Final Report Summary - BAMI (The effect of intracoronary reinfusion of bone marrow-derived mononuclear cells (BM-MNC) on all-cause mortality in acute myocardial infarction)

Executive Summary:

Although the long term prognosis of patients suffering acute myocardial infarction (AMI) has improved since the introduction of reperfusion therapies and primary angioplasty, the 1 year mortality of patients with AMI and resultant left ventricular dysfunction (LVSD) is still fairly high. A major reason for this is an inadequate regenerative response to the myocardial necrosis sustained in the heart following AMI. There is previous evidence that intracoronary transfer of bone marrow derived stem cells, on top of standard reperfusion treatment, improves Left Ventricular function and reduces infarct size.

The foundation of stem cell therapy as a treatment for cardiac disease is based around the concept that myocardial infarction results in large-scale cell loss, and heart failure occurs as a direct result of this loss. The idea that stem cells could be used to replace lost or damaged cells to reverse the effects of cardiomyocyte loss has evolved over the past 15 years. Several small to intermediate size trials have demonstrated mixed results. Improvement in the LV function was noticed in trials such as TOCARE-AMI, BOOST, BONAMI and the largest REPAIR AMI. However, no significant changes were observed in LEUVEN-AMI, ASTAMI, REGENT, HEBE trials. The surrogate endpoints used in studies that have shown biological effect need translating into mortality and morbidity data to provide conclusive evidence of the benefits of cell therapy in acute myocardial infarction. Furthermore, the reparative properties of these stem cell preparations may well be variable, depending upon the method of preparation and their delivery. A definitive outcome trial was, therefore, designed to address the therapeutic benefit of this approach to stem cell therapy and also to clearly identify a standard process for preparation of cells which could be marketed and used across different countries.

The BAMI trial, investigating the effect of intracoronary reinfusion of bone marrow-derived mononuclear cells (BM-MNC) on all-cause mortality in acute myocardial infarction, started on the 1st Nov 2011 and finished on the 31st Oct 2017 (including a 1 year extension). It was originally a five-year project. Existing bone marrow procurement, cell processing and cell reinfusion techniques data were reviewed and standardised techniques for each of the procedures were successfully selected for BAMI. The study protocol, Investigational Medicinal Product Dossier, Investigators Brochure and other documents were then produced. The clinical trial was delayed during the regulatory approval processes following changes in regulations as a result of which only 3 out of the 7 cell processing centres planned for the study were suitable, i.e. found to be fully GMP licensed. This had a considerable knock-on effect on subsequent timelines – the start of the clinical trial was delayed by nearly 12 months. The overall recruitment rate was also significantly lower than anticipated. As the study progressed, it became apparent that the initial target of 3000 patients would be unachievable. The study was revised based on the actual recruitment rate and redefined as an estimation trial, whereby the primary objective was to provide estimates of event rates, predominantly in the BM-MNC group, and estimates of the treatment effect and their associated 95% confidence intervals. The social science element included in BAMI (Work Package 7), which studied the progresses of regulatory approval and
practical trial implementation across the partaking centres, has analysed and published on the diverse hurdles encountered across the BAMI trial.

The BAMI trial is in the patient follow-up phase and final patient outcome data can be reported after this will have completed in autumn 2019. Despite not achieving its initial target of 3000 patients, BAMI is now the largest phase III trial of its nature in the field of cardiology (375 patients randomised). This number of patients means the trial is not powered to provide the initially planned hard endpoint results, yet it is expected to provide valuable data in the field for current and future studies. The main results so far demonstrate successful standardisation of the bone marrow procurement and the cell manufacturing technique. Other results will become available once the follow up period ends. Additionally, based on its accompanying analysis of the experiences of partners with ethics approval and implementation, partner UNEXE is now in a position to provide recommendations on possible improvements of the translation of EU regulations into effective clinical practice.

Project Context and Objectives:
Summary Description of Project Context and Objectives

Myocardial infarction occurs when one or more of the three epicardial coronary arteries blocks (invariably due to the rupture of a lipid plaque and subsequent activation of the clotting system leading to thrombus formation) and is fatal in approximately 30% of cases. The main principle for the treatment of acute myocardial infarction has until now focused on restoring flow down the coronary artery as soon as possible, thereby minimising the amount of cell death caused by the interruption of blood flow. One of the first treatments was thrombolysis, a drug administered intravenously to dissolve the clot, which can, unfortunately, also cause bleeding. It is relatively recent that the use of balloon angioplasty and stent insertion has been shown to improve restoration of coronary blood flow beyond that achieved by thrombolysis alone. The development of this strategy has reduced death from myocardial infarction by a further half compared to the reductions achieved by thrombolysis. This therapeutic development has been brought about by improvements in angioplasty technology, as well as the evolution of adjunctive pharmacotherapy, which means one of the main complications of angioplasty in the acute setting, abrupt vessel closure due to thrombus formation, is now a rare event. Despite this very direct approach to the treatment of myocardial infarction and the delivery of prompt reperfusion, myocardial necrosis and subsequent heart failure are now emerging as an ongoing issue given that overall more patients are surviving the acute event of vessel closure. Unfortunately, the factors that continue to lead to myocardial damage are beyond the therapeutic potency of acute angioplasty. Importantly, approximately half the amount of myocardial damage occurs as a result of restoring blood flow (ischaemia-reperfusion injury) due to local toxins and oxidant stress that are produced by ischaemic tissue. Now that timely restoration of blood flow has become an achievable target there is a need to address the pathogenic factors that lead to myocardial injury and indeed the long-term consequences (i.e. the prevention of subsequent heart failure).

There is previous evidence that intracoronary transfer of bone marrow derived stem cells, on top of standard reperfusion treatment, improves Left Ventricular function and reduces infarct size. The foundation of stem cell therapy as a treatment for cardiac disease is based around the concept that myocardial infarction results in large-scale cell loss, and heart failure occurs as a direct result of this loss. The idea that stem cells could be used to replace lost or damaged cells to reverse the effects of cardiomyocyte loss has evolved over the past 15 years. Several small to intermediate size trials have demonstrated mixed results. Improvement in the LV function was noticed in trials such as TOCARE-AMI, BOOST, BONAMI and the largest REPAIR AMI. However, no significant changes were observed in LEUVEN-AMI, ASTAMI, REGENT, HEBE trials.

