

Brussels, 25 May 2021

COST 075/21

DECISION

Subject: Memorandum of Understanding for the implementation of the COST Action “Improving biomedical research by automated behaviour monitoring in the animal home-cage” (TEATIME) CA20135

The COST Member Countries will find attached the Memorandum of Understanding for the COST Action Improving biomedical research by automated behaviour monitoring in the animal home-cage approved by the Committee of Senior Officials through written procedure on 25 May 2021.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA20135
IMPROVING BIOMEDICAL RESEARCH BY AUTOMATED BEHAVIOUR MONITORING IN THE ANIMAL HOME-CAGE (TEATIME)

The COST Members through 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, 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 document amending or replacing them.

The main aim and objective of the Action is to map and compare the strengths and limitations of the different home-cage monitoring (HCM) systems, by developing a new European-based scientific and technical inter-disciplinary network to provide guidance on their appropriate use and to identify gaps where further technological developments, consensus-building discussions and capacity-building training is needed. This will be achieved through the specific objectives detailed in the Technical Annex.

The present MoU enters into force on the date of the approval of the COST Action by the CSO.

OVERVIEW

Summary

Animal use for scientific purposes is guided by the principles of 3Rs (Reduction, Refinement and Replacement). Developing refined experimental conditions can substantially improve animal welfare and importantly, enhance the translational value and data reproducibility.

Novel and emerging technologies allow 24/7 collection of behavioural data in undisturbed mice, the most widely used species in biomedical research. These recently developed technologies minimize the impact of stressors, such as human interaction and testing in novel arenas, which are known to influence data collection and animal welfare. It is now possible to assess a more naturalistic behavioural profile in familiar environment, such as the animals' home-cage. In addition to promoting welfare, it can improve research in a wide spectrum of research fields ranging from psychology and neuroscience to translational psychiatry and neurology, and may further provide valuable insights into other types of pathologies and genetic alterations. However, addressing the complex problem of monitoring the full 24-hour behavioural repertoire of a rodent still presents many challenges, with each technology having its strengths and limitations.

The aim of this Action is to bring together European organizations developing and using automated home-cage monitoring technologies, combining experts in mouse behaviour, laboratory animal science and data science, to critically and transparently assess the potential of these technologies, to develop user guidelines and standard operating procedures and to identify needs for further technological development, including analysis of big data.

The Action will also contribute to building capacities for adoption of these technologies by holding workshops, laboratory rotations and disseminating knowledge.

Areas of Expertise Relevant for the Action <ul style="list-style-type: none"> • Basic medicine: Behavioral neuroscience (e.g. sleep, consciousness, handedness) • Biological sciences: Zoology, including animal behaviour • Biological sciences: Bioinformatics • Biological sciences: Genomics, comparative genomics, functional genomics 	Keywords <ul style="list-style-type: none"> • Laboratory mouse behaviour • Innovative automated phenotyping • Home-cage monitoring • Data reproducibility • 3Rs
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Specific Objectives

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

Research Coordination

- By using the network complete a comparison of the current state-of-the-art and future requirements for HCM systems by survey of the wider community, literature review and collecting information about current research using HCM (WG1-WG2).
- Determine strengths and future requirements for HCM by comparing experimental design and parameters measured in members' laboratories and sharing baseline data collected (WG2).
- Develop a common understanding of the technical and scientific improvements needed, based on evaluation of existing HCM systems and collaboration with SEMs responsible for technical improvements who are part of the Action (WG2-WG3).

- Determine ways to potentially integrate datasets from the different HCM systems available to Action participants (WG3).
- Communicate results of comparisons and evaluations to the wider research community and inform stakeholders to help promote the use of HCM (WG5).

Capacity Building

- Develop a new network of researchers and other stakeholders across Europe to reduce fragmentation of HCM development and share best practice on their development and use (WG1).
- Establish stakeholders and communication channels and possibilities for knowledge transfer to promote the emerging field of HCM research (WG4-WG5).
- Encourage the use of HCM by using the breadth of knowledge and expertise available in the network to exchange knowledge through training (WG4) and communication and dissemination (WG5).
- Develop new lasting forums to bridge behavioural and data science to achieve breakthroughs in the integration and analysis of complex data sets (WG3).
- Establish a European network of mouse behaviour analysts ensuring representation from Early Career Investigators and researchers from countries with less capacity in the field of home-cage monitoring including ITC (WG1)

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1 Soundness of the Challenge

1.1.1 DESCRIPTION OF THE STATE-OF-THE-ART

The Action “Improving biomedical research by automated behaviour monitoring in the animal home-cage” (**TEATIME**) aims to:

1. Develop a framework to enhance the sensitivity, reliability, and reproducibility of behavioural measures from laboratory rodents.
2. Strengthen pan-European preclinical research by establishing standards and guidelines to promote emerging tools.
3. Improve data relevance and reproducibility in compliance with animal welfare and ethical considerations.

Much of biomedical research is heavily reliant upon animal models for fundamental, discovery research, for example for the characterization of genes/proteins, physiological functions or pathological states. Mice and rats are the most widely used laboratory rodents for these purposes. The analysis of behaviours and behavioural responses to environmental stimuli is particularly important in this context, because they represent evolutionary conserved mechanisms of an organism’s ability to survive, thrive, reproduce and adapt to environmental conditions. Behavioural analysis is not only instrumental to progress in neuroscience, ethology and psychology, but also in other fields of the life sciences, such as preclinical neurological and psychiatric research, as well as for testing neurological effects of therapeutic drugs. Recording, interpreting and understanding normal behaviours and their variability across the population of a species is necessary to determine which behaviours are pathological, and thus to assess the impact of genetic alterations, environmental changes, or therapeutic interventions. Classically, the interrogation of many behaviours in laboratory rodents has involved the use of ‘out-of-cage’ tests. Many different paradigms have been developed, including mazes, activity monitoring and cognitive reward-based tests. These are widely used to evaluate specific types of behaviour, and these paradigms are considered a “gold standard”, although such tests usually reflect only a snapshot in the life of an experimental animal.

“Out-of-cage” observational testing for characteristics is very useful in describing overt phenotypes, present for much of the time, but risk missing sporadic or intermittent events. Furthermore, measuring the progression of a phenotype, potentially over many months, can be difficult whilst relying on assays that may be susceptible to changes in the testing environment or the experimenter. In addition, “out-of-cage” adds complexity to the testing which may pose a challenge to reproduce across laboratories, as well as over time. These observations are often completed during the working day and miss spontaneous night activity.

