European Cooperation
in Science and Technology
- COST -

Secretariat

Brussels, 9 June 2011

COST 4141/11

MEMORANDUM OF UNDERSTANDING

Subject : Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action TD1103**:** European Network for Hyperpolarization Physics and Methodology in NMR and MRI

Delegations will find attached the Memorandum of Understanding for COST Action TD1103 as approved by the COST Committee of Senior Officials (CSO) at its 182nd meeting on 17 May 2011.

MEMORANDUM OF UNDERSTANDING

For the implementation of a European Concerted Research Action designated as

COST Action TD1103

EUROPEAN NETWORK FOR HYPERPOLARIZATION PHYSICS AND METHODOLOGY IN NMR AND MRI

The Parties to this Memorandum of Understanding, declaring their common intention to participate in the concerted Action referred to above and described in the technical Annex to the Memorandum, have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 4154/11 Rules and Procedures for Implementing COST Actions, or in any new document amending or replacing it, the contents of which the Parties are fully aware of.

2. The main objective of the Action is to develop and optimize robust strategies for the generation of spin hyperpolarization that provide a dramatic sensitivity increase of NMR techniques for a wide range of applications including medical diagnostics, molecular dynamics and structural investigations of biomolecules.

3. 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 44 million in 2011 prices.

4. The Memorandum of Understanding will take effect on being accepted by at least five Parties.

5. The Memorandum of Understanding will remain in force for a period of 4years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of Chapter IV of the document referred to in Point 1 above.

A. ABSTRACT AND KEYWORDS

Nuclear Magnetic Resonance (NMR) spectroscopy, microscopy and imaging techniques (MRI) play a crucial role in numerous fields of science ranging from physics, chemistry, material sciences, biology to medicine. However, despite all their versatility, the key issue is frequently sensitivity, which limits the applicability of NMR spectroscopy and imaging techniques in the case of fast dynamical processes and detection of low concentration molecules in both *in vitro* and *in vivo* applications. The Action aims to stimulate and accelerate collaborations and joint research efforts between European groups into hyperpolarization physics and methodology with the goal to develop robust strategies for sensitivity enhancement in NMR and MRI. Coordinated short-term scientific missions (STSMs) will make it possible to fully exploit the potential of unique scientific instrumentation which already exists in a number of European groups. Summer schools and workshops will provide education and training for the early stage researchers that are entering the interdisciplinary research field. The scientific programme is organised into 5 different working groups that focus on key issues related to the topic of the Action. The scientific programme of this Action is supported by a wide range of research groups thus generating a high added value for the European research landscape.

Keywords: Hyperpolarization, Nuclear Magnetic Resonance, Magnetic Resonance Imaging, Dynamic Nuclear Polarization, Sensitivity Enhancement

B. BACKGROUND

B.1 General background

Nuclear Magnetic Resonance (NMR) spectroscopy, microscopy and imaging techniques (MRI) play a crucial role in numerous fields of science ranging from physics, chemistry, material sciences, biology to medicine. The high information content of modern multi-dimensional NMR spectroscopy makes it possible to obtain structural and dynamical information with atomic resolution. In addition, owing to the low energy excitation in the MHz frequency region, the method is non-invasive, making it one of the most important imaging modalities in medical diagnostics. However, despite all its versatility, the key issue is frequently sensitivity, which limits the applicability of NMR spectroscopy and imaging techniques in the case of fast dynamical processes and detection of low concentration molecules in both *in vitro* and *in vivo* applications.

Several ‘hyperpolarization’ strategies are used to increase the nuclear spin polarization and thus the magnetic resonance sensitivity by a factor of up to 10000 and more. Two of these strategies are based on the transfer of the much bigger electron spin polarization onto the nuclear spin system either during a chemical reaction (Chemical Induced Dynamic Nuclear Polarization, CIDNP) or by using microwave fields (Dynamic Nuclear Polarization DNP). Parahydrogen Induced Polarization (PHIP) is based on the correlation between a particular quantum mechanical spin state and a rotational state in diatomic hydrogen. In a chemical reaction the hydrogen spin state can be used to generate target molecules with high spin polarization. In optical pumping (OP) electrons are excited by the interaction with polarized laser light and subsequently the polarization of the excited electrons is transferred from metal ions onto noble gas atoms such as helium, xenon and krypton. Although the hyperpolarization strategies differ in their underlying physico-chemical principles they have a number of issues in common.

