed within each of the WGs. During networking events, brainstorming sessions will be organised with the aim to carefully match supply and demand for advanced MRI in glioma research and diagnostics. These interdisciplinary discussions will inevitably lead to new insights and spark new developments in glioma research.

Transfer of knowledge will happen by:

- **Encouraging ECIs to undertake STSMs** to external research labs or clinical institutes to gather or share multidisciplinary data, develop or test standardised data analysis software, and perform pilot studies. This will allow the ECIs to increase their network and gain valuable knowledge from different institutes/countries. ECIs from ITCs traveling to non-ITCs will be preferred - ensuring increased contact with non-ITCs to boost advanced MRI research in ITCs.
- **Organising networking and teaching events**, such as training schools, symposia, meetings, and conferences. These events will be tailored to knowledge transfer between all stakeholders within this COST Action.
- **Communication with the general public**, which will be ensured through being one of the main tasks of one of the WGs. In addition, a Science Communication Officer will be appointed who will be responsible for dissemination of knowledge to the general public.

Career development will happen for:

- **Early Career Investigators**. At the proposal stage, almost 50% of the proposers are ECIs, who will greatly benefit from working within this COST Action. Not only will this COST Action ensure that the majority of STSMs is undertaken by ECIs, the representation of ECIs within the network of proposers should be reflected as much as possible when forming the Action's Management Committee. Having ECIs in key roles of the Action would ensure ample opportunities for them to develop their careers in this field. Also via the creation of a mentorship program within this COST Action the Senior Investigators will provide mentorship to the ECIs and will introduce the ECIs into their respective networks.

- **Inclusiveness Target Countries.** Within the pan-European network in this COST Action, a specific focus will be on intensifying research in glioma imaging diagnostics in ITCs. Not only will this happen via stimulating STSMs from and to ITCs, but also by ensuring as much as possible that at minimum one networking event per year will occur within an ITC. Moreover, the network will be open to new members and participation from other members of ITCs will be sought further, e.g. via communications in multiple languages such that national/local media outlets can also be used.

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

Dissemination to general public

A close collaboration with existing communication channels to the general public (e.g. (inter)national patient organisations) will be established to reach patients and caregivers in an efficient way and to assure a patient-oriented approach, in which two-way communication is fostered. Several specific dissemination strategies will be applied:

- **Website and social media**. A layman's website specific for patients, caregivers and the general public will focus on raising the awareness for the necessity of advanced MRI glioma.

Additionally, patients will be able to collect basic information on the procedures related to advanced MRI techniques for preparation. Furthermore, contact information on the stakeholders involved, for each country, such as clinical institutions and patient organisations, will be enlisted after their approval. Finally, layman's summaries and presentations, as well as press releases on the results of this COST Action will be published on both the website and social media. **For this website, the patient and the caregiver are the main envisaged end-users.** Therefore, the participation of patients, caregivers and patient organisations will be required to develop a patient-friendly website, adapted to each nationality and language.

- **Newsletters.** Layman summaries and press releases on the results of this COST Action will be disseminated via newsletters to stakeholders related to the general public, including patient organisations and those who have subscribed to the newsletter.
- **Public and patient engagement.** Supporting participation of Action members in public science exhibitions and presentations. Representatives from patient organisations will be invited to networking events. Press releases will be encouraged and published on the website and on the social media accounts, supervised by the WG '*Dissemination*'.
- **Promotional materials (e.g. brochures).** Information in layman's terms regarding the necessity of advanced MRI for glioma will be distributed to all stakeholders related to the general public, institutions such as hospitals, and public science exhibitions.

Dissemination to policy makers

- **Policy guidelines.** The designated WG '*Stakeholder Relations*' will focus on reaching the critical mass of experts from international bodies of glioma research and clinical practice (e.g. the EORTC), which will give weight to the recommendations resulting from this COST Action. The network resulting from this COST Action will continue to work together with local and national organisations and institutes, such as the European Society of Radiology iGuide, to ensure implementation of advanced MRI for glioma diagnostics across European countries.

4 IMPLEMENTATION

4.1 COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

4.1.1 DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

This COST Action will have 5 WGs, each focusing on achieving one out of 5 Objectives (section 1.2.2.). Each WG will be multidisciplinary, with each of the members assigned by the Management Committee (MC). When electing the WG Leaders, balance in gender, age, and geographical location will be upheld. A schematic overview of the Work Plan can be seen in Figure 3.