To overcome these limitations and to be able to better explore the possibilities opened by new mouse and rat strains, laboratory animal science is capitalising on progress in electronic monitoring technologies to record the voluntary, unprovoked behaviour of rodents in their home cages. This type of home-cage monitoring (HCM) is undoubtedly set to increase as it reveals more information on 24-hour behaviour of novel rodent strains. Indeed, modern phenotypical characterization of laboratory rodents increasingly incorporates the monitoring of animals in their home cage, as shown in Fig. 1.

Several related goals have been pursued through the development of HCM systems, namely automated behavioural assessment in a non-intrusive manner, leading to a reduction of experimenter interference

and bias in animal testing, as the experimenter has been identified as the most likely source for variation. The handling of animals for short tests is always an interference, as the animals are taken from their familiar social and physical environment, usually during their rest period, which inevitably causes a certain amount of stress. In addition, the influence of the circadian rhythm is often neglected in testing, as testing can only be performed at one or a few points in time and not continuously. Moreover, the availability of continuous data on behaviours in the home cage could potentially yield novel information that cannot be gleaned from sporadic behavioural assessments at specific time points.

Documents by year

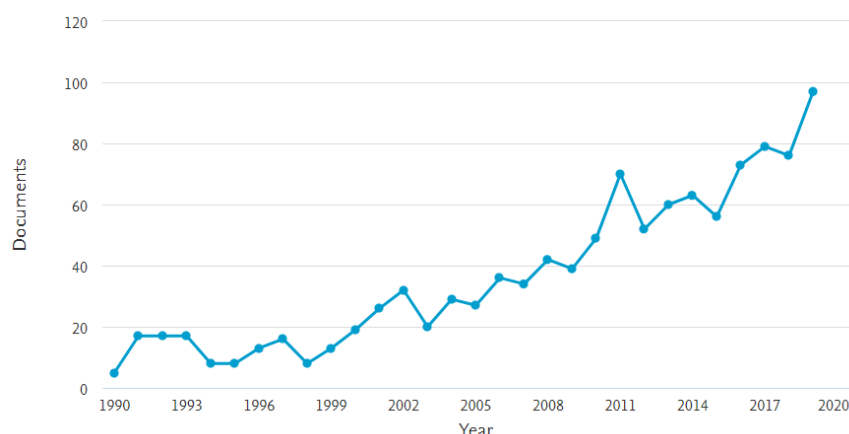


Figure 1: Scopus search with keywords “home cage” AND “mice” (record date 01/11/2020)

Furthermore, inadequate understanding of disease-relevant biological mechanisms and of the specific related behavioural alterations is seen as a possible cause for the lack of translational success in pre-clinical neuropsychiatric research. Thus, adding a more “holistic assessment” of behaviours by continuous HCM is an important methodological advancement to complete our knowledge of what a normal behavioural repertoire for laboratory animals looks like and to potentially improve the translation of pre-clinical results to clinical treatment. Finally, automated HCM also constitutes a significant improvement for assessing the welfare of the animals during their life in laboratory, e.g., before and during experiments, or during recovery from procedures. Such continuous monitoring allows for rapid intervention by animal care takers and veterinarians at the earliest sign of potential animal suffering.

Achievement of these goals is expected to not only refine existing experimental approaches, but also lead to an increase of reproducibility of test results, which has a great potential to reduce the number of experiments needed. Such approaches align with the principles of Replacement, Reduction, and Refinement of animal research (“3Rs”), which are at the core of modern laboratory animal research. In summary, HCM systems have a great potential to significantly improve our understanding of normal behaviour and disease-relevant aberrations and to improve both research validity animal welfare.

1.1.2. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

At present it is still largely unknown how powerful HCM systems can actually be in delivering concise metrics of animal behaviour and in decreasing the number of confounders inherent to out-of-cage paradigms. Although there is some evidence that HCM systems may indeed improve the reproducibility of behavioural assessments between sites/facilities and over time, a network of users is urgently required in order to lay the foundation for collecting data systematically. With these new technologies, it

is yet to establish standards of best practice, to review how they perform compared to more traditional tests and standard, “out-of-cage” protocols, and to decide which experimental design serves which purpose best. At least partially, this uncertainty is due to the fact that the different HCM systems apply a variety of technologies, either separately or in combination, e.g., video-recording, RFID-transponders, measuring vibrations of the cage or changes in electromagnetic fields and interruption of infrared light beams. Each technology has strengths and limitations and no all-in-one system exists. Most importantly, reliably recording the behaviour of an individual in a group of animals is still a challenge for most of the systems. It is important to note that for welfare reasons the single housing of mice or rats should be avoided as much as possible. There are virtually no studies recording “normal” home-cage behavioural profiles of a given strain housed in groups. All of this makes it difficult for the scientist to establish new HCM systems and plan the experimental design for a specific study.

This is problematic, because usage of inappropriate methods may actually increase the number of animal experiments needed, instead of decreasing it, since inconclusive data cannot answer the scientific question, may lead to misinterpretation of the data and therefore prompt the need for further or unnecessary experiments.

An additional challenge is that continuously monitoring behaviour 24/7 produces enormous amounts of data, which is an extraordinary task to deal with, not only for storage, but also for quality control and analysis. On the other hand, such large data sets are a treasure trove for which there are no instructions yet on how to use them best. There is, therefore, a great potential for discovery of previously unknown mouse behaviour to identify diseases or treatment effects. However, it is still unknown to what extent metrics can be translated between platforms, facilities and over time. A comprehensive analysis and the preparation of accepted guidelines is urgently needed to actually meet the goal of reducing the need for animal experiments through improved reproducibility. All the innovative ideas in this field need sharing for improvement, both of data for comparison and of algorithms to analyse complex data sets and possibly integrate different systems.

This COST Action, which stems from a bottom-up process by stakeholders in 23 Cost Member States, including 12 ITCs, is a timely, unique opportunity to evaluate the potential usefulness of the different HCM systems available. Such a joint, coordinated effort leverages the combined knowledge of the European research community of rodent behaviour analysts, focuses resources, creates synergies and prevents parallel or divergent developments. If successfully implemented, HCM systems may represent a significant leap forward in reading and understanding normal spontaneous behaviours of lab rodents, as well as closing current translational gaps. Undoubtedly, this Action will assist in putting the European research community at the forefront of deploying and developing HCM technologies on the global scientific stage.