All hyperpolarization techniques lead to the generation of a non-equilibrium state that relaxes back to the thermal equilibrium after a certain time span. The life-time of the non-thermal spin polarization ranges from a few 100s milliseconds to some tens of seconds, depending on properties of the sample (e.g. the non-thermal polarization of ^{1}H nuclei usually has much shorter life time than for ^{13}C nuclei). The problems arising for all hyperpolarization strategies include: (i) In several applications relaxation processes can limit the use of these techniques or require rapid administration techniques to samples or patients. (ii) Since the high spin polarization is short-lived, efficient data acquisition schemes are required to maximise the information about the sample that can be collected in a short period of time. (iii) The use of these techniques requires non-standard hardware developments and experimental setups and (iv) although the general principles underlying the generation of non-thermal spin polarization are well established the fine details of these strategies are still complex and difficult to predict theoretically.

There is a rapidly growing large number of European groups that work in the field of NMR hyperpolarization techniques trying to overcome the problems outlined above by using novel strategies such as the generation of long-lived spin states, the design of novel hardware components such as sample shuttle systems that make it possible to perform fast changes of the static magnetic field or the implementation of highly efficient sampling strategies that enable the acquisition of data in a few tens of milliseconds for multidimensional correlation experiments (ultrafast multidimensional spectroscopy) or rapid imaging. Encouraged by the wide range of novel developments currently taking place it is proposed to establish a COST Action with focus on hyperpolarization methodology and physics in NMR and MRI and with the main objectives to generate a forum for groups working in these fields and to facilitate the exchange of information on the European level.

There are several reasons why COST provides the best framework for this Action: Since the number of European research groups that are becoming actively involved in research topics related to the theme of this Action is rapidly increasing, a funding scheme for the network is required that makes it possible for groups to join also at a later stage. In a survey carried out across Europe more than 40 different research groups with complimentary expertise have already expressed their strong interest in the implementation of the COST Action. Many groups have already attracted substantial funding on the national level for their individual research topics and in many cases unique instrumentation has been developed and implemented. The COST Action will enable access to these unique facilities for early stage researchers during STSMs. In addition, it will provide an opportunity to develop a coordinated pan-European training program that is urgently required to meet the needs of young scientists who want to enter the field of hyperpolarization physics and methodology. An additional advantage of the COST scheme is the possibility to include research groups from neighbouring countries and countries with mutual agreements.

B.2 Current state of knowledge

Any strategy that can be used to generate high non-thermal spin polarization will also provide a dramatic increase in MRI and NMR sensitivity. Several strategies were proposed in the 50s and 60s but their general exploitation and development into techniques with wide applicability was limited by the capabilities of the available hardware at this time. Only recently, as a result of cumulative advances being made in engineering, chemistry, biology and physics, experimentally feasible strategies have emerged that could potentially overcome the sensitivity limitations of conventional NMR in a wide range of applications. DNP currently appears to be the most promising candidate in this respect. This method has the potential to enhance the sensitivity in solid-state and solution NMR spectroscopy as well as in MRI applications. Theoretically the gain in sensitivity for NMR spectroscopy could approach three orders of magnitude. In conjunction with fast changes of the sample temperature a signal enhancement of up to four orders of magnitude has been experimentally verified. There is currently a huge interest in the academic and the commercial sector to develop DNP techniques into routine strategies. On the national level substantial research grants for the development of suitable hardware for DNP experiments were awarded to groups based in several COST countries. On the European level the feasibility project BioDNP was funded within the Framework 6 with the goal to develop hardware for liquid state DNP applications.

The three other hyperpolarization strategies (PHIP, CIDNP and OP) are based on particular properties of the target molecules and can therefore be used to generate high spin polarization in certain classes of molecules (and atoms). All three strategies have their own unique advantages. OP techniques are the method of choice for the generation of highly polarized gases used in the exploration of surfaces or in novel MRI schemes for the medical diagnosis of lung conditions. PHIP techniques can generate highly polarized spin states in an relatively simple experimental set-up and recent progress has shown that in combination with suitable chemistry techniques it may be possible to use PHIP as a source of polarization for a wider range of reactive systems. CIDNP experiments require radical pairs. In liquid-state, protein surfaces and folding processes can be studied. Use of artificial photosynthetic reaction centres might allow the development of solid-state photo-CIDNP in a generally applicable method for signal enhancement, in particular for the investigation of surfaces.