The reasons for the inconsistent findings from previous smaller clinical trials are unclear, but possibilities include variations in the number of cells delivered, timing of delivery after Acute Myocardial Infarction (AMI) and differences in the cell isolation protocol. A meta-analysis has been performed on the impact of BM derived cells after AMI and comprises 811 patients. This confirmed the safety of a BM derived cell treatment option after AMI and overall stem cell therapy was associated with an improved LVEF of 2.99% and reduction in myocardial scar by 3.51% in comparison to controls. There may have been several
reasons for the less impressive results in humans, including suboptimal study designs which have been diverse, particularly with regards to the timing of BMSC delivery and type of AMI treated. Therefore, an increasingly pressing need for a definite cell therapy trial emerged. This trial needed to take into consideration the methods of the then largest study, REPAIR AMI, which had shown a maintained benefit on cardiac function and mortality, and also the lessons learned from other trials.

In 2003 the European Society of Cardiology encouraged the formation of a Task Force to assess the role of stem cell therapy in the treatment of cardiac disease. The group was composed of key opinion leaders in the field who had contributed to the clinical translation of the basic science. In 2006 the Task Force published its consensus document regarding the state of the field, together with recommendations for developing this promising area of clinical translation. One of the recommendations was to proceed to large randomised control clinical trials to establish the true value of this exciting potential new therapy.

BAMI brought together the key opinion leaders and pioneers in the field of regenerative medicine for the cardiovascular system. Taking into account the latest evidence, and their experience, the group formulated the BAMI proposal based on the following principles:

- Autologous bone marrow cell therapy for the treatment of acute myocardial infarction is the most direct and simple method of testing the potential of cell therapy to restore the cardiac function of damaged myocardium
- To date the clinical trials of autologous bone marrow derived cells appear safe with some studies showing efficacy
- Various methodologies have been used in performing the published studies despite the common source of cells (the bone marrow)
- Surrogate measures of outcome in myocardial infarction have failed to demonstrate the magnitude of effect seen in pre-clinical models. Although this may mean that the animal data does not translate into man, it may also mean that the surrogate measures are not sufficient to judge effect in man
- In order to definitively address the tantalising results of some of the clinical trials, an outcome study is now warranted based on the measurement of hard clinical end-points (death and MACE)

According to the consortium, originally consisting of 21 partners (17 clinical), BAMI's trial design had the potential to explore the therapeutic benefit of bone marrow derived cell therapy in acute myocardial infarction and establish it as a recognised therapy to significantly improve outcome. Being aware of the challenges of conducting an academic phase III clinical trial across many countries in Europe, the team of 21 partners included a social scientist experienced in this area who would participate during the approval and implementation phases of BAMI to advise on ethical approval procedures and study the effects of regulatory harmonization on trial practice.

As well as performing a definitive outcome study, the agreed objective from the Task Force members was to clearly identify a standard process for preparation of cells that could be applied across the different countries and hence lead to a marketable product. The BAMI project involved three European SMEs, two of which are pioneering biopharmaceutical companies, t2cure GmbH and Celyad, to help establish this cell therapy, both during the BAMI project and in the post project period.

**PROJECT OBJECTIVES**

The set of objectives defined for the study were initially scientific/regulatory in focus, following on to clinically driven objectives. These were to:

- Create a pre-clinical dossier for a standardised method for the preparation of bone marrow mono-nuclear cells for intra-coronary injection;
- Standardise an intracoronary infusion method that allows for the safe and efficient delivery of cell therapy to the coronary artery;
- Design a definitive randomised control clinical trial to assess whether a standardised mono-nuclear cell product confers an all-cause mortality benefit in patients with acute myocardial infarction who undergo primary angioplasty (25% reduction on top of standard therapy).
• Account for the challenges encountered with regulatory approvals and practical implementation of this largest academic stem cell trial yet.

The added benefit of combining the extensive experience of these members of the European Society of Cardiology in clinical trials of cardiac regenerative medicine into a single consortium project was, on its own, an opportunity to set a standard method of delivering this therapy (taking into account all previous clinical trials in this area to date), decisively understand its impact on this group of patients and rapidly translate it to clinical practice if it was proved to be beneficial. It was expected that the design and execution of the clinical trial would take up the majority of the time/resource spent on this project. The trial completed recruitment during the BAMI project and has entered a 2-year follow up period.

Project Results:
Description of main S & T results/foregrounds

WP1
Standardisation of bone marrow cell collection method

Using the expertise available in the consortium from previous regenerative medicine studies, the method most likely to be used for the procurement of the bone marrow was an agreed objective from the beginning of project. Project partner C3BS performed a full review of the data available in order to devise the best harvesting method. This was achieved and project partner t2cure produced standard operating procedures (SOP) for the best harvesting method. The procedure consisted of using a bone marrow aspiration needle and 5 x 10mls heparinised syringes to aspirate a total of 50mls of bone marrow from the iliac crest (spina iliaca posterior (SIPS)) following local anaesthetics with approximately 10ml of e.g. 2% scandicain. The syringe was positioned in the spongiosa of the SIPS.

In addition to the instructions for the bone marrow aspiration procedure, t2cure also provided a list of compulsory materials to be used during the procedure in order to ensure that the starting material for the bone marrow aspirate processing was homogenous.

A separate SOP was produced to ensure that the harvested bone marrow was handled in compliance with good clinical practice, as described in transportation of biological product regulations UN3373, and also to ascertain that the specifications for storage and transportation were respected and the quality of the product maintained. These specifications were produced based on the previous data available from the REPAIR-AMI trial which included but was not limited to:

• Time from bone marrow harvesting to start of the cell processing had to be 24 hours or less
• Bone marrow was to be maintained at controlled ambient temperature at all times

Figure 1 (attached) is an example of what was included in the SOP and in every contractual agreement between clinical sites and their courier service to ensure these specifications were met.

Figure 1 - Example of Timelines for Bone Marrow and t2c001 Shipments

The SOP also included a bone marrow aspiration procurement report and blood collection templates, as well as labelling instructions, to standardise the information collected but, most importantly, to maintain safety and accuracy throughout the process.

A training video was also produced by project partner UHF to demonstrate the correct techniques for the bone marrow aspiration procedure, packaging and delivery of the cells back into the patient. This video was distributed to each of the national coordinating centres by the BAMI trial office at their initiation visit. The video was used by the National Coordinating Centres (NCCs) to train their satellite centres.

Key achievement of this Work Package
The consortium agreed on the standardised bone marrow aspiration technique adopted on the BAMI trial in line with the timelines set out in the description of work. All the associated materials were also created which included the SOP, training video, data collection forms and list of compulsory bone marrow aspiration kits.