The main scientific aim of this Action is therefore to map and compare the strengths and limitations of the different existing systems, to provide guidance on their appropriate use and to identify gaps where further technological developments, consensus-building discussions and capacity-building training is needed. It will develop a new European-based scientific and technical inter-disciplinary network and facilitate interactions with international networks and provide new collaboration activities, particularly between Early Career Investigators and across wide geographical locations, especially bringing in ITC. These networks will increase the efficiency of European research and its impact at a global level.

The key stakeholders are researchers working across different disciplines who are using and helping to develop the HCM and associated data curation and analysis; companies producing and selling the HCM; policy makers in particular for laboratory animal welfare and those directing the use of FAIR Guiding Principles for scientific data management and stewardship; producers and vendors of lab animals; experts in biocomputing, data analysis and machine learning; other projects and consortia collecting

and disseminating phenotyping data. The Action will also outreach to the wider community of researchers and clinicians performing behavioural research, research funders and policy-makers and the general public.

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 progress beyond the state-of-the-art by, first, assessing the current capabilities of HCM and the developments and coordination needed to address the critical issue of determining to what extent HCM of behaviour can **substitute**, replace and/or augment the “out-of-cage” standard tests widely used today which are referred to as the gold standard. Second, this Action will address the question of how amassment of 24/7 cumulative records of spontaneous/unrestrained in-cage activity can, if subjected to a data-driven and unbiased analysis, provide **additional** insights into mouse behaviour that could not be gained by the use of previously available methods. Third, this Action will address whether these new technologies can deliver **reductions and refinement** in animal experimentation.

The members of this COST Action will approach this challenge by identifying, gathering and co-ordinating community requirements for HCM in Working Group 1 (**WG1**, Fig. 2). In a survey of the wider research community in Europe and internationally, the Action will reach out to academic scientists, users of preclinical animal models in biotech and pharma industry, and animal welfare experts to establish the behaviours and physiological parameters which are difficult, if not impossible to measure in a conventional laboratory animal setting. This information, gained by the analysis of the results of this survey, will identify areas to explore to determine if HCM can substitute, augment or replace standard out-of-cage tests. It will also guide the development of the other working groups to develop HCM methods, including previously unrecorded or inaccessible data, which may provide insights into mouse behaviour not recorded with standard out-of-cage tests. These previously unrecorded datasets will potentially form new standard measurements for preclinical research.

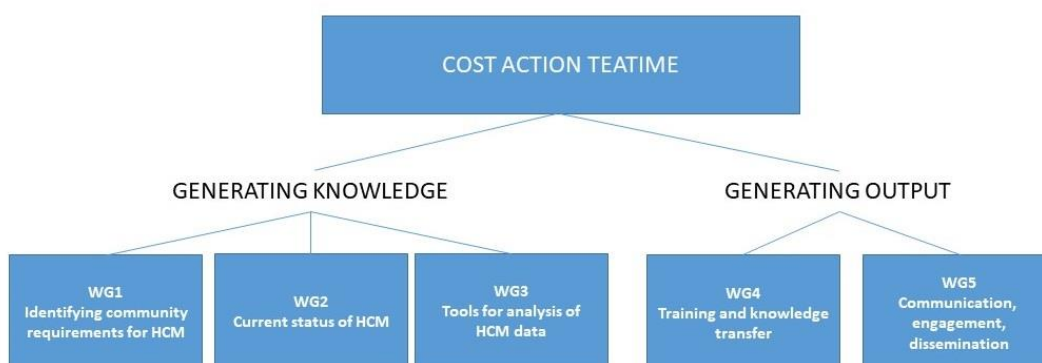


Figure 2: Schematic overview of the Action Working Groups (WG) for progressing beyond the state-of-the-art

In parallel, the members of this COST Action will conduct a systematic review of publications using HCM technologies and further assess and catalogue the current status of the range of HCM equipment available or in development in their labs (**WG2**). The Action will also survey the existing systems worldwide, through the existing literature and by consulting with profit and non-profit suppliers/developers of HCM instruments. This will include collecting information about technical specifications, capacities, and importantly, the use of such instruments in current research; resulting in a critical evaluation of cost/benefit of each system. Specific attention will be paid to the rationale for the experimental designs and the relevance of recorded parameters. The potential to analyse specific brain/behavioural domain areas and related diseases, with respect to the research questions being addressed, will be evaluated with regard to the needs of the community revealed in WG1. The objective of WG2 also involves comparing experiences with different HCM systems, particularly evaluating the practical aspects of designing and setting up experiments and data exportation. The proposers will also provide and share, as far as possible, baseline data collected in the members' laboratories or coming from the literature. The overriding aim being to promote data-sharing, result validation and further development of data analyses.

Ultimately the efforts of WG2 will result in a catalogue of existing HCM systems with an evaluation of the parameters they measure and their relevance to preclinical studies. This evaluation will address the questions at this point on how far HCM can replace/augment "out-of-cage" standard test, the potential for HCM to be established as gold standard testing and what additional insights it can provide into the normal behavioural repertoire. Importantly, this catalogue will also identify and detail gaps and needs for improvement in terms of further technological developments. This information will direct the establishment of guidelines to build bridges between the existing systems in order to improve/extend their usefulness for better evaluation of behavioural functions and improving the translation of preclinical research to humans. In addition, this information will allow the assessment of what contribution HCM can make to the 3Rs. A published report for appropriate HCM use, selected experimental designs and sample protocols will benefit a wider scientific community and future generations of scientists adopting the HCM approach.

To better explore and apply the data produced by HCM, a number of efforts are underway by Action members to develop novel machine learning and bioinformatics tools and apply existing machine-learning platforms to analyse the vast amount of data yielded from 24-hour monitoring systems. **WG3** will bring together those efforts, to share bioinformatics ideas, resources and work toward the integration of data between different systems to enhance the output of both. To support this integration and ensure that bioinformatics tools and historical example data are findable and accessible, this working group will also identify and reach out to existing resources and initiatives that provide this functionality (e.g. <https://elixir-europe.org>, <https://fairplus-project.eu>). This will assess address the question of whether analysis of 24/7 cumulative records of spontaneous/unrestrained in-cage activity can provide additional insights into mouse behaviour that could not be gained by the use of previously available methods.