Substantial progress has also recently been made in the control of relaxation. Pioneering research has demonstrated the existence of long-lived spin states in certain classes of molecules. These long-lived spin states show particularly slow relaxation (relaxation rates are slowed down by 1 to 3 orders of magnitude) and could therefore, in principle, also be used to store high spin polarization over a long time.

Another field of research in NMR with high relevance to the theme of this Action is the use of sophisticated acquisition schemes to read out the NMR signal very rapidly while retaining a maximum of information encoded in the signal. These methods become of increasing importance in rapid medical MRI techniques but also in multi-dimensional spectroscopy.

The European magnetic resonance community currently has a strong position in academic research related to hyperpolarization physics and methodology. In particular, there is strong expertise in all four hyperpolarization strategies available between a large number of groups across Europe while in other parts of the world research in this field is frequently linked to a few dominating scientists.

Significantly more progress could be made in hyperpolarization physics and methodology research if the research activities would be better coordinated across Europe, information and expertise could be exchanged between the various fields of research described above and, importantly, training could be provided to researchers in their early stage when entering this multidisciplinary field.

B.3 Reasons for the Action

The Action has the potential to generate an impact economically (by leading to new commercial products and providing novel strategies for pharmaceutical screening), scientifically (by providing insight into the detailed physics of the hyperpolarization process) and technologically (by developing new methods and instrumentation that could become standard tools in many NMR and MRI applications). Since MR based techniques are used in so many different disciplines and applications, not only the participating groups but the larger scientific communities and many national and EU funded programs will benefit from advances in this field and the synergistic effects generated by sharing of expertise, of facilities and of teaching young scientists. Thus, although the goals of this Action are highly focused, the implications for many application areas in the event of its success are huge.

Currently research into hyperpolarization strategies in various COST countries is an important field that attracts large national funding awards. However, although national research initiatives already exist, the field lacks coherence across Europe and is even split into strands pursuing research into different hyperpolarization strategies. The network will give leverage to access the substantial national funding that this area has received throughout the EU (especially in Germany with large instrumentation funds provided by the German Scientific Council, the Netherlands and in the UK through the Basic Technology Program). To maximize the outcome of the COST Action it is proposed to stimulate exchange of information and expertise as well as to coordinate the provision of training in workshops and on unique research facilities in Europe to early stage scientists.

The COST framework offers three different means to stimulate exchange of information and to coordinate the research effort in the field of hyperpolarization research in the COST countries:

- The STSMs scheme is the best instrument to bridge the gap between technology developers and the end users who have particular applications in mind. Only during a site visit and experimental trials will it be possible for both the technology developer and the end user to find solutions together to adopt the technology to the requirements of the application;
- Scientific meetings and expert discussion groups involving researchers from different disciplines are important to align the research strategies and foster collaborations;
- Schools and workshops are extremely useful to help disseminating the experimental know-how and advances in understanding the theory to early-stage researchers.

One outcome of the Action is of course an increase of these three activities involving all interested groups across the COST countries. The quantifiable scientific outcomes of the Action always depend on the progress achieved during the course of the Action. It is anticipated that by the time the Action is concluded the following achievements will have been made with support through the COST Action:

- The theory and understanding of complex quantum systems will be improved substantially with methods published for simulating the dynamics of large numbers of coupled spins. This advance will be crucial for understanding the effect of any hyperpolarization technique when applied to solid state systems;
- Progress in understanding the principles underlying the generation of long-lived spin states will be made and strategies will be published describing how to generate these states experimentally;
- A substantial extension will made to the class of chemical and biological systems that can be studied by means of hyperpolarization-based NMR techniques, paying special attention to biologically important molecules;
- A set of suitable methods will be described for fast data acquisition strategies while maximizing the information that can be derived from these measurements. This advance will have important implications for medical diagnostics and also for research into molecular dynamics;

- Substantial progress will be made in the development of appropriate instrumentation for the application of hyperpolarization strategies.

Since many different research disciplines are involved in the COST Action including chemistry, medicine, biology, engineering and physics the Action is trans-domain. There is a clear benefit of bringing together chemists, physicists and engineers for stimulating discussions including also the end users that are predominately based in the medical, biological and biochemical communities. The detailed advice and feedback of the end users is crucial for the optimization of the hyperpolarization strategies and it is a particular goal of the Action to bridge the divide between the various disciplines.