WP2
Standardise bone marrow preparation procedure and optimising cell reparative potential

The second aspect of standardisation was processing of the cells. The main purpose was to devise the most effective, reliable and easy method that would then be applicable on a wider scale as a treatment option in any country. Two different procedures for bone marrow processing, that were both capable of delivering the desired mono nuclear cell fraction, were compared:

1. A central processing facility approach based on project partner t2cure’s Advanced Therapeutic Medicinal Product t2c001
2. A medical devices-driven point of care (POC) bedside approach

The consortium decided the t2cure method would most likely lead to a positive result in the clinical trial, based on preclinical/clinical data. t2c001 manufacturing was performed according to GMP principles, within GMP facilities equipped with a class A workbench and maintained at the temperature of 22± 4 degrees Celsius. A closed transfer system was used.

T2cure was responsible for the Investigational Medicinal Product (IMP) management. As part of this role they produced an SOP for bone marrow preparation and cell optimisation. This document detailed the processing techniques and contained standardised data collection forms such as the release report form, which set the final quality control and release criteria for all cell processing centres to use and abide by.

A clear cascade of communication was established to inform t2cure and the Chief Investigator (CI)/sponsor of any issues and discuss an appropriate plan of action.

Additionally, t2cure was responsible for training all cell processing centres on the project – the DRK-Blutspendedienst Baden-Württemberg-Hessen GmbH, Fundación para la Investigación Biomédica del Hospital Gregorio Marañón, Cardiology Stem Cell Centre Rigshospitalet and Lugano Cell Factory. A comprehensive contractual agreement was also drawn up and signed between each of these cell processing centres and t2cure to establish clear delegation of duties and ensure compliance with the method of processing.

Throughout the project, t2cure retained oversight by organising regular quality assurance tests (Round Robin Tests) for all cell processing centres to confirm that the quality and standard of IMP production was being maintained. T2cure also reviewed all procurement report forms, processing and application reports, manufacturing and release report forms. Deviations were addressed on a case by case basis.

Key achievement of WP
T2cure’s approach of manufacturing the Advanced Therapy Medicinal Product (t2c001) was selected as the best technique for the BAMI trial based on the clinical and preclinical data available. A comprehensive IMP Dossier and an Investigator’s Brochure were both created by t2cure and reviewed by regulatory authorities. Necessary processes were also put in place for quality assurance and oversight.

WP3
Standardise method of bone marrow cell delivery post AMI

The third standardisation aspect was for the cell delivery method post AMI. There are a variety of methods available for the delivery of cells, but intracoronary was the preferred route post AMI. In the experience of the consortium members performing such procedures, there was an initial choice between the ‘stop-flow’ and the continuous infusion technique. After an
assessment of previous data (including large amounts of unpublished data), taking into account factors such as timing of
injections, volume and duration of injection and infusion technique, the consortium decided that the chosen technique for the
BAMI trial would be an intracoronary infusion technique which involved infusing cells through an over-the-wire balloon
catheter. The intracoronary route was the most common route, and supported by a large body of evidence in relation to
methodology and safety issues. The technique had also been tested in conjunction with t2c001 in previous clinical trials. The
diagram in Figure 2 (attached) shows an overview of the chosen setup:

Figure 2 - BM-MNC infusion setup

The schedule of the infusion was defined as follows:

- Balloon inflation
- Angiography to confirm occlusion immediately after sufficient inflation
- Infusion of cells immediately after angio / 10-20 seconds
- Deflation of balloon after 3 minutes
- Break 3 minutes
- 2nd balloon inflation time schedule and infusion as above
- Pause 3 minutes
- 3rd balloon inflation time schedule and infusion as above

The instructions were detailed in the protocol and in a cell reinfusion SOP produced by project partner QMUL. This was
distributed to all the clinical partners on the project for implementation. In conjunction with these, a training video
demonstrated the standardised technique for the cell delivery procedure for all clinical partners to have as a reference and
also to distribute to their satellite centres for training purposes.

Key achievement of WP
The consortium chose the intracoronary route using a ‘stop-flow’ technique for the infusion of the bone marrow derived
mononuclear cells because of the evidence available in support of this choice and the previous experience within the
consortium. The detailed standardised procedure was described in the study protocol and a cell infusion SOP. The off-label use
of the over-the-wire balloon for the delivery of the cells was successfully approved for use in the study by the sponsor country
regulatory authority.

WP4
Clinical trial design and analysis

After review and consultation, the consortium agreed on three main aims of standardisation for the BAMI project:
- Bone marrow procurement
- Cell separation and IMP manufacturing technique and
- The cell reinfusion technique

The above-mentioned SOPs, which were developed and approved by the consortium, formed the basis of the study and
allowed the planning, standardisation and implementation of other elements of the study such as the finalisation of the study
protocol, designing of the electronic data capture system, logistical, recruitment strategy and monitoring planning.

The consortium produced a Work Plan Strategy whereby other project activities were laid out. These included:
- Recruitment of satellite centres to ensure maximal recruitment and universal applicability
- Dissemination of results of the project to scientific, clinical, industrial community in addition to the wider general public
• Efficient use of the limited funds in performing the clinical trial including the standardisation of the cell preparation technique

The study protocol was designed with the collaboration of the consortium as a whole to carry out a multinational, multicentre, randomised, controlled, open-label parallel group phase III study.

Key elements of the initial protocol included:

¥ Patients with an acute ST-elevation MI and acute revascularisation to be screened for the study

¥ Treatment group to receive an intracoronary infusion of BAMI therapy via conventional Percutaneous Coronary Intervention (PCI) using an over-the-wire balloon from 2 to 8 days after successfully reperfused AMI

¥ Control group to receive standard care alone

¥ Potentially eligible patients to undergo an echocardiography (universally available at recruiting centres) between 2 and 5 days after primary acute PCI to ensure that cardiac function had been compromised by the infarct (ejection fraction<45%)

¥ A central Echo Core Lab was established to assess the ejection fraction in a uniform manner across all study sites by a quantitative method. Eligible patients would then be randomised

¥ Not more than 72 hours may elapse between bone marrow aspiration and investigational medicinal product administration;

¥ Therapeutic aspects in accordance with guidelines from the European Society of Cardiology

¥ After considerable debate amongst the consortium, all-cause mortality was chosen as the primary endpoint. Secondary endpoints included MACE, development of heart failure and change in cardiac function.