Working Group 1 – Advanced MRI biomarkers for glioma characterisation
This WG will focus on achieving the first Research Coordination Objective: "Coordinating the identification and quantification of advanced MRI biomarkers for the application in the field of glioma, via the harmonisation of imaging protocols, and the standardisation of analysis pipelines in an open-access manner". It will do so by reviewing state-of-the-art literature to identify the most pertinent existing, advanced MRI biomarkers for detection, diagnosis, prognosis, and treatment of glioma, and by combining emerging analysis pipelines. The resulting tool will be distributed on open-access platforms (e.g. on GitHub). Special attention will be given to identify existing gaps in the discovery of gliomas biomarkers.

Tasks

1. Enable knowledge sharing by reviewing the existing MRI techniques, methods combining these techniques, and data analysis methods to obtain advanced MRI biomarkers for
    - glioma characterisation;
    - discriminating therapeutic effects (pseudoprogression and radiation necrosis) from recurrent disease (progression);
    - monitoring and early detection of adverse effects in glioma treatment.
2. Promote best practice among pan-European research institutes by creating an open-access analysis pipeline for the quantification of advanced MRI biomarkers for glioma.

Working Group 2 – Multi-site data integration
This WG aims to coordinate multi-site date integration and enable the creation of large datasets in glioma diagnostics by combining heterogeneous data sets from sites across Europe (second Research Coordination Objective). Additionally, this work will pave the way for *radiomics* to improve glioma imaging diagnostics and prediction of treatment response. WG2 will focus on:

- *Data privacy*: how to inform participants, collect consent for data sharing, and ensure de-identification of data and anonymity of metadata (Privacy Impact Assessment) in accordance with General Data Protection Regulation?
- *Data infrastructures*: which tools and databases are available and how to use them to automate multi-site integration?
- *Data portability*: how differences in acquisition parameters can be conveyed with enough details and using a common framework to support future post-processing?

Tasks

1. Review existing standards on data privacy and resources for data exchange in glioma imaging research:
    - Research and clinical resources;
    - Data standards;
    - Ethics (e.g. "Open Brain Consent").
2. Review existing data sharing infrastructures.
3. Specify a common data structure to store and convey advanced MRI metadata. In order to facilitate data exchange and interoperability across data platforms, the WG will extend the international BIDS guidelines in setting up the structures for sharing advance MR imaging data.

Working Group 3 – Clinical translation
The WG will focus on achieving the first Capacity-Building Objective to foster cross-border information exchange about past and current clinical trials and studies of glioma in order to develop multi-site, multidisciplinary, pan-European clinical studies.

Tasks

1. Create a European-wide overview of studies of glioma diagnostics and follow-up from all Action Participants' institutes. This will be achieved by:
    - actively encouraging participation of Action members, focusing on members of ITCs and NNCs, hereby increasing their role within the European research network and boost the impact of the Action;
    - building a network of people with various clinical expertise and use this network to support interdisciplinary co-operation within Action participants' institutions to allow inclusion of non-imaging data from radiotherapy planning, pharmacological treatment, clinical outcome, neurocognitive testing, quality of life surveys, and biopsies to obtain complete information on disease stage, progress and long-term health;
    - work together with WG2 '*Multi-site data integration'* on facilitating data exchange between relevant stakeholders.
2. Coordinate the preparation of retrospective and prospective studies by
    - identifying the clinical needs for advanced MRI biomarkers in the diagnosis and treatment follow-up of glioma;
    - connecting Action members and stakeholders for the set-up of projects, aiming at the validation of the use of advanced MRI biomarkers for studying the tumour grading, level of infiltration, mechanisms of damage, comparing radiation planning schemes and pharmacological interactions, and potentially predict long-term quality of life and neurocognitive outcome.
3. Stimulate development of advanced and patient-friendly MRI-programs for clinical settings to gather prospective glioma imaging data, by
    - involving patient organisations to guarantee the patient interests, in collaboration with WG '*Stakeholder relations*';
    - developing recommendations to do so, which will be made broadly available to the general public in collaboration with WG '*Dissemination*'.