B.4 Complementarity with other research programmes

The COST Action is complimentary to the Framework 7 ITN Metaflux. While Metaflux aims to train young researchers in the application of DNP to studies of metabolic fluxes, the COST Action focuses on the methodology and underpinning physics of hyperpolarization strategies. Therefore, Metaflux is mainly concerned with applications while the COST Action aims at the optimization of the technology. In addition, Metaflux involves four academic groups while already more than 40 European groups have signalled their interest in the participation to the COST Action.

C. OBJECTIVES AND BENEFITS

C.1 Main/primary objectives

The aim of the Action is to develop and optimize in a concerted European initiative robust strategies for the generation of spin hyperpolarization that provide a dramatic increase in the sensitivity of NMR spectroscopy and imaging experiments for a wide range of applications including medical diagnostics, molecular dynamics and structural investigations of biomolecules.

C.2 Secondary objectives

The objectives of this Action exceed the capability of any individual group, since they involve:

1. The development of appropriate hardware optimized for routine applications of the four hyperpolarization strategies (DNP, CIDNP, PHIP, OP);
2. Theoretical modelling of the hyperpolarization strategies to acquire a full understanding of the underpinning physical principles;
3. The development of optimal methodology (including sample preparation, sample handling) for the application of hyperpolarization strategies to the various application fields;
4. The development of strategies for the control and minimization of the polarization loss by relaxation or other processes during administration;
5. The development and optimization of appropriate fast signal acquisition strategies for hyperpolarized samples (including both spectroscopy and imaging applications).

This Action is clearly multidisciplinary, since it requires the close co-operation between physicists, chemists, engineers, biologists and medical researchers. Bringing together the expertise of several scientific communities that currently do not interact strongly will enable fast progress in developing generic approaches for the use of hyperpolarization techniques. In this way, not only the participating groups will benefit directly from this Action but there will be considerable input into other research areas indirectly involved in the Action.

An additional objective of this Action is to reach and maintain the leadership of the European NMR groups in the development and application of hyperpolarization techniques. One of the important goals is to make unique instrumentation available that was designed by a number of European groups working in this field. In particular, there are a number of facilities that have been set up with substantial costs involved as a result of funding provided on the national and European level (e.g. the UK Basic technology program and the EU framework 6 BioDNP feasibility study). The Action will make it possible for participating researchers to test their own ideas using these facilities in STSMs. Another important goal of this Action is to make training to the younger generation of European scientists available in the multidisciplinary field of spin hyperpolarization physics and methodology.

In the long term Europe can only retain its leading role in this field if the younger generation of scientists is taught the theoretical and experimental background, thus enabling them to lead their own research in spin hyperpolarization. Regular workshops and schools will contribute substantially to sharing the expertise of scientists working on the development of hyperpolarization strategies with the larger NMR and MRI communities and will thus enable a rapid technology transfer across European groups.

C.3 How will the objectives be achieved?

The objectives of this Action can only be achieved in a reasonable time frame if co-operation is facilitated between the various European groups with complementary expertise. For a single group it is difficult to substantially advance the field because of the breadth and complexity of the hyperpolarization techniques. On the contrary, networking will encourage exchange of information, skills and ideas as well as provide access to unique instruments and hardware. The STSMs of the Action offer an efficient instrument to exchange expertise and setup links between research groups. It is worthwhile to stress the importance of interactions between the end user community and the instrument designers for this Action. Without continuous feedback by the users any development of methodology and hardware design runs the risk of having a limited applicability. In this respect STSMs can also assist to bridge the gap between developer and user.

C.4 Benefits of the Action

The scientific outcome of the Action will have a strong impact in a range of different disciplines. Numerous novel applications of NMR spectroscopy will become feasible through an increase in sensitivity and robust strategies for the application of hyperpolarization including the observation of fast molecular dynamics and binding, the investigation of molecular surface structures and the application of NMR techniques to very small spin ensembles in nanoscience. MRI techniques are frequently used in medical diagnostics and the improvement of their sensitivity will have a substantial impact on applications in molecular imaging, a field of research that produces strategies for visualization of the *in vivo* metabolite distribution and the location of specific molecular events in the human body.

In addition, the development of robust hyperpolarization strategies will have an impact on the commercial sector with the design of potential novel hardware compounds as well as the supply of specific chemical products required for the hyperpolarization techniques.

The impact that the Action will make on the European science landscape will be a strong coordination of research activities in the field of hyperpolarization, the establishment of a well functioning network between the participating groups and also importantly, the provision of education and training for early stage researchers in this fast emerging field.