A clinical events committee (CEC) was appointed for the study. This was a concept commonly used in large international clinical trials to allow for unbiased and uniform classification of clinical events reported by local investigators across all investigational sites. This central, independent CEC who were blinded to the treatment assignment met on a regular basis throughout the recruitment phase of the study to adjudicate clinical events as listed in the CEC charter devised by the committee. Dr Jozef Bartunek was elected as the coordinator of the events adjudication, acting as a point of contact between the CEC and the rest of the consortium. The charter was developed to provide guidelines to ensure a uniform approach by the adjudicators. To facilitate the adjudication process, a separate electronic case record form (eCRF) section was created for electronic adjudication.

A statistical analysis plan was designed and was a working document finalised towards the end of the study, once the data had been cleaned. Based on power calculations performed by the designated study statistician, using a test plan according to O’Brien and Fleming (1979), 450 events would be necessary for an event-driven superiority trial and it was expected that 3000 randomised patients with a 1:1 randomisation treatment vs control (i.e. 1500 per arm) would be required to achieve this target.

Stopping rules were defined around the interim analysis that was set to be performed after 6 months follow up of 1500 patients, as per the initial plan for the study. However, due to the considerably lower recruitment rate than expected and following a protocol amendment, a decision was made not to perform interim analysis.

The Leuven Coordinating Centre (LCC), part of project partner GUH, was initially identified as the Contract Research Organisation (CRO). The LCC would provide the eCRF, the randomisation system Interactive Voice Recognition Service (IVRS) and any other documents designed to facilitate the running of the study. Their role would be to produce all SOPs and
coordinate data management, pharmacovigilance, training and monitoring, including site initiation visits. However, shortly after the beginning of the project, the LCC confirmed they would only be able to provide and maintain the eCRF and IVRS services. Since employing an external CRO would have been both time consuming and expensive, the coordinator, QMUL, put together a central coordinating office (BAMI Trial Office, BTO). The BTO, which consisted of a clinical trial manager, a monitor and a data manager, took over the remaining responsibilities from the LCC, namely the clinical trial management, monitoring and data management.

Accurate data collection is a fundamental part of any clinical trial. The LCC produced a web based eCRF using OpenClinica software which was tailored to the study protocol and reviewed by the consortium and Sponsor. The LCC worked together with the sponsor and the BTO to ensure the database captured all data required and was as user friendly as possible. Once finalised, the LCC performed validation tests and activated the live version. A data entry manual was also produced to give detailed instructions for the use of the database.

The list of eCRF reports and the frequency with which the reports should be produced and provided to the BTO and the CI was agreed with the LCC. These reports were an integral component of the BTO and CI’s oversight of the study progress and sites compliance, whilst providing at the same time essential data for the Data Monitoring Committee to review.

The LCC also provided the IVRS for patient registration and randomisation. Furthermore, this system had an integrated facility for the core lab to enter the echocardiography reading for the Left Ventricular Ejection Fraction (LVEF), which was the ultimate inclusion criterion to allow the randomisation of the subjects. An instruction manual was also provided for the IVRS. Training for using the system was provided by the BTO staff member performing initiation visits and the manuals were filed in their investigator files for reference. The LCC maintained both the eCRF and IVRS systems throughout the life of the study.

The sponsor, alongside the BTO, developed a monitoring manual based on an internal study risk assessment performed in order to ensure complete oversight, stringent monitoring of the data collected and ascertain adherence to Good Clinical Practice.

As mentioned before, the study protocol was substantially amended to change the aim of the study as the recruitment rate was considerably lower than expected. Due to the scientific importance of the study, the consortium agreed on recruiting for as long as possible – until October 2017. Based on the average rate of recruitment up to April 2016, it was predicated that a conservative range of target recruitment would be 350-460 patients by the end of October 2017. Therefore, this rendered the statistical power of the superiority primary objective very low. Hence, this trial was redefined as an estimation trial, whereby the primary objective was to provide estimates of the event rates in primarily the BM-MNC group and estimates of the treatment effect and their associated 95% confidence intervals.

The statistical methodology was updated to reflect this change in the study objectives. The focus of all analyses would be on estimating rates and treatment effects and providing their associated 95% confidence intervals. Any p-values would be for purely exploratory reasons.

The DMC and the CEC continued meeting throughout the study. Although no safety concerns were raised by the DMC, the committee was worried about the recruitment rate and the aim of the study. The above-mentioned amendment cleared the raised concern.

Key achievement of WP
The consortium was successful in designing a study and standardising a protocol across 9 countries. They have been responsive to the need, based on the actual recruitment rate, for a change in the objective of the study which was approved and successfully implemented.
Regulatory and ethical affairs management

A submission pack for regulatory and ethical approval was put together by the BTO. The pack included, but was not limited to, essential study documents such as the investigational medicinal product dossier, the investigator’s brochure, the protocol, patient information sheet and the informed consent form. It was decided that the project would undergo the Voluntary Harmonisation Procedure (VHP). Two member states decided to opt out of the VHP – Poland and Finland. Therefore, it was agreed that these two countries would only submit for regulatory approval once VHP approval was obtained for the remaining trial participants. With the participating centres’ track record of previous experience in small to medium size trials with bone marrow derived mono nuclear cells, no major hurdles were expected. BAMI was the first study of its size reviewed by the VHP process. During this initial process it came to light that, under the new European Medicines Agency’s (EMA) regulations, out of the 7 cell processing centres selected for the study only 3 were GMP compliant. This meant major logistical adjustments had to be made to adhere to the regulatory requirements – i.e. sending cells to be processed abroad, bearing in mind the time constraint. Once all the grounds of non-acceptance were addressed, a positive decision was obtained. Each country then submitted to their respective competent authorities and ethics committees. A total of 8 partner countries submitted and obtained approval for the study from their local competent authorities and ethics committees. Initial ethical approval for each clinical partner was sent to the European Commission as agreed.

The study underwent a total of 4 substantial amendments to the protocol. All amendment submissions were coordinated in a similar manner by the BTO, with all local country submissions being performed by each NCC. Amendments could only be implemented in any specific country after approval was obtained from both the sponsor and the local regulatory and ethics committee.

In theory, the VHP system brings harmonisation in the process and should expedite local competent authority approvals (within 10 days of submission). However, in practice this was not always the case. For example, despite Italy being part of the VHP, local approval was obtained after the usual length of time (60 working days). A similar situation was observed in Spain. Project partner UCSC also encountered some delays obtaining approvals from the Italian competent authority (AIFA) due to local procedural policies which required halting the amendment review if there was another one in progress. The consortium and the BTO tried to limit the impact of this local policy on the project by spreading the amendment submissions over time.

During the recruitment period of the study there were two inspections carried out by local competent authorities – at project partners FNBRNO and VZW. FNBRNO had very positive feedback from the inspection, and no critical findings were identified at VZW.