Progress beyond the state-of-the-art will be achieved by capacity-building training and knowledge transfer (**WG4**) through Short Term Scientific Missions (STSMs), training workshops and webinars, offered by the network of laboratories established by this COST Action with particular emphasis on Early Career Investigators of all genders and across a wide geographical area, especially in ITC. A framework will be established to allow historic raw data obtained with different HCM systems to be exchanged and compared, including data on wildtype animals and disease models wherever possible. Specific questions, to be answered by these comparisons, include the sensitivity of the different systems to detect aberrations in different behavioural domains, and the reproducibility of strain- or model-specific phenotypes in different HCM systems, as well as behavioural alterations based on disease progression in longitudinal data of animal models. These comparisons will result in the identification of the strengths

and limitations of the different systems, which will be fed back into WG2 and be used for the development of guidelines.

The COST Action network will also hold open community workshops available to researchers of all stages and across a wide geographical area (**WG5**) to share ideas and disseminate results of the consortium with the biomedical community, including pharma, biotech, academia, equipment companies and lab animal welfare organisations. The Action will also present the work of the consortium at international conferences (i.e., talks, poster, booths, and flyers) to reach out to the wider scientific community. To communicate the results to the non-scientific public, the Action will prepare and disseminate material for press and digital media.

In summary, this Action will provide a scientific review and recommendations for applying HCM for different purposes (addressing research questions and monitoring animal welfare and husbandry) and provide an evaluation of the opportunities for HCM for the enhancement of reproducible scientific data and improving animal welfare and the 3Rs. It will develop a lasting network of European researchers and industrial partners, that can continue to work together to increase the uptake and impact of this research at a European and global level.

1.2.2 OBJECTIVES

1.2.2.1 Research Coordination Objectives

- By using the network complete a comparison of the current state-of-the-art and future requirements for HCM systems by survey of the wider community, literature review and collecting information about current research using HCM(WG1-WG2)
- Determine strengths and future requirements for HCM by comparing experimental design and parameters measured in members' laboratories and sharing baseline data collected (WG2)
- Develop a common understanding of the technical and scientific improvements needed, based on evaluation of existing HCM systems and collaboration with SEMs responsible for technical improvements who are part of the Action (WG2-WG3)
- Determine ways to potentially integrate datasets from the different HCM systems available to Action participants (WG3)
- Communicate results of comparisons and evaluations to the wider research community and inform stakeholders to help promote the use of HCM (WG5)

1.2.2.2 Capacity-building Objectives

- Develop a new network of researchers and other stakeholders across Europe to reduce fragmentation of HCM development and share best practice on their development and use (WG1)
- Establish a European network of mouse behaviour analysts ensuring representation from Early Career Investigators and researchers from countries with less capacity in the field of home-cage monitoring including ITC (WG1)
- Establish stakeholders and communication channels and possibilities for knowledge transfer to promote the emerging field of HCM research (WG4-WG5)
- Encourage the use of HCM by using the breadth of knowledge and expertise available in the network to exchange knowledge through training (WG4) and communication and dissemination (WG5)
- Develop new lasting forums to bridge behavioural and data science to achieve breakthroughs in the integration and analysis of complex data sets (WG3)

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

In the last few years, there has been an increase in the use of HCM systems to evaluate mouse behavioural parameters (Fig. 1), reducing the intervention of experimenter, allowing a more naturalistic behavioural repertoire to be measured and improving animal welfare. Among the wide range of commercial or home-made systems available, most (if not all) publications surveyed referred to a **specific** HCM system to address specific questions relative to a defined behaviour (mainly activity) or for evaluation of a disease outcome.

To our knowledge, there is no evidence of an existing coordinated network effort devoted to the assessment of possibilities, limitations and knowledge dissemination of a **wide range** of HCM systems. This Action will build the first network for a concerted assessment of HCM systems, aiming to improve their possibilities and use for evaluating brain functions and behavioural abnormalities in preclinical research. The consortium will identify the most commonly used HCM systems worldwide, survey their capacity to evaluate different behavioural domains using functional and disease-based strategy and promote their use through workshops and other dissemination tools.

Although this COST action is focussed rodents, similar tools are being developed for other laboratory animals (including NHP), agricultural species (such as pigs) and indeed humans in order to measure abnormal behavioural traits. We will foster interactions with these groups, especially in the field of data analysis and AI tools for interpreting behaviours.

The Action network would also add value to the current discussions taking place within the scientific community about the benefits of such monitoring systems.

2.2. ADDED VALUE OF NETWORKING IN IMPACT

2.2.1. SECURING THE CRITICAL MASS AND EXPERTISE

This Action brings together comprises network of nearly 60 scientists from 23 European countries, including 12 ITC, with strong expertise in a wide range of behavioural domain areas. It is planned to increase this network, in the early stages of this Action, through the work of WG1 and in particular attract more Early Career Investigators (currently 21% of Action proposers). The number and distribution (Fig. 3) of current Action members makes it a true Pan-European network of excellence in animal behaviour analysis. The different partners involved are routinely using integrated approaches in behavioural studies using different set-ups and parameters to address scientific questions related to any behavioural domain, in line with arguments that converging/overlapping data from different tests/parameters do increase the strength of results and the relevance of the potentially observed phenotypes. In addition, participants in the Action have experience and are equipped with HCM systems and can provide either established protocols and/or validation data. Some of the most limiting aspects for feasible use of the existing HCM systems are problems related to experimental design and data analyses. Inclusion of experts in functional analysis, machine learning strategies and bioinformatics in the Action will improve

the interchanges for experimental design and analysis of recorded parameters, and thus facilitate and promote the use of these technologies as explorative tools.

2.2.2. INVOLVEMENT OF STAKEHOLDERS

Members: All the different members of this Action from academia and industry that are users/developers of HCM systems, or interested in their use, will be involved by collecting and comparing information about the type of technology used, capacity and costs. Some of the partners will also survey the existing systems worldwide through inventories, systematic review of the existing literature and from interaction with suppliers of HCM technologies. To better understand the possibilities of each system, the participants using existing HCM systems will provide a list of the parameters recorded (or that can be recorded) by each system, their ability or potency to evaluate specific brain function or behavioural abnormality, and the practical difficulty or ease to get such parameters with the associated informatics tools. The proposers will also provide and share, as far as possible, baseline data already collected.

International organisations: The Action will evolve to reach out to international organisations and platforms such as FENS, IMPC, EARA, ETPLAS, etc.

Trainees: The Action will be heavily involved in training Early Career Investigators (students and post-docs) and any other users interested in learning the potentials of different types of HCM systems. The training could be tailored to specific research interests in different behavioural domains. Early Career Investigators will be given the opportunity to be on the Management Committee and lead WG.

Behavioural research equipment producers and vendors: will be involved in participating in the workshops and invited to share their knowledge with the aim of improving the flexibility of each system.