C.5 Target groups/end users

The target groups of this Action are groups which are currently active in the Field of hyperpolarization methodology and physics development or which will enter this field in the near future. Feedback from 41 European groups has already been used in the preparation of the Action for the COST Action. The feedback was obtained through the distribution of a 3-page questionnaire to 45 European research groups. The strong feedback demonstrates the high interest of the target groups in the establishment of the Action. End users of the methodology development proposed in this Action work at the interface between the NMR community and other communities carrying out more application-oriented research, such as medical or biochemical research groups. Since it is paramount that feedback from the end user is channelled to the developers a number of groups in this field have been already approached in the preparation of the Action.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

The main tasks of the COST Action "Hyperpolarization physics and methodologies for NMR and MRI applications" are to bring European experts together, to facilitate collaboration between different groups, to enable access to unique scientific instrumentation and to provide training for the young generation in the emerging research field of spin hyperpolarization. These key tasks are complemented by the scientific goals of this Action that comprise:

1. The development of robust hyperpolarization strategies for medical and non-medical applications of MRI and NMR spectroscopy;

2. The design and testing of optimal hardware for hyperpolarization strategies;

3. The evaluation of different hyperpolarization schemes for different application fields;

4. The development and implementation of robust and versatile schemes for signal acquisition in experiments using hyperpolarization;

5. The development and testing of advanced schemes for the control of relaxation.

The means used to achieve the key tasks have already been mentioned in B.3 (Reasons for the Action). Briefly, the COST Action offers three important strategic means to stimulate exchange and align research activities across all COST countries: STSMs establish local contact between different research groups and can be used to bridge the gap between developers and users, meetings can be used for discussions, dissemination and exchange as well as generating coherent research strategies, and workshops and schools are important for the training of early-stage researchers.
The Action will be a success if it attracts participants (the 'human means') from many different disciplines since only with their input and expertise from many different fields of research will it be possible to achieve the scientific goals and make progress in the complex research of hyperpolarization strategies.

D.2 Scientific work plan – methods and means

The COST Action work plan is organized into a scientific program for five working groups (WGs). Each group will focus on major issues related to the use of hyperpolarization in NMR and MRI. It will be the responsibility of the five working groups to achieve progress towards the scientific aims of the Action.

- *Working group 1:* Hardware and instrumentation for hyperpolarization.
- *Working group 2:* Theoretical understanding of hyperpolarization strategies.
- *Working group 3:* Strategies to minimise the effect of relaxation on spin hyperpolarization.
- *Working group 4:* Strategies to maximise the information that can be acquired using hyperpolarized spin systems.
- *Working group 5:* Synthetic chemistry - physics interface in hyperpolarization methodology.

In all WGs researchers are involved from a wide array of scientific disciplines, since an interdisciplinary approach is an absolute requirement for the fulfilment of the WG goals.

Working group 1: The currently on-going rapid development of novel strategies for hyperpolarization is made possible by the design of new hardware components. For example, the availability of high power microwave sources and the intelligent design of resonating structures are essential to establish DNP MAS (Magic Angle Spinning) NMR as an experimental strategy with great potential. Similarly, OP requires efficient facilities for spin-exchange, solid-state photo-CIDNP for illumination at low temperature under MAS conditions. This WG will serve as a forum for European groups that are currently involved in active hardware design and instrument development. By keeping the focus of this working group intentionally broad it is hoped that exchange of information between groups working in complementary fields is stimulated. In many respects the implementation and realisation of the various hyperpolarization strategies relies on similar hardware components. For instance, fast shuttling strategies that can be used to quickly change the strength of the static magnetic field have been used to demonstrate the possibility of storing high spin polarization in long-lived spin states and to separate the generation of spin polarization from the signal detection. Laser technology is important for fast temperature jumps, CIDNP and optical pumping. Cryo-temperature technology is used both in PHIP and DNP applications.

WG 1 will interact closely with all other WGs since theoretical insight and novel strategic concepts will have immediate implications on the required hardware components and instrument specifications.

WG1 will have the following objectives:

1. To stimulate exchange of information between hardware designers and instrument developers working on the various HP strategies;

2. To continuously carry out and update a comprehensive survey of the unique instrumentation in Europe currently used in hyperpolarization MRI and NMR;

3. To coordinate and provide access and training on unique instruments;

4. To organize workshops in hardware design and instrument development. Skills and expertise in this field of research are not ubiquitously available between early stage researchers and there is an immediate need to provide training to enable creative research in the field covered by the COST Action.