Drug Safety Update Reports (DSUR) and Annual Progress Reports (APR) were produced yearly by the BTO, with the contribution of the IMP management team at t2cure, and submitted to the competent authorities and ethics committees (where applicable) in the UK, followed by each member state (Routine practice in clinical trials).

Key achievement of WP

A key aim of the study was to find a unified approach for submissions to competent authorities and ethics committees in a large multinational/pan European study. The submission process set up by QMUL in that effect was efficient. BAMI was the first study of its size to be reviewed and obtain a positive decision from the Voluntary Harmonisation Process. The VHP helped to stream feedback from all the competent authorities and allowed the consortium to produce standardised and unified study documents for local submission. However, a few local regulatory differences remained which led to the principles of VHP not being fully adhered to in countries such as Spain and Italy.

WP6

Clinical trial and recruitment
In preparation for the start of the clinical trial, the BAMI trial office finalised all study documents, created guidelines/SOPs for all necessary study procedures, from pharmacovigilance to document transfer and the communication pathway. In order to ensure the execution of the clinical trial was straightforward, the consortium, sponsor and the BTO signed a number of contractual agreements with the different parties for clear delegation of responsibilities. As part of the agreements set up by the sponsor, each participating country had a designated National Coordinating Centre, which was responsible for the coordination of the BAMI research activities in their respective country and for the communication between sites and BTO/sponsor.

A feasibility questionnaire (SUQ) was designed for each clinical site to complete and send to the BTO in order to assess not only feasibility but also highlight any potential issues to be resolved prior to site initiation. A step by step site activation cascade - Figure 3 (attached) was devised by the BTO:

Figure 3 - Recruiting Centre Activation Cascade
Once an NCC was deemed ready (assessed by means of an initiation checklist), the BTO performed an onsite initiation visit which included slides presentation, eCRF training, monitoring files, etc. followed by the activation of the site if all requirements were met.

In March 2013, a meeting was organised by the project coordinator QMUL for the study coordinators which aimed to
1. Provide an update on the status of the study
2. Open a platform of discussion for all the participating clinical partners with regards to hurdles raised during submission/approval and setting up phase
3. Explain the above activation cascade and to list the outstanding action points
4. Reiterate the responsibilities of the NCC in the coordination of the study locally, including setting up of local agreements and resolving local issues

The first NCC to be initiated was QMUL in October 2013. Most of the clinical partners were activated by August 2014. Project partner UEF was initiated much later, in January 2016. This was because of delays in local submissions and internal issues that needed resolving first. In Germany, the Federal approval for radiation also caused delays. A total of 37 recruiting centres were activated by the NCCs.

It was expected that recruitment of the first patient on the study would be within 6 months of the project start. Unfortunately, this was not achievable due to unexpected delays that arose mainly following the need to reorganise the logistics of cell processing. Initially only 3 (out of 7) cell processing centres were able to manufacture the IMP. Mitigation plans to deal with the big financial gap caused by the sudden increase in the number of third parties and subcontractor cost due to the need to provide courier services and CPCs were put in place.

Partner sites not initiated: 8 out of the 17 clinical partners who were initially planned to recruit patients opted out of patient recruitment for various reasons, such as logistical issues, extra financial burden due to inability to process cells in their own cell processing units and local restrictions on research work. While project partners AP-HP, ICS HUVH, UCL, KCH and MHH remained on the project, UR, OUS, and SUM exited the project.

The patient recruitment rate was considerably lower than expected. This was identified fairly early into the clinical trial and was also a concern for the Data Monitoring Committee. The Executive Steering Committee met on top of the regular consortium meetings to address the situation. At every meeting it was agreed that every effort should be made to not only continue, but also maximise recruitment. This triggered several contingency actions such as approaching more satellite centres to join the study. There was interest from centres in Switzerland, The Netherlands, Serbia, Turkey and Iran. A centre in Switzerland and one in The Netherlands were successfully activated.
Numerous efforts were made to bring on board other cell processing centres to reduce the logistical issues faced by some clinical centres. Lengthy and difficult contractual negotiations and the considerably higher costs meant that only one more cell processing centre was able to be activated – the Lugano Cell Factory. Reasonable amendments were made to the protocol to address other issues identified, such as widening the bone marrow aspiration-cell reinfusion window to 72 hours, in attempts to eliminate recruitment hurdles while maintaining the integrity of the trial.

A consortium request to extend the project for another year until 31st October 2017 was granted by the European Commission and it was agreed that patient recruitment would be extended to 4 years (up to October 2017). This was also approved by competent authorities and ethics committees.

Despite all efforts to tackle the recruitment rate, it became clear that the target was over ambitious and there was a need to redefine the trial as an estimation trial. Therefore, interim analyses planned at the beginning of the trial were no longer relevant and were removed from the adjusted statistical analyses.

Based on a risk assessment performed by the sponsor, a monitoring manual listing the minimum monitoring requirements was produced. Monitoring is paramount in any clinical trial to ascertain all trial procedures and data collection are being performed accurately and according to the protocol, GCP-ICH and other relevant regulations. As stipulated in the monitoring manual, the BTO monitored all initiated NCCs who, in turn, were delegated to monitor all their recruiting centres and report back to the BTO a summary of their monitoring activities and findings on a 6-monthly basis. The BTO then reported all NCCs’ monitoring findings to the Sponsor on the same 6-monthly basis.

NCC and satellite site monitoring was carried out as per the monitoring manual and national monitoring plan (adaptation from the monitoring manual at a country level). An effective escalation process was put in place by the BTO to tackle incidence of non-compliance. Two sites had to halt recruitment – Righospitalet, due to competing studies, but resumed recruitment after approval of amendment 6.0 and UCSC’s Gemelli hospital due to delays in approval of amendment 5.0 and amendment 6.0 and non-compliance to GCP due to staffing issues. Since then the latter site has used the services of their internal CRO to work on the findings and action points set by the BTO monitor with very positive results.

Key achievements of WP
BAMI has achieved its target of being the largest phase III trial in the field of regenerative medicine in cardiology, with a total of 375 patients recruited to the study. One of the biggest successes of this project is, despite not achieving its initial target, the non-stop perseverance of this academic consortium led by QMUL in overcoming the various hurdles in making this the largest study in this field (REPAIR-AMI being the previous largest with 200 patients). BAMI has also demonstrated the abilities of an academic led consortium to set up and run a logistically complex phase III trial and collaboratively resolve difficulties faced.