Working Group 4 – Stakeholder Relations
This WG aims to achieve the second Capacity-Building Objective to allow this COST Action to act as a pan-European network for advancing glioma MRI and translating advanced MRI biomarkers from

bench to bedside, bridging between MR imaging scientists and stakeholders from key international and multidisciplinary organisations on glioma research, industry collaborators, clinical practice, and patient organisations. This WG is initiated to ensure lasting collaborations with stakeholders inside and outside the network.

Tasks

1. Liaise with stakeholders within the field of glioma or MR-imaging, including:
    - key international consortia/organisations with a focus on glioma research and/or imaging biomarkers, such as EORTC, GLASS, PanCare, EANO, QIN, and EIBALL by representing the Action within general meetings, conferences, and leadership of these consortia;
    - industry collaborators such as Medical Software Solutions, mediri, Quantib, General Electric, Siemens, and Philips;
    - clinical practice, such as neuroradiologists, radiographers, neuro-oncologists, radiation oncologists, neurosurgeons, neuropsychologists, (molecular) biologists, and pathologists, via their respective (inter)national societies;
    - local, national and European policy makers, for example via ESR IGuide;
    - patient organisations representing the interests of patients diagnosed with glioma and their care givers.
    - relevant, established COST Action groups to enhance knowledge sharing, such as COST Action CA16103 *'Magnetic Resonance Imaging Biomarkers for Chronic Kidney Disease',* CA17117 '*Towards an International Network for Evidence-based Research in Clinical Health Research*', and CA17140 '*Cancer nanomedicine - from the bench to the bedside*'.
2. Identify other organisations and institutes with complementary expertise and data (e.g. MRI, cognition, genetics) to actively engage with throughout the Action.
3. Coordinate communications between all stakeholders by informing:
    - the WGs on fundamental scientific and clinical connections for active exchange of knowledge, expertise and data sharing/collecting opportunities;
    - key international consortia/organisations on imaging innovations and technologies as identified and developed by the Action.

Working Group 5 –Dissemination

This WG will focus on achieving the third Research Coordination Objective to disseminate the Action's goals and results in tailored manners to all relevant stakeholders, including the scientific and clinical communities, patient organisations, and the general public. Strong connections with the other WGs are mandatory, and will be ensured via overlapping membership.

1. Facilitate the dissemination of the Action's results to all stakeholders: the research community in- and outside the Action, the clinical practice, as well as to the general public. The WG will instate a Science Communication Officer, who is responsible for
    - the website and social media profiles such as a LinkedIn group, Facebook page, and Twitter account;
    - the generation of scientific, clinical, and layman's promotional materials for the Action;
    - the guidance and management of open-access publications and presentations, including dissemination meetings, as well as press releases for the general public;
    - the dissemination of recommendations for best clinical practice for both academic and general centres, based on the results from the Action;
    - the dissemination of information about the necessity of advanced imaging for good clinical care for experts, patients, and the general public.