In joint projects and discussions in meetings WG 1 will focus initially on the following goals:

1. Optimisation of sample shuttling strategies;

2. Optimisation of experimental set-ups for OP;

3. Development of continuous flow devices for the production of hyperpolarized solutions using PHIP DNP and OP;

4. Comparison of various DNP strategies (liquid state – high field, liquid state low field in conjunction with sample shuttling, low temperature DNP in conjunction with dissolution or sample melting);

5. Developing CIDNP and PHIP based strategies to monitor chemical reactions in real time by means of NMR.

Working group 2: Despite early publication of the use of various hyperpolarization techniques, theoretical models of the mechanisms based on the quantum mechanical formalism of NMR were only recently developed. This is in part due to the complex nature of the physical systems consisting of many coupled quantum objects. This working group will provide a forum for theoreticians working on gaining insight into the underpinning physico-chemical processes of hyperpolarization strategies. Since there is substantial overlap of the physics involved, for instance in the theory of CIDNP and DNP, exchange of information between different research groups will lead to a synergistic effect that enables much faster progress in the theoretical understanding by establishing a forum for discussions.

In details WG 2 will have the following objectives:

1. Coordination and facilitation of the exchange of expertise and information between groups working on the theoretical description of hyperpolarization strategies;

2. To provide training in workshops to the experimentalists and the young generation of scientists. In particular, the theoretical skills and methods required to analyse hyperpolarization strategies in detail are usually not taught in graduate level introductory NMR courses at universities. Hence the COST Action will provide dedicated training programmes to help develop the theoretical understanding and expertise required for creative research in this field;

3. To summarize and publish advances made in the theoretical description of hyperpolarization physics.

In coordinated collaborations and meetings WG 2 will focus initially on the following scientific goals:

1. Full scale modelling of DNP in both solid and liquid state;

2. Full scale modelling of solid-state CIDNP including spin diffusion;

3. Detailed understanding of relaxation dependence during magnetic field changes;

4. Analysis of the limiting factors during hydrogenation reactions using para-hydrogen;

5. Full scale modelling of polarization transfer and relaxation in coupled multi-spin systems.

WG 2 will strongly interact with WG 3 and WG4, recommendations from the theoretical side will also be useful for the success of WG 5.

Working group 3: Recent pioneering research shows that polarization can be stored over a prolonged period of time in long-lived spin states. This strategy has great potential for both studies of molecular dynamics and, in particular, for use in medical diagnostics. In addition to these recent advances it is well established that spin polarization can be transferred from the hydrogen spin system to ^{13}C nuclei that usually relax with much slower rates. The most efficient strategies for this transfer in solid state however are still not fully understood. WG 3 bundles together the various European research activities in relation to strategies that are used to control the loss of spin polarization through relaxation processes. WG 3 will interact closely with WG 2 and for the experimental realization with WG 1.

WG 3 will have the following objectives:

1. Establishing a forum for discussions related to spin relaxation and its control;

2. Facilitation of collaboration between European groups in this field;

3. Provision of training to the younger generation of researchers in workshops.

It is foreseen, that the following scientific goals will be addressed in WG 3:

1. Strategies to evolve spin systems into long-lived spin state;

2. Understanding of symmetry conditions required for long-lived spin states, particularly in multi-spin systems;

3. Development of practical protocols particularly for applications in medical diagnostics.

Working group 4: Several sophisticated NMR acquisition schemes have been proposed amongst which the recent experimental demonstrations of gradient assisted ultrafast multi-dimensional spectroscopy techniques are currently showing the biggest potential for application to hyperpolarized molecules. For MRI protocols there are currently initiatives to use sparse sampling strategies to shorten the image acquisition time whilst retaining the imported spatial information. Recently, a strong synergy in the development of MRI techniques and NMR spectroscopy has become apparent that is, to a great deal, motivated by the use of hyperpolarization in both application fields. WG 4 will bring together the experts in Europe and neighbouring countries to discuss and develop optimal acquisition strategies to be used in conjunction with hyperpolarized spin systems.