WP7
Towards harmonised ethical standards

The researchers collected initial data on the expectations of clinicians concerning the approval processes around BAMI at the start of the project and contributed to the ethics approval process with the VHP. The second and major phase of research started almost a year later than envisaged, because of delays in hospital initiation, which had to be completed to obtain reports and views on how it had gone. In spring 2014 (after ethical approval had been obtained to interview BAMI clinical staff and facilitators) the qualitative research commenced. BAMI PIs, clinicians and nurses at recruiting sites and NCCs as well as team members working on BAMI-wide infrastructure (Sponsor, echo-lab, randomisation process, monitoring) have been interviewed. Throughout the six years, WP7 team members attended and recorded every consortium meeting. WP7 used a multi-methods approach and the data collected include 40 qualitative interviews with BAMI partners in Belgium, the Czech Republic and the UK.
Republic, Denmark, Finland, France, Germany, Italy, Poland, Spain and the UK between May 2014 and October 2017. It held a focus group discussion on BAMI, the regulatory situation and what such a trial needs in June 2017 and used mini-questionnaires to gauge the views of PI’s during the BAMI kick-off meeting and again at the final consortium meeting in Oct. 2017. Most of the sociological data has been analysed and first results have been reported. Three publications on the effects of regulation and national differences in clinical and approval practice on BAMI have been published already (see notes in the Significant Results below and publication details under WP8, dissemination). One article including more recent data and analysis is under review (see below). Analysis of the latest and complete data sets is on-going, and the dissemination of results and final recommendations are in preparation. At least two more publications are at different stages of progress covering a retrospective analysis of the whole BAMI project and its implementation issues and findings as well as a more detailed discussion of the situation of clinician-scientists and their motivations to conduct clinical trials.

Significant results
The findings are wide-reaching when contextualised in relation to the development of translational stem cell based regenerative medicine and its scientific realisation, and clinical implementation affected by reimbursement regimes and practicalities in service delivery. The policies in place to harmonise research and translational medicine across Europe add cost and have been time consuming for BAMI, delaying the initiation of study centres and patient recruitment. They also caused multiple problems to adapt everyday local routines embedded in local medical service provision to the standardised protocol at recruitment sites, which again are costly to implement. Prof. Hauskeller’s continuous involvement and research in BAMI and the first interviews with BAMI team members showed that such delays arise from and in return lead to other logistical, technical, ethical and cost issues.

1) The effects of EU and local regulations on the trial plans
The ATMP classification of the BAMI procedure and the new Voluntary Harmonisation Procedure had multiple effect on BAMI, affecting not least the laboratory processing requirements and consequently trial logistics, time plans and financial positions (see Hauskeller and Baur 2017, Travelling Cells). We published these findings in

This chapter discusses how scientific conditions of Randomised Controlled Trials and the direct effects of the regulatory environment affect the trial protocol and the implementation of BAMI.

2) The effects of EU harmonisation on implementation in the multinational setting of BAMI
Because clinical practice is embedded and intertwined with reimbursement practice in diverse health care systems, employment and labour laws, etc., aspects of societal organisation and social and ethical values and practices affect how clinical teams work on the ground. The VHP does not replace local ethics approval and we found that the stipulations in a VHP approved protocol did not satisfy all National Competent Authorities and/or local ethics committees who sought amendments, stricter rules or specific alterations. Changes to the BAMI protocol, but also issues such as language barriers, and different insurance regulations in Europe have delayed the initiation of new study centres and increased cost

An interview-based journal article presenting some of the cultural issues raised especially by nurses and NCCs, including differences between local ethics/clinical practice and harmonization demands.

3) The cost aspect has been critical in BAMI and questions were raised as to whether academic researchers can stem a phase III trial or whether the regulations affecting such a trial make such trials too difficult to conduct for academic teams. This would severely limit the research freedom of clinicians and in the following article we present findings to suggest to clinician
scientists what to prepare for when conducting multinational trials.


An analytic article for practitioners on the scientific clinical trial and the problems encountered in BAMI in relation to regulations as well as cultural differences and what this means for future such trials.

4) Ethical issues are involved in the regulation, research and clinical introduction of stem cell regenerative medicine. Expectations are high whilst potential medical risks exist and human cells used for research and medicine are seen as ethically problematic in many countries. The cost of bringing new treatments to the clinic adds further complexity to this problem, as non-profitable lines of inquiry might remain unrealized regardless of their clinical value. The experience from BAMI has been discussed in this context in

• Hauskeller, C. European Regulation as a Barrier to stem Cell Regenerative Medicine (Under Review)

5) Issues with patient recruitment: We identified several issues, including altered logistic practices in some countries causing patients who would screen favourably for BAMI inclusion not being recruited because they would no longer be at the BAMI site when the BM-MNC reinjection would otherwise happen. Other issues are motivational, affecting clinician-scientists will and ability to focus their team on recruiting for an academic trial. These themes are still under analysis and findings will be published over the following two years (whilst BAMI completes).

Overall Finding: We could collect detailed data in BAMI on the complexity of clinical scientific trials compared to other scientific experimentation. The conduct of a large clinical trial is highly dependent on and affected by multiple factors that are unrelated to the treatment or procedure trialled. Whether it is regulatory classification schemes that prescribe particular laboratory procedures to be used across very broad groups of stem cell uses, local cultures and ethics, or regional efficiency gains in delivering angioplasty, they don't affect the standardised protocol for testing the BAMI procedure but they very much shape the everyday work required to accommodate any trial within the practice frameworks established. Discussions of the role and feasibility of the phase III clinical trial are underway and our findings contribute to reflections on the tensions between effective governance and responsible and forward-leading research.

Recommendations addressing clinical teams who embark on a multinational stem cell trial in Europe were published as part of Hauskeller’s article in Regenerative Medicine:

Clinicians preparing multinational clinical trials in Europe might want to prepare for:

• Discussion with the regulator in the preparatory stage might be useful, to be certain that you are familiar with the regulatory procedures that will be in force when the trial starts.

• Access to licensed cell processing facilities must be arranged, affordable and staffed.

• If cell or cell product transportation is necessary, consider all licensing and export permission needs.

• Clinical practice on the ground varies in many little ways. Harmonised protocols require detailed alignment and extra capacity to adapt for National Competent Authority or local ethics approval requirements.

• Cultural issues differ by location, state, country and traditions. Provisions must be available to cater for local needs so that they can be aligned to scientific and VHP protocols.

• Time delays and the multiple ways in which they affect the cost of equipment, staff and cause more time delays and regulatory re-approvals should be avoided if at all possible.

• A very big team that makes a timely concerted effort might be preferable but requires a firm management structure to govern a large consortium of partners with different roles.
Administration and management of the project

With a project of this size it was very important for the management team to have overview and control of the technical progress of the project, ensuring schedules were respected.