Pharmaceutical companies (safety screens, toxicology, pharmacology): will be involved in evaluating the reliability of screens using automated HCM systems in combination with existing screens.

Clinicians and charitable organisations for diseases: will benefit from our network by participating in the discussions aimed at refining mouse models of human diseases with the help of HCM. These monitoring systems could add important value to the validity of new and existing models by measuring parameters continuously for longer periods of time (longitudinal studies). In fact, currently similar 24/7 techniques (e.g., accelerometers) are being deployed in the human population for social, psychology and psychiatric research to map behavioural profiles to various conditions.

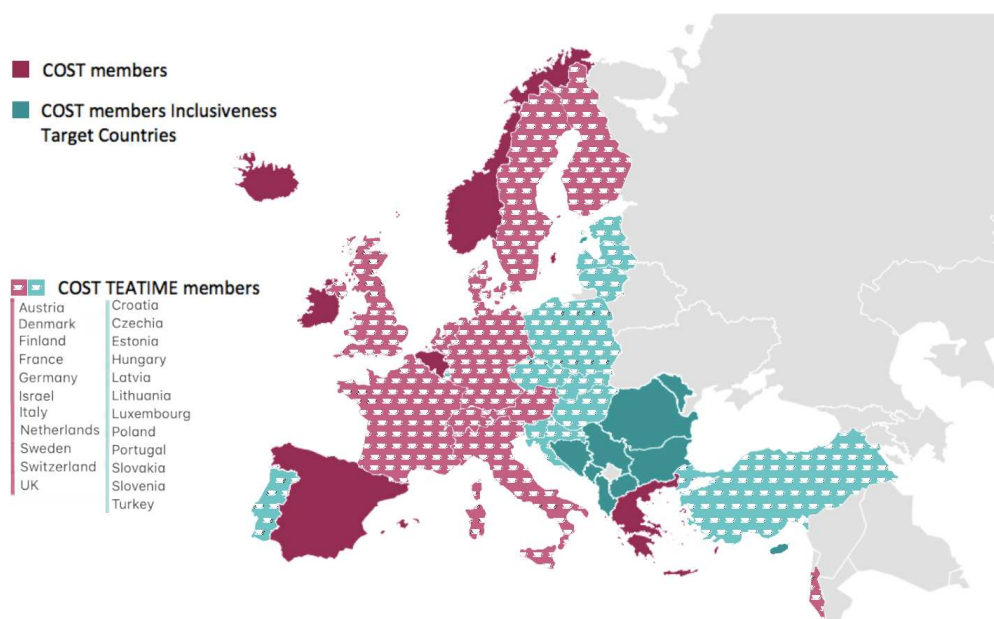


Figure 3: Map of participating countries (TEATIME members indicated by tea-cups)

Representatives for lab animal welfare: Representatives of 3Rs centres in Europe will be involved (<https://ec.europa.eu/jrc/en/eurl/ecvam/knowledge-sharing-3rs/knowledge-networks/eu-3rs-centres>) to contribute to the implementation of such monitoring systems that prioritize the reduction of animals tested, the refinement of the procedures by reducing stress and invasiveness and possible replacement of less reliable behavioural tests.

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

Not applicable

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 absence of a well-established community of professionals carrying out biomedical research on HCM systems in academia and industry prevents exchange of knowledge and experiences, hindering the development of HCM systems to their full potential. TEATIME aims to bridge this gap by establishing a European expert network in the field of behavioural phenotyping of rodent models. The research institutions involved include large research infrastructures, specialized academic groups in the field of animal behaviour, heads of animal facilities and specialists in laboratory animal science, as well as pharmaceutical companies and CROs involved in fundamental and preclinical research. The multidisciplinary group of TEATIME partners will form the basis for fundamental innovative developments in the field of HCM. These groups have not been brought together in such a focussed, collaborative network before, so this Action will have a significant impact on increasing European cooperation, as well as aiding the implementation and further the development of automated home-cage monitoring in Europe and potentially beyond.

Given the complex nature of animal behaviour, quantitative acquisition and analysis of behavioural data will largely depend on: the experience of the scientists involved, standardized and reproducible experimental setups and designs, unbiased registration of test-output metrics and correct statistical methods. TEATIME will address these issues, by agreeing upon and establishing standards (disseminated and promoted by publishing guidelines), offering training, and establishing a platform to discuss and implement innovations, along with a dedicated website. Through this, TEATIME will also greatly impact training and education of students and Early Career Investigators in behavioural science in Europe.

The expected knowledge and expertise transfer between academia and industry in this Action aims to meaningfully develop practical applications for this technology, with measurable improvements in both the quantity and quality of the scientific output and animal welfare monitoring. This, in turn, is expected to positively affect the reliability of results from animal research and consequently improve their translational value. These outcomes will improve the competitiveness of European behavioural research on the international level and increase its visibility. Increasing collaborations between researchers and industry will aid companies in Europe developing these technologies and help disseminate their use to a wider audience.

Since small rodents are idiosyncratically susceptible to changes in environmental conditions (e.g., light, vibration, odour) and to the presence and interaction with humans, this is a common source of variability and biases 'noise' in all animal experiments, particularly in neurobehavioural studies. The potential of this technology for understanding of natural, undisturbed behaviour of mice in their home cage is a game-changer in laboratory animal science, and its development and promotion by TEATIME can further expand its impact on future research. In particular, higher methodological resolution and better data analysis tools will improve research quality thereby consolidating baseline, preclinical, and clinical research, which finally result in better health research.

TEATIME will further the 3Rs in a meaningful way. For example, Replacement can be achieved by offering the means to share the bioinformatics methods and tools to explore and analyse existing large datasets on home-cage behaviour and to allow new knowledge and insight to be gained without need for repeating redundant animal studies. Reduction can be achieved by the improvement of the ‘noise/signal’ (or effect/variability) ratio, which is the key determinant in sample size calculation. Increasing ‘signal’ through more sensitive methods and improved data collection and reducing ‘noise’ by minimizing disturbances, will therefore help reduce the number of animals necessary to answer a specific research question. Obtaining a substantially larger and more detailed dataset through HCM without using more animals is also aligned with the principle of Reduction. Refinement is furthered by reducing stress generated by removing cages from racks, and animals from their cages, and exposing them to unfamiliar stimuli (e.g., light, odour, sounds), by instead allowing expression of more naturalistic behaviour and social interaction in their home cages. Improved animal welfare monitoring will increase opportunities for early detection of behavioural indicators of pain and distress, hence allowing prompt addressing of these problems, as well as identification of early humane endpoints.