The objectives of WG 4 are:

1. Establishing a forum for discussions and to coordinate research into signal acquisition schemes;

2. Organizing hands on workshops to communicate the ideas and results discussed in this WG to the other participants of the COST Action;

3. Publishing detailed advice and analyses for optimal sampling and signal acquisition strategies.

The scientific goals for WG 4 to focus on include:

1. The optimisation of fast spectroscopy protocols;

2. The development of sparse sampling techniques for both spectroscopy and imaging applications;

3. The use of multi-receiver and transmitter configurations to maximise data acquisition.

Working group 5: The interface between synthetic chemistry and physics. Several of the hyperpolarization strategies require the synthesis of molecules tailored for optimal efficiency. PHIP needs suitable target molecules, DNP is based on the use of appropriate radical molecules and, in particular, solid-state CIDNP could be possible on artificial molecular structures. The latter case would make it possible to develop solid-state CIDNP into a generally applicable enhancement method. This working group will create an interface between synthetic chemists and physicists in which possible solutions will be discussed that are related to the sourcing and synthesis of dedicated molecular systems such as hyperpolarizable molecules for MRI and bio-compatible molecules.
The objectives of this WG are:

1. Bundling the expertise available in the chemical synthesis of radical systems, CIDNP capable molecular structures, and appropriate PHIP target molecules;

2. Establishing contacts between chemists and physicists and other scientists from the biological and medical research fields.

The scientific goals of WG 5 are:

1. Optimisation of synthetic routes for molecular structures required in hyperpolarization techniques;

2. Understanding the relation between structure and function of radical pairs and CIDNP active molecular centres;

3. Designing dedicated molecules that enable hyperpolarization for bio-NMR and MRI.

The organisation of the scientific programme of the Action into 5 WGs makes it possible to cover all important issues related to the use of hyperpolarization in MR technology and accommodate groups from COST countries with a wide range of expertise. It will be possible to modify or broaden the scientific goals of the WGs during the course of the Action if required by progress and new scientific developments.

E. ORGANISATION

E.1 Coordination and organisation

The organization of the Action and its management will be in agreement with the COST Action regulations and procedures. In more detail the MC (Management Committee) will appoint:

1. Working Groups Coordinators whose role is to oversee the coordination of the individual WGs;

2. A STSM Manager, who coordinates the logistics of the STSMs and chairs the STSM panel;

3. A School Coordinator who acts as the central person for the coordination of summer schools and workshops (this appointment will be made on an annual basis);

4. A Website Manager who is responsible for the representation of the Action through its website;

5. A Dissemination Manager who coordinates the dissemination activities, advertises the COST Action and provides interested people and organizations with the necessary information.

Steering Committee: Furthermore, the MC will appoint a steering committee (SC) that will handle all immediate activities and report to the MC meetings. The SC consists of Action chair (AC), Action vice-chair (AVC), the STSM Manager, the School Coordinator and the Dissemination Manager.

A website detailing all relevant information for the COST Action with contact information of the various coordinators and committees will be generated within three months after the first Kick-off meeting. Apart from the updated schedule of the Action and detailed information about the activities of the WGs, there will be also an online submission form for STSMs and a list of facilities being made available to participants of the Action.

STSM panel: The STSM panel will be chaired by the STSM Manager and consists of the 5 WG coordinators plus another member of each workgroup as well as the AC and AVC. It is envisaged that applications for STSMs must be made at least 6 months in advance before the actual date and decisions are made within 3 months after the application is received. 39 STSMs are planned during the 4 year duration of the Action.

The School Coordinator will also invite early-stage researchers to participate in the organisation of the school programme.

The following milestones will be used as progress indicators for the organizational part of the Action:

- Kick-off meeting with appointment of Action representatives, identification of strategic goals, objectives and means to reach them (scheduled for the first month);
- Website design and implementation (online before the end of the fourth month after Start of Action);
- WG meetings;
- Training schools in theoretical and experimental aspects of spin hyperpolarization (4 schools, labelled T, E in timetable provided in section F));
- Publication of joint high impact scientific papers arising from collaborations during the COST Action;
- Final conference (labelled F in timetable, section F).

E.2 Working Groups

This COST Action is structured in five Working Groups led by the Working Group coordinators and a deputy coordinator. These will be responsible for:

1. Coordinating WG meetings;

2. Establishing, and controlling the fulfilment of WG milestones;

3. Reporting and announcing WG activities at SC and MC meetings;

4. Controlling the representation of the WG activities on the Action website;

5. Advertising and coordinating STSM within and between WGs;

6. Disseminating results of the WGs and encouraging exploitation of research progress;

7. Editing written WG reports and joint scientific publications.

E.3 Liaison and interaction with other research programmes

A close interaction with the Framework 7 ITN Metaflux is planned. The Action will organize a number of schools which will also be of interest to early stage researchers of the ITN Metaflux. The coordinator of the ITN has already expressed his interest in participating in the COST Action as well as two other groups involved in the ITN.