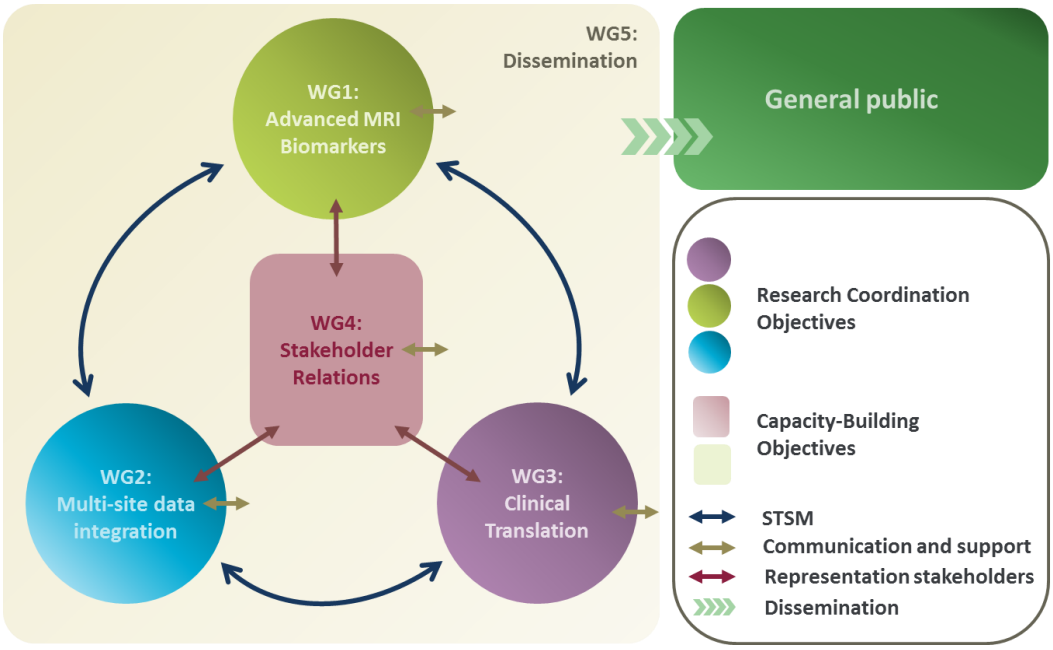

Figure 3. PERT chart of work plan. Note the interaction between the WGs via various routes, denoted by coloured arrows. Communication between the Action and the general public will be ensured via WG5.

This COST Action will be managed by the Management Committee (MC), the MC hold the responsibility for the overall management and implementation of COST Policy.

Tasks

1. Foster pan-European and interdisciplinary knowledge exchange by following-up and supervising the local organisation of Action-related events and taking responsibility for
    - the organisation of MC & WG meetings;
    - the organisation of scientific and clinical training schools;
    - the management and evaluation of STSMs: the participation of ECIs and linking institutes in ITCs with leading European science hubs will be strongly encouraged. (the call for STSMs will always be open and decisions will be made during MC meetings);
    - the facilitation of (teleconference) research meetings for specific collaborative projects.
2. Ensure a balanced representation of gender, ECIs and ITC members within this COST Action and its activities by:
    - distributing targeted promotion for all activities to ECIs and ITC members and encouragement to apply for STSMs;
    - prioritising STSM proposals of ECIs and ITC members;
    - facilitating interdisciplinary collaborations to enhance career opportunities for ECIs;
    - monitoring mentorship of ECIs by the Action's Senior Investigators;
    - highlighting the work of promising ECIs and ITC members on a regular basis on the website and in the newsletter (member of the month);
    - involving ECIs and ITC members in the organisation of the training schools, providing presentation opportunities for ECIs, and organising ECI oriented networking events.

4.1.2 DESCRIPTION OF DELIVERABLES AND TIMEFRAME

Working group 1 – Advanced MRI biomarkers for glioma characterisation

- Two open-access review papers on the existing and emerging techniques to obtain MRI biomarkers [month 18]:
    - The first review paper will focus on the characterisation of glioma to improve tumour heterogeneity mapping to go towards more personalised medicine and support a more accurate diagnosis.

    - The second review paper will focus on the characterisation of treatment monitoring and response assessment to allow for a better distinction between tumour progression and pseudoprogression, and to aid earlier adaptation of the therapy in case of adverse treatment effects.
- An open-source analysis pipeline for quantifying the advanced MRI biomarkers for glioma. [month 48]
- An open-access methodology paper of the analysis pipeline describing the theories and methods for the quantification of advanced MRI biomarkers for glioma. [month 48]

Working group 2 – Multi-site data integration

- A review of existing data and metadata standards and repositories for data exchange in glioma imaging research. [month 18]
- BIDS specifications to represent (1) advanced MRI datasets and their biomarkers and (2) patients' non-imaging metadata. [month 26]
- Sample consent forms that enable data sharing and comply with the European data protection regulation in as many European languages as possible. [month 48]

Working group 3 – Clinical translation

- Overview of studies on glioma diagnostics and follow-up measurements from Action participating institutions. [month 12]
- Recommended glioma scan protocols for clinical application of advanced MRI. [month 24,48]

Working Group 4 – Stakeholder Relations

Up-to-date statistics, reported during MC meetings, about:

- Representation in the Action and vice versa (where appropriate) from established international glioma research organisations and consortia, industry, and clinical practice. [ongoing]
- Scientific and educational presentations about the (results of the) Action at key international glioma meetings, particularly outside the imaging arena. [ongoing]
- Representation from patient organisations within the Action and the identified patient interests for involvement in the public dissemination. [ongoing]