These potential scientific applications and 3Rs benefits will rely on the ability to fully explore the current capabilities of HCM systems, as well as future innovations. HCM can make a significant contribution to the harm/benefit assessments that determine which animal research is deemed acceptable from an ethical, scientific, and social point-of-view, by contributing more precise and comprehensive welfare data, as well as opportunities afforded by larger, more reliable datasets. The easing of the harm/benefit dilemma put forth by animal research can also generate a more positive personal and social impact as regards acceptance of this type of research, as well as a more benevolent view of scientists and animal care staff associated with animal research, bringing a positive impact to the public discussion on this topic.

TEATIME is expected to make a significant contribution to digitalisation, by moving behavioural research from the “5-minute test” paradigm to automated, long-term data logging and artificial intelligence/machine learning technologies to analyse large datasets (‘big data’).

The establishment and improved dissemination of good practices will contribute to both harmonising and improving current behavioural analysis, not only by raising standards in facilities where HCM technology is already being used, but also by widening interest and use by researchers, in academia and industry, not yet familiar with this technology.

3.2. MEASURES TO MAXIMISE IMPACT KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

This COST Action will ensure stakeholder involvement covering all categories, balancing different perspectives, and being inclusive. The various stakeholder groups will be invited to participate in working groups according to their expertise in the WG activities. TEATIME will create a network platform to allow the transfer of knowledge among the members of the Action (and beyond) and enhance communication through a web-based resource, annual meetings, workshops and the organization of mobility programmes, all of which will enable researchers and students from the different groups of the Action to undertake STSM for work and/or studies. The network will remain open to additional groups or equipment manufacturers throughout the duration of the Action.

The proponents will map current gaps in design, analysis and reporting of studies based on HCM systems, and agree on methodological standards for the work carried out by the network and disseminate best practice to the broader scientific community by means of published guidelines, as well

as courses and workshops. To reach out to a wider audience of researchers, as well as the general public, the TEATIME consortium will develop an e-learning course and educational on-line videos, which will both be hosted on the TEATIME website, but also made freely available in the upcoming resource library of the Education and Training Platform for Laboratory Animal Science (ETPLAS).

Aside the collaboration with ETPLAS, which will ensure the availability of all TEATIME deliverables even after the end of the Action, links with the European Animal Research Association and 'Animal Research Tomorrow' organizations, along with national laboratory animal science associations, will be explored to better improve dissemination of calls-for-action, workshops and courses, TEATIME achievements, and deliverables.

The broad diversity of participating countries and European languages in the TEATIME consortium will be explored to make available all deliverables in several languages and national outlets, furthering the capacity for impact in both the scientific community at large and the general public.

Career development will be provided by opportunities for training and STSMs for Early Career Investigators, as well as giving them opportunities to perform roles on the Management Committee, WG leadership and other coordination roles.

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

At the beginning of the COST Action a dissemination plan will be established, which can be adapted and updated in the course of the Action in discussion with members and stakeholders. A dedicated website for TEATIME will be created at the start of the Action. Liaison with other scientific programmes and networks will be built and supervised by the Management Committee using links with Action members that are involved in these related external programmes. In this regard, representatives from other programmes who are already part of this network will be tasked to ensure appropriate coordination between these programmes and the relevant WGs. Web portals will be coordinated and links to and from other programmes established, allowing integration of the Action with existing programmes and networks building on, and feeding, the current efforts.

Organisations that are not yet part of the COST Action will be invited to join or contribute to relevant working groups. More industrial partners will be invited to the Action meetings and workshops in order to attract interest in the exploitation of results. Companies in the European biotechnology/bioengineering industry (equipment manufacturers) will take advantage of progress made by the Action and thus gain a competitive edge.

Members of the COST Action will attend relevant EU or international meetings, scientific conferences and workshops to highlight and disseminate actions and developments; the Action will be presented as talks, posters or mentioned during discussions where appropriate. This target audience will be very relevant for recruitment of new partners to the Action and to establish links and synergies with related networks. If possible, some COST meetings will be held in conjunction with meetings of existing programmes.

The success of this COST Action relies also on the interactions with the new Horizon Europe Research and Innovation programmes. Relevant links and portals for communication will be established as these new programmes begin to identify how increased excellence in HCM can contribute to Horizon Europe.

EU Directive 2010/63/EU (amended by Regulation (EU) 2091/1010) introduced for the first time for many members states, the need to report retrospectively the severity of suffering encountered animals used

in science. Subsequently there have been many national and international debates and discussions on how to accurately measure and record severity (including an EU working group). Members of this COST Action will interact closely with these initiatives and proactively seek engagement with the Commission with a view of offering a more comprehensive way of reviewing animal suffering.

Regulatory and Ethical organisations such as Animal Research Tomorrow will be invited to specific meetings or working groups. Patient association organizations will be part of the target audience, either by participating in the Action meetings or WGs, due to their interest to accelerate the translation of preclinical development to clinical therapies.

Different dissemination tools will be used to reach the highest number of target audiences. Dissemination will be considered as a routine item in the agenda of the MC. A website and dissemination coordinator will be nominated to ensure development and updating of the dissemination plan, based on MC and workgroup outcomes. The website will be aimed at participants and target users, containing salient information about items developed and the results of actions undertaken (networking, training activities, scientific events and publications) and will be supported by designated WG members.

A curated catalogue of existing HCM systems, listing all relevant features, advantages and disadvantages, and cost-benefit assessment of each system will be made available to all TEATIME members and stakeholders. Events organized by TEATIME like workshops, training courses, and STSM, especially for Early Career Investigators, will help to disseminate the results of this COST Action beyond the circle of participants, in particular in ITC, thereby strengthening competitiveness of European behavioural sciences.

4. IMPLEMENTATION

4.1. COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

4.1.1. DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

WG1: IDENTIFYING, GATHERING AND CO-ORDINATING COMMUNITY REQUIREMENTS FOR HCM

Objectives:

- To direct and advise the development of standards, guidelines, training, and development in HCM according to community needs.
- To establish networks within and between different community user groups within Europe who share interests in developing welfare assessment criteria, behavioural phenotyping and bioinformatics analysis using HCM systems.

Task 1: To identify and engage with a broad range of stakeholders of the Action. This includes contacting national and international interest groups in behavioural studies (e.g., IBANGS, FENS), animal welfare (e.g., FELASA), pharma companies and organisations (e.g., EFPIA), laboratory animal veterinarians (ESLAV), biotechnology and equipment companies and existing networks in Europe (e.g., Infrafrontier) and internationally (e.g., International Mouse Phenotyping Consortium). Information will be distributed widely throughout these communities via this COST Action. Contact details of people

interested in engaging with the Action will be sought, as well as permissions for inclusion in the Action mail-list.