E.4 Gender balance and involvement of early-stage researchers

This COST Action will respect an appropriate gender balance in all its activities and the Management Committee will place this as a standard item on all its MC agendas. The Action will also be committed to considerably involve early-stage researchers. This item will also be placed as a standard item on all MC agendas.

As a starting point to attract also more early-stage researchers who are young parents to schools and workshops of the Action it is proposed to arrange childcare free of charge if required.
It is also suggested to involve early-stage scientists in the organisation of school and workshop programmes (see E.1)

F. TIMETABLE

Year	**1st year**				**2nd year**				**3rd year**				**4th year**			
Period	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
MC meetings	K		1				1				1				1	1
WG meetings			1				1				1					
Conferences	L														F	
STSMs		1	2	3	3	3	3	3	3	3	3	3	3	3	2	1
Training schools			T				E				T				E	
Other issues	W															

K = kick-off meeting, F = Final L = Workshop, T = summer school with focus on theory, E = summer school combining theory and experimental training, MC = management committee, W = web site, WG = work group, STSM = short-term scientific mission.

The initial Workshop will be used for setting up the WGs (Section C). Discussions within the MC will ensure that the work is well-focused, that collaborations between the participants are initiated or further developed. A first joint WG Meeting will be organized to allow for collaborations within and between the different WGs to be formed and to outline the aims of the Action. After this meeting, three joint WG Meetings will be held during the Action. Additional meetings of the individual WGs are possible and will be organised if a need for meeting arises. The work on all the individual projects will be on-going in parallel over the four years of the COST Action. Meetings and conferences aim to initiate proposals for STSMs within the tasks. The final Joint Working Group Meeting will be organized as a large-scale conference, involving all participants of the COST action. The MC will meet at the start of the Action and each successive year (some meetings coinciding with the WG meetings). The last six months will be devoted to the preparation of a synthesis of the results achieved, together with the final report. This Action will be finalized in the last meeting of the MC.

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: BE, CH, DE, DK, ES, FR, IL, IT, NL, PL, UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 44 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

The following Non-COST Country have expressed their interest to participate: New Zealand and Russia.

H. DISSEMINATION PLAN

H.1 Who?

One of the tasks of the SC and MC is the continuous process of identifying target groups that may be interested in the Action. These target groups include the wider scientific community, higher education facilities, policy stakeholders, SMEs and the general public. Special emphasis will be provided to end users such as SMEs, the commercial sector represented by NMR instrumentation manufacturers and of course politicians and lobbyists who are actively involved in the decision making process for further research policies and funding on a European and national level.

Important targets for the dissemination are also students in the early career stages. The highly interdisciplinary research of the Action requires more young scientists to pursue careers in this field. Active targeting of early states researchers offers also means to counteract the shift in the gender balance that in physical sciences is still largely male dominated.

H.2 What?

The communication of activities and results of the Action will be achieved by different means depending on the target community. The utilization of different communication channels will be the most efficient way to increase the awareness of the Action.

The following communication channels are planned.

Communication in the scientific community related to the field:

- Publications in high profile international journals by groups participating in the Action;
- Joint publications of two and more groups involved in the COST Action in peer-reviewed journals;
- Invitation of leading international scientists to teach in schools and present in workshops;
- STSMs to increase information flow between different groups and countries.
- Edition of special issues of high impact journals;
- Compilation of tutorial books and manuals for early-stage researchers.

Communication in the general scientific community and in the industrial sector:

- Announcement of Action workshops, schools and other activities in general scientific journals and though websites;
- Participation in large-scale international and national conferences with broad focus;
- Participation in scientific exhibitions and fairs to reach the industrial sector as well as SME.

Communication in the general public and policy stakeholders:

- Provision of a general introduction to the Action on the website;
- Publication of articles in newspapers or reports on television news or scientific reportages;
- Lobbying to national and European decision makers or organisations involved in the implementation of scientific strategy goals.

H.3 How?

The communication strategy of the Action aims to

- Use a wide range of media to broaden the impact of the scientific achievements; including press releases, the web, science exhibitions and newspaper contributions;
- Adopt means of communication for different groups;
- Optimise distribution of the intended information after identification of relevant target groups;
- Transfer the most valuable information to support further new technologies.

____