Working group 5 –Dissemination

- Action website and social media profiles (LinkedIn, Facebook, Twitter) for communication within and outside this COST Action (scientific, clinical and public) [month 6].
- Scientific, clinical, and layman's Action promotional brochures to inform all stakeholders during scientific and public conferences and events related to glioma and MRI [month 12].
- Bimonthly newsletter to all stakeholders of this COST Action [ongoing]
- Layman's summaries (website and social media), press-releases (media) and layman's presentations (scientific and public events) based on the Action's scientific output [ongoing].
- Multi-language recommendations for best clinical practice for both academic and general centres, based on the results and publications from this COST Action, published on the website [month 48]

4.1.3 RISK ANALYSIS AND CONTINGENCY PLANS

The following risks were identified and contingency plans for these events were prepared:

- **Interdependency of WGs.** To work towards achieving the main aim of the Action, the WG1-3 are closely interlinked. Slower progress in individual WGs might thus affect the other WGs. In order to mitigate the risks if this occurs, the deliverables of each of the WGs are made achievable even without reaching the goals that are set for the other WGs. Nonetheless, joint timely work within all WGs will lead to higher overall efficiency and it will therefore be ensured via Action meetings and STSMs that the flow of information between the WGs remains constant. Areas of slow progress will be identified according to the Gantt diagram, such that they can be addressed in time.
- **Environment for data sharing**. With the combining of heterogeneous datasets, one potential risk might be an insufficient environment for data-exchange. However, WG2 '*Multi-site data integration*' in itself is mitigating this risk: it will comprise of experts in the field of data-sharing and big data analyses, who are experienced in dealing with ethical issues concerning data sharing.

- **Size of the network**. As a new network, a potential issue arises by the number of people involved: too small network might lead to insufficient available clinical data and too few clinical experts involved to reach the critical mass that is required to reach the Objectives of the Action. The mitigation strategy for this is three-fold: (1) the inclusion of the WG4 '*Stakeholder Relations*'. This WG will at minimum have members that are well-established researchers and clinicians with established networks including international organisations, and will continue to reach out to established and new stakeholders during the Action. (2) The strong emphasis on the *openness* and *inclusiveness* of the network, which in practice means that all Action Participants will be encouraged to spread the word about the Action, e.g. via visibility in major conferences, and invite new Participants to make themselves known to the Action MC. (3) Focus on actively including and recruiting members form ITCs, where the diagnosis of glioma is equally prevalent as in non-ITCs, and encourage inclusion of their datasets to the common registry resulting from this Action.
- **Turnover of members of the Core Group**. It may be so that during the Action lifetime, members of the Core Group of the Action move to another country or become unable to proceed with their roles. The former case may not be unlikely, as a significant proportion of the Core Group is aimed to be constituted by ECIs. In case of a change of COST country, the Action MC will strongly encourage the new country to become a member of the Action, should this not yet be the case. To mitigate any issues of a Core Group member not being able to continue or moving to a non-COST country, the MC Substitute List will remain up to date throughout the lifetime of Action, such that a replacement will be found swiftly, while maintaining the gender and seniority balance.

4.1.4 GANTT DIAGRAM

MC	Tasks (numbered)	Year 1				Year 2				Year 3				Year 4			
	1. Management of Action																
	MC&WG meetings organisations																
	Training Schools organisations																
	STSMS organisation																
	2. COST Policy Implementation																
WG	**Tasks (numbered) or Deliverables (italics)**	**Year 1**				**Year 2**				**Year 3**				**Year 4**			
1	1. Review of existing advanced MRI biomarkers of glioma.																
	Two review papers																
	2. Create and maintain an open-access analysis pipeline																
	Open-access analysis pipeline + Review paper																
2	1. Review existing standards on data privacy.																
	2. Review existing data sharing infrastructure.																
	Review paper																
	3. Specify Common data structure for storing and sharing																
	BIDS specification																
	Sample consent forms in multiple languages																
3.	1. Create inventory of European-wide glioma studies.																
	Overview of glioma studies																
	2. Stimulate development of innovative, patient-friendly clinical MRI protocols in glioma.																
	Scan protocols																
4	1. Stakeholders engagement																
	2. Identification of potential new Action Members																
	3. Communication within the Action																
	Statistics about representation																
5	1. Dissemination to all stakeholders																
	Website & social media launched																
	Brochures & promotional materials																
	*Multi-language publications about results Action**																
	Recommendations & policy guidelines																

** For details see Section 4.1.2.*

REFERENCES

1. Incidence and mortality rate of cancer in the brain in Europe 2012: http://eco.iarc.fr/eucan/Cancer.aspx?Cancer=34

2. Olar A, Wani KM, Alfaro-Munoz KD, Heathcock LE, van Thuijl HF, Gilbert MR, et al. IDH mutation status and role of WHO grade and mitotic index in overall survival in grade II-III diffuse gliomas. Acta Neuropathol. 2015;129(4):585–96.

3. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Vol. 131, Acta Neuropathologica. 2016. p. 803–20.

4. Chang PD, Malone HR, Bowden SG, Chow DS, Gill BJA, Ung TH, et al. A multiparametric model for mapping cellularity in glioblastoma using radiographically localized biopsies. Am J Neuroradiol. 2017;

5. Chow D, Chang P, Weinberg BD, Bota DA, Grinband J, Filippi CG. Imaging genetic heterogeneity in glioblastoma and other glial tumors: Review of current methods and future directions. Am J Roentgenol. 2018;

6. Kickingereder P, Bonekamp D, Nowosielski M, Kratz A, Sill M, Burth S, et al. Radiogenomics of Glioblastoma: Machine Learning–based Classification of Molecular Characteristics by Using Multiparametric and Multiregional MR Imaging Features. Radiology. 2016;

7. Hyare H, Thust S, Rees J. Advanced MRI Techniques in the Monitoring of Treatment of Gliomas. Current Treatment Options in Neurology. 2017.

8. Van Den Bent MJ, Afra D, De Witte O, Ben Hassel M, Schraub S, Hoang-Xuan K, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: The EORTC 22845 randomised trial. Lancet. 2005;366(9490):985–90.

9. Hlaihel C, Guilloton L, Guyotat J, Streichenberger N, Honnorat J, Cotton F. Predictive value of multimodality MRI using conventional, perfusion, and spectroscopy MR in anaplastic transformation of low-grade oligodendrogliomas. J Neurooncol. 2010;97(1):73–80.

10. Mehrabian H, Desmond KL, Soliman H, Sahgal A, Stanisz GJ. Differentiation between Radiation Necrosis and Tumor Progression Using Chemical Exchange Saturation Transfer. Clin Cancer Res [Internet]. 2017;clincanres.2265.2016. Available from: http://clincancerres.aacrjournals.org/lookup/doi/10.1158/1078-0432.CCR-16-2265

11. Wang S, Martinez-Lage M, Sakai Y, Chawla S, Kim SG, Alonso-Basanta M, et al. Differentiating tumor progression from pseudoprogression in patients with glioblastomas using diffusion tensor imaging and dynamic susceptibility contrast MRI. Am J Neuroradiol. 2016;

12. Sagiyama K, Mashimob T, Togaoa O, Vemireddy V, Hatanpaa KJ, Maher EA, et al. In vivo chemical exchange saturation transfer imaging allows early detection of a therapeutic response in glioblastoma. PNAS. 2014;111(12):4542–7.

13. Aquino, Gioppo, Finocchiaro, Bruzzone, Cuccarini. MRI in Glioma Immunotherapy: Evidence, Pitfalls, and Perspectives. J Immunol Res. 2017;

14. Petr J, Platzek I, Hofheinz F, Mutsaerts HJMM, Asllani I, van Osch MJP, et al. Photon vs. proton radiochemotherapy: Effects on brain tissue volume and perfusion. Radiother Oncol. 2018;

15. Karunamuni RA, Moore KL, Seibert TM, Li N, White NS, Bartsch H, et al. Radiation sparing of cerebral cortex in brain tumor patients using quantitative neuroimaging. Radiother Oncol. 2016;

16. Group PTC-O. Proton therapy centres in operation [Internet]. Available from: https://www.ptcog.ch/index.php/facilities-in-operation

17. Eurostat. Healthcare resource statistics - technical resources and medical technology [Internet]. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Healthcare_resource_statistics_-_technical_resources_and_medical_technology

18. Fathi Kazerooni A, Nabil M, Zeinali Zadeh M, Firouznia K, Azmoudeh-Ardalan F, Frangi AF, et al. Characterization of active and infiltrative tumorous subregions from normal tissue in brain gliomas using multiparametric MRI. Journal of Magnetic Resonance Imaging. 2018;