Task 2: Develop and pilot a broad-ranging survey and/or targeted questionnaires including:

- Current usage of conventional behavioural and welfare monitoring tools
- Issues and challenges with conventional testing tools
- Current usage of HCM in the biomedical community
- Requirements for new automated technologies
- Hurdles to adopting new technologies

Task 3: Analysis of survey data and publication of a summary report to be circulated around stakeholders and interest groups and used to inform other WGs. Initiate a dialogue with profit and non-profit suppliers of equipment.

Task 4: Circulation and publicity of the systematic review and the outcome of the survey.

WG2: CURRENT STATUS OF HCM

Objectives:

- Determine strengths and limitations of different HCM systems by comparison among systems and to established and validated methods.

Task 1: Catalogue the current status of the range of equipment available and in development.

Task 2: Evaluate concise metrics of animal phenotypes delivered with regard to physiological function.

Task 3: Members equipped with HCM systems share experience on designs, data, and propose actions to stakeholders (equipment suppliers, developers, WG4 members) to enhance usefulness for better promotion of HCM systems use.

Task 4: Lay a foundation for a user-guide and framework for concise training activities in WG4, based on experience of existing HCM user community and concurrent development. This forms the basis for the gold standard guide this Action aims at delivering.

Task 5: Members with HCM contribute to practical and theoretical training courses and workshops of WG4 designed to implement appropriate equipment in interested laboratories and to promote HCM use.

Task 6: Contribute to global outreach together with all Action members.

WG3: DEVELOPMENT OF NEW TECHNOLOGIES, ANALYSIS TOOLS AND DATABASES

Objectives:

- Establish interdisciplinary meetings to enable the production of a road map for innovations in data analysis and technological improvements in HCM.
- Facilitate sharing and archiving of these efforts, stimulate interaction between Action participants and experts in biocomputing and machine learning.
- Disseminate report of current needs, potential solutions, improvements and innovation of equipment, software or bioinformatics tools to stakeholders.

Task 1: Enable Machine Learning technologies: In recent years, machine learning (ML) has emerged as the pre-eminent approach to large-scale data analysis, where state-of-the-art models are based on neural networks (NNs). In the “supervised” setting, NNs learn to extract patterns from large quantities of manually annotated data, usually in the form of discrete labels (classes). Historically, this has posed a considerable challenge due to a lack of sufficiently large datasets within a single institution. Fusion of datasets from multiple institutions offers a solution to this problem but presents its own challenges in terms of logistics and standardisation. A key aspect of this WG therefore will be to investigate standardised behavioural phenotyping protocols based on controlled vocabularies (ontologies) to facilitate dataset sharing and integration. Existing platforms such as IMPReSS (<https://www.mousephenotype.org/impress>) and the Neuro Behaviour Ontology (NBO, <https://www.ebi.ac.uk/ols/ontologies/nbo>) will be investigated and evaluated for this purpose.

In addition, unsupervised learning will be investigated to address the open question of what constitutes “normal behaviour”. Recent work in the ML field has shown the potential for deep NNs to learn patterns from data in the absence of labels, distilling the information present into a phenotypic “barcode”. By training such a model on data in the absence of abnormal behaviour or welfare concerns (i.e., wild-types), it is possible to detect behavioural anomalies as deviations from what the model learned previously.

Task 2: Produce an inventory of existing platforms and data repositories for sharing of data, models and software tools to facilitate interaction among Action members for the work in WG3 (e.g., Github) that have the functionality for public dissemination of the results of the Action.

Task 3: Sharing of limitations of current technical designs and needs for innovation of equipment and technologies.

Task 4: Develop and share software and bioinformatics tools. Validate code. Identify limitations in the data output/format of current commercial solutions.

Task 5: Produce an inventory of limitations experienced when integrating hardware and software of different systems (e.g., HCM with telemetry etc.) or vendors with solutions to overcome these limitations.

Task 6: Explore feasibility of a repository for published HCM datasets: There are several open-access repositories for storage of published –omics datasets that facilitate sharing and re-use of data. To ensure that historic and/or published HCM datasets are findable and accessible after publication, this WG will also identify and reach out to existing resources and initiatives that may host these data.

WG4: TRAINING AND KNOWLEDGE TRANSFER

Objectives:

- Promote networking and training opportunities among members through lab exchanges, sharing of experimental designs, data and technical knowledge, including bioinformatics.
- Organize training courses at various levels of expertise, also open to the wider scientific community.

The achievements of these objectives will be available on a dedicated website and in specific publications of Guidelines and protocols, in collaboration with the other WGs (mainly WG2 and WG3).

WG4 will focus on three tasks: setting up a dedicated website, developing a training program and management of short-term scientific missions for stakeholders.

Task 1: Set up a dedicated website: A substantial body of information on HCM in laboratory rodents will be collected on this website. Sustainability will be achieved by decision during the Action on whether to host and maintain the website by one of the partners or to merge later with the many international consortia working on mouse phenotyping. The website will provide stakeholders with up-to-date information about the available HCM systems combined with manuals, short video tutorials, troubleshooting, SOPs and guidelines, examples of study designs, sample protocols (with WG2), data analysis manuals, open-source software and raw data of representative experiments (with WG3). There will also be information on Action meetings, events etc., a Q&A section and on-line presentations about the research carried out with the HCM systems.

Task 2: The **training** program will be organized for different levels and target groups. This task is especially important, as this kind of training delivered by highly-qualified international faculty is not generally available, but very much needed. It will also include lab exchanges between members. The **Introductory** training will be an intensive lecture course introducing the participants (max 30) to the field of behavioural neuroscience, starting with the gold standard tests by behavioural domains related to disease modelling and ending with the general concepts of HCM. The **Advanced** training will be for people with experience in basic testing and an interest in HCM. Advanced training will be organized as a yearly workshop for max 16 participants, where different HCM systems are presented in detail, focusing on their advantages and limitations, related to basic behavioural profiling and disease modelling. Handling of the “big data” is specifically highlighted and addressed. A special emphasis during Introductory and Advanced training is placed on interaction between the students and faculty and giving the students the opportunity to present their work by short oral communications. The **Expert** training will be focused on only one HCM system at a time and combined with hands-on training and its specific application to a particular research purpose.