Clear delegation of formal administrative responsibilities to a project manager was also necessary to facilitate the organisation and development of the project. The following duties were delegated to EURAM:

- Taking meeting minutes
- Monitoring progress and driving corrective actions forward
- Review progress against the economic, industrial and operational objectives and targets
- Organisation of Technical, Exploitation Board and Kick Off meetings
- Collation of all deliverables, milestone reports, mid-term reports, final report, report on gender, societal and ethical issues of exploitation submitted to the EC and other partners
- Management and monitoring of the project against plans, submissions and organisation of the cost statements and maintenance of consortium agreement
- Guidance on matters relating to the EC project execution procedures and Consortium Agreement
- Resolution of any administrative or contractual issues within the consortium.

A management structure was set up to divide responsibility of the management into key sections. Committees were set up to manage the project, troubleshoot, provide unbiased adjudication of the events on the project and to perform the safety review of the project. The agreed structure is illustrated in Figure 4 (attached)

Figure 4 - BAMi management structure

Additionally, such an ambitious project needed to have a careful risk contingency plan based on risk assessments of each work package. At least two of these contingency plans had to be executed:

Recruitment falling behind target
Recruitment to the study was considerably slower than expected at all sites from the beginning of the project. The slow recruitment was exacerbated by 8 clinical partners not being initiated, as mentioned above. Executive Steering Committee and Steering Committee meetings were held to address the issue and additional centres were invited to join the study. The European Commission granted a one-year extension and agreed that recruitment of patients would continue until the end of the project in order to maximise recruitment. Additionally, local efforts were made to overcome logistical issues listed in the work package 6 section and protocol amendments were submitted in an effort to tackle some of the other issues identified such as safely widening the temperature and time frame ranges.

Insufficient budget to perform the trial
With an initial target of 3000 patients the trial experienced funding issues from the outset that were magnified when the plan for local cell processing centres (thereby minimising shipping costs) changed due to the new EMA regulations. This meant that the majority of partners incurred unexpected shipping costs not to mention significant logistical issues that had to be overcome. Each partner made every effort to reduce their costs to a minimum, including using their travel budget towards patient recruitment and securing deals on discounted or free equipment for use on the study at their clinical sites. Moreover, each clinical partner agreed to secure extra funds to self-fund the 2 year follow up period outside the EC grant when it became clear that this was needed to achieve meaningful recruitment. In addition to this, some partners committed to also contribute to a central pool of funds to cover the coordination costs of the 2 year extension. The grant, managed by QMUL, was also reconfigured after partners dropped out.
The risks that were planned for but did not require execution were:
Failure to agree on a standardised method of cell harvest, preparation and administration
Failure to construct the most up-to-date protocol
Different regulatory issues throughout Europe limit the participation of the consortium

The consortium met at least once a year to monitor and discuss the progress of the project. Whenever there was any particular concern, the Steering Committee/Executive Steering Committee convened as appropriate, usually via teleconference. Action plans were minuted and followed up to completion by EURAM and the coordinator, QMUL.

Regular meetings and telephone or e-mail communications were maintained with the European Commission’s allocated Scientific Officer to inform of any relevant updates or seek advice where necessary.

After EURAM left the project, all the project management and administration was taken over by QMUL.

Key achievements of WP
The consortium established a management structure for a clear delegation of the various management duties on the project. This was successfully implemented and resulted in smooth running of the project on the whole. The numerous challenges encountered on the project were dealt with through the appropriate channels, triggering the relevant contingency plans where necessary.

Potential Impact:
Scientific Impact of the BAMI project
The BAMI trial has had considerable impact on the clinical scientific community. It has been discussed at international cardiology meetings during the 5 years of the EU award. One of the BAMI PIs – Prof Andreas Zeiher – has given annual updates at key meetings e.g. European Society of Cardiology and Professor Mathur was invited to present the trial at a meeting in the US, attended by all key investigators working in this field of research. The BAMI project is seen to be the pivotal trial of autologous cell therapy in acute myocardial infarction and the final results are likely to have an important impact on this area of research. More specifically, the publication of the BAMI trial results has the potential of fulfilling the scientific objective of the project, which is to understand the role of autologous cell therapy in patients with recent acute myocardial infarction.

The final BAMI consortium meeting identified two important sub-studies that will be prepared for publication using BAMI data. Also, in the UK, the BAMI trial has been used to supply data for a UK Medical Research Council funded PhD project which is currently being written up. As described in more detail below, the logistical issues that were encountered, as well as the differences in the regulatory approach across a United Europe, are the subject of further publications that will help similar projects achieve their aims in the future.

On a scientific organisational level, the BAMI project has prompted multiple new collaborations within the consortium leading to grant submissions. Members of the consortium have also gone onto form a new regenerative medicine working group of the European Society of Cardiology, as well as a transatlantic partnership to link the European programme with the USA’s. The European Society of Cardiology Task Force for stem cells in cardiac disease (originators of the BAMI FP7 application) has published an up-to-date consensus document that will further guide investigators to planning clinical trials of cell therapy in the future.

Societal and socio-economic impact of the BAMI project and its findings
BAMI has been the highest recruiting stem cell clinical trial to date. As an academic trial, relying on a multinational group of University research teams, it incorporated a reflective study element (WP7) designed to:
- account for the experiences and present an analysis of the areas where such cooperation works well and efficiently, often
fostered by harmonised infrastructures and governance institutions
- analyse potential problems with running large regenerative medicine trials in Europe

This social scientific research component studied and reported on the hidden practical challenges to the translation of new science into clinical practice affecting the trial. The knowledge created and its potential impact has already had some impact on regulatory considerations and research in clinical translation, but more impact might arise over the coming two years during which the BAMI project, including WP7 work, continues.

BAMI informed changes in regulation and regulatory procedures
BAMI was one, if not the first, clinical trial that experienced problems with the regulatory rules in place at the time of its commencement. Its progression within these regulations illustrated certain problems which were reported on, and led to rapid response in the form of improved regulations and procedures. This has improved governance procedures and will benefit future trials in Europe. The following 5 impact points have been disseminated by the Work Package 7 team to both expert and wider audiences:

1) BAMI was the first big multinational trial to use the new Voluntary Harmonisation Procedure (VHP) introduced by the EMA. We have experienced and reported on unreliable practices in the realisation of the initial VH procedure, and shortly after BAMI achieved VHP approval, the procedure was changed to increase cooperation and compliance of National Competent Authorities with the approval procedure.