Task 3: Short-term scientific missions (STSM) will be used for extended Expert training in specialist laboratories for gaining extensive theoretical and practical knowledge. According to the budget available, WG4 will propose the scheme for STSMs annually to the Action MC for approval. In addition to longer STSM (2-4 weeks) for Early Career Investigators, the Action will encourage short (2-3 days) visits of more senior researchers for exchange of scientific knowledge, combined with seminar at the host laboratory. All these activities should enhance and facilitate the collaboration between the laboratories beyond the scope of this Action.

The participants for the courses, workshops and STSMs will be selected through open calls by applying the best practice of equality and inclusiveness in terms of gender, age and geographical location.

WG 5: COMMUNICATION, ENGAGEMENT AND DISSEMINATION

Objectives:

- Reach out to all stakeholders and clearly signal that the Action is interested in their opinion and contribution and expressly encourage active participation.
- Openly discuss the work of this Action with all possible stakeholders, including biomedical community, academia, pharmaceutical industry, biotech companies, equipment companies, scientific societies, lab animal welfare organisations, funding organisations and disease organisations with an interest to promote also pre-clinical research, as well as the general public and media.
- Serve the overarching common interest in advancing behavioural characterization based on HCM to replace more distressing animal experiments in the long term.

Task 1: Organize community workshops bringing together the stakeholders and present the current state of the art as well as openly discuss the desired future perspective for behavioural phenotyping using HCM.

Task 2: Disseminate results of community workshops to all members of TEATIME but also to the different communities and interest groups represented by the above-mentioned stakeholders. To meet this need, a variety of distribution channels will be selected, e.g., for reaching out to academia and biomedical community the Action will publish meeting reports in scientific journals, on our website and will reach out to international societies (i.e., IBANGS, FELASA, FENS). Members of the Action are also in close contact with the European Network of 3R Centres (EU3Rnet) for disseminating our work with special emphasis on enhancing animal welfare.

Task 3: Present the work of this Action, as well as the results derived from the community workshops to the scientific community at international conferences.

Task 4: Prepare and disseminate communication material and press releases to communicate the results to the non-scientific public. Cooperate intensively with science communication organizations such as “Understanding Animal Research” (www.understandinganimalresearch.org.uk/) and “Tierversuche verstehen” (www.tierversuche-verstehen.de).

Task 5: Establish and maintain the contact network with organisations which are not members, but interacting partners of this Action, such as those providing phenotype data, key funding agencies, disease and patient driven organisations, 3Rs/welfare officer organisations like ESLAV/FELASA, profit and non-profit organisations supplying HCM equipment.

4.1.2. DESCRIPTION OF DELIVERABLES AND TIMEFRAME

No	Title	mo
1	WG1: Pan-European, multidisciplinary mail list of interested stakeholders with appropriate GDPR permissions: Target 500 individuals, companies, etc.	6
2	WG2: Establishment of a catalogue of HCM systems available and in development	6
3	WG4: Website established with basic information about Action members, goals and activities	6
4	WG5: First draft of a communication and dissemination plan produced and agreed, Y1-Q3	7
5	WG5: Distribute minutes of Action Management Committee and associated Work Group meetings	10
6	WG4: Website populated with SOP's, manuals, video tutorials and material from courses	11
7	WG1: Survey(s) on current use of and requirements for HCM, developed and circulated to stakeholders	12
8	WG2: Evaluation of parameters provided by each system with regard to physiological/behavioural domain areas: and pushing to improve/extend their usefulness	12
9	WG2: Systematic review paper on current status of HCM systems drafted for publication	12
10	WG4: First introductory training course held and report and course manual published on website	12
11	WG1: Report on cross-community engagement with stakeholders using, developing and interested in HCM technologies	18
12	WG4: First advanced workshop on HCM - course report and manual published on website	18
13	WG3: Determine methods to test if ML can be used to identify “normal” and abnormal behaviour in HCM	21

14	WG5: Report on activities and outcomes of communication and dissemination to scientific and wider stakeholders	20
15	WG2: Identification and proposition of actions (to WP3 and others) to build bridges between systems and to provide improved experimental designs and data analysis	22
16	WG5: Distribute minutes of Action Management Committee and associated Work Group meetings	23
17	WG2: Publication of results (e.g. in CPMB) describing Benchmarking and Guidelines for utilisation of HCM systems, with selected experimental designs and protocols	29
18	WG3: Production of a roadmap for innovations in data analysis, data curation and ontologies existing omics repositories to enable development of an HCM data repository	30
19	WG4: Second advanced workshop on HCM - course report and manual published on website	31
20	WG5: Report on activities and outcomes of communication and dissemination to scientific and wider stakeholders	33
21	WG3: Identify key researchers in ML and neural networks who have an interest in HCM and organise interdisciplinary meetings to determine how to work together	34
22	WG5: Distribute minutes of Action Management Committee and associated Work Group meetings	34
23	WG3: Report on progress of participants sharing software and bioinformatics tools to analyse the output of HCM	35
24	WG4: Second introductory training course held and report and course manual published on website	36
25	WG4: Website populated with data analysis manuals, open-source software and raw data of representative experiments	39
26	WG3: Production of a roadmap for innovations in data analysis, data curation and ontologies existing omics repositories to enable development of an HCM data repository	42
27	WG5: Distribute minutes of Action Management Committee and associated Work Group meetings	43
28	WG5: Report on activities and outcomes of communication and dissemination to scientific and wider stakeholders	45

4.1.3. RISK ANALYSIS AND CONTINGENCY PLANS

Risk: IT technological/challenge for data provision – Mitigation: Recruit additional expertise in the field, liaise with existing data repositories.

Risk: In person training & meetings not possible (e.g., COVID) – Mitigation: Promote webinars. Consider delaying physically training/meetings where possible.

Risk: Capacity/poor engagement in Working Group from the different countries - Mitigation: Redundancy of expertise allowing back-up plans. Constantly promote Action to encourage new members.

Risk: Failure to outreach outside the network – Mitigation: Members of the Action network are part of several scientific international programs. Dissemination plan developed.

Risk: Sustainability of website – Mitigation: Liaise with existing repositories.

Risk: Integration of a large network of diverse researchers - Mitigation: Have separate WG meetings as well as plenary sessions, facilitate contributions from all Action members.

Risk: Diverse public opinion and different national approaches in research to animal welfare and animal usage in research – Mitigation: make sure that animal welfare it always a topic for discussion at networking and MC meetings and as part of communication and dissemination. GANTT Diagram.