2) Following a 2010 change to the implementation of Advance Therapy Medicinal Product regulation in Europe, BAMI had been classified as Advance Therapy Investigational Medicinal Product. This was one of the factors causing the delays, increased costs and amendments to process and outcome targets. Recent specifications to how ATMP regulation is applied to the wide range of research approaches using human cells and tissues means that under current conditions a trial such as BAMI could likely proceed in a less demanding regulatory regime more effectively, which will benefit other similar trials.

Regulatory harmonisation and diverse local clinical care and practices
The multinational design of BAMI allowed the researchers to identify concretely the effects of harmonisation on the implementation of the scientific protocol and on everyday trial conduct across the many recruitment sites in different countries.

3) A medical procedure, even one as focussed as a 2-day intervention on patients after AMI, is interwoven with many other institutional practices and customs within a society and its cultural practices. European harmonisation leads to a cascade of new problems that arise from trying to align these elaborate everyday local practices within a standard set to ensure the scientific unity and credibility of a trial. This is a significant academic finding and its analysis is also impactful concerning the benefits and problems of the detailed alignment which is required by the highest standards of scientific medical progress. We have published these findings in an article in Science as Culture, open access, and also reported them in talks to diverse audiences, including expert groups who work on improving the scientific clinical trial in relation to the effective clinical translation to new therapeutic approaches.

Public responsibility: research funding, regulation, and a duty of care
The value of new stem cell procedures and cell-based medicines for the wider public, especially patients and clinicians, depends on whether they can access and use them. Affordability must be balanced against the regulatory tasks of ensuring safe and efficacious therapy development, with scientifically validated treatments arising from publicly funded research.

4) In a situation where similar medical procedures to the one trialled can be obtained by patients in private clinics – albeit not wearing the seal of scientific validation – the tensions arising from patient needs on the one hand and the extended time to bring new procedures and medicines into the clinic on the other hand, becomes an issue. BAMI illustrates the problems of
running large clinical trials on treatment options that are valued little by industrial researchers and trial sponsors. The needs
to reflect on and communicate the importance of scientific validation practices in medicine and for governance suitable to
realise new treatments more quickly, have been outlined in diverse audience presentations.

5) The market price which the BAMI procedure and similar procedures would incur depends on the regulatory set-up in which
they are trialled and shown to be efficacious. It is of great importance for the future of regenerative medicine whether or not
its products and procedures are affordable within, and for, European health care systems. WP1 in BAMI compared delivery
methods of the BAMI procedure. Due to regulatory reasons, coupled with the interests of enterprises, the procedure tested in
BAMI became much more expensive to deliver both during the trial and for health care providers. An assessment of the
therapy cost-benefit ratio will be performed once future results become available.

Further insights with social, economic and governance impact on the dynamics in stem cell regenerative medicine in clinical
practice in Europe may arise. The interview data on the retrospective assessments of BAMI participants on the key issues
affecting BAMI are being analysed. Together with the findings from focus group research, conversations in the final year of
patient recruitment and the questionnaire at the close of the recruitment phase, the wider BAMI team is preparing a
publication reflecting on these issues overall. A separate point explored in the last year are the clinicians’ motivations to
partake and stick with this trial despite the difficulties experienced and competing research projects. For the sociology of
medicine, but also for clinician scientists, a better understanding of motivations to conduct clinical trials in the academic
versus the commercial setting contributes to a better understanding of the many challenges for rapid clinical translation. This
matters to maintain public trust in biomedical research as well as for the career development of researchers in academic (bio-
)medicine.

Dissemination and Exploitation

Appropriate dissemination is essential to facilitate the exploitation of BM-MNC treatment from the BAMI trial. A project specific
website was created at the beginning of the project. It had both a public and private area and was maintained and updated
throughout the study by EURAM. It was used as a vehicle for dissemination of information within the consortium and to the
wider professional and general public.

Additionally, the project created a Twitter account https://twitter.com/BAMIFP7 to post information as the project progressed.
This account followed key organisations in the field (e.g. European Society of Cardiology, American Heart Association and a
variety of Cardiology Journals and Societies) and is also connected with companies who were directly/indirectly involved in the
project (Celyad (Partner 17), Miltenyi Biotech, Lonza, Medtronic). The Twitter feed is embedded as a widget on the BAMI
homepage to ensure public visibility of project’s news via the website, in addition to those who follow the BAMI Twitter
account.

An Exploitation Steering Committee composed of representatives of the consortium was appointed to control the exploitation
of the project results. The committee met regularly. C3BS, later renamed CELYAD, was designated as responsible for the
exploitation management. An exploitation management plan was drawn up. The figure 1 (attached) shows the planned
incoming steps to reach the market with the BAMI product.

Dissemination activities conducted to date by BAMI project partners have been recorded on the Participant Portal. These have
been diverse and have addressed industrial, academic, scientific and clinical communities within Europe and internationally.
The diversity of the type of dissemination and audience is reflected in the table 1 (attached)

In the UK, after recruitment and randomisation of the first patients to the treatment arm of the trial, a press release was
issued by Barts (the subcontractor to P1 QMUL) on 20th February 2014. In parallel, the BBC in the UK reported news items on
the evening TV and radio news, ITV ran a feature on the evening UK TV news on 21st February, and this triggered widespread
interest amongst the UK media. As a result, the story also featured in media reports worldwide in several countries including Australia, Malta, Ghana, Russia, Poland, Germany, Greece and Italy. This stimulated enquiries from the public to the BAMI Trial Office and also to some of the project partners, with patients contacting clinical sites, showing keenness to join the study.

The interest expressed from the clinical trial community has been very encouraging. These included research teams in Serbia, Turkey, the Netherlands, Switzerland and a team who conducted the BONAMI trial in Toulouse. During the annual stem cell symposium in Madrid 2016, Dr Enca Martin Rendon highlighted the importance of the data being generated by the BAMI trial for the completion of the meta-analysis carried out by her team in Oxford (UK), of stem cells in the Acute Myocardial Infarction cohort.

There is wide recognition of the importance of the trial for the future of stem cell research in cardiology. To date, a Google Scholar search shows that BAMI is referred to in over 170 papers. Most authors eagerly await BAMI’s results to determine whether BM-MNCs are a future viable therapeutic option for patients with recent acute myocardial infarction, and many others suggest further research projects should be placed on hold until the results are published. The potential impact of BAMI in this field of research is second to none and the lessons learned throughout the trial will be an invaluable contribution to the development of stem cell research.

List of Websites:
https://horizon2020.wixsite.com/bamifp7

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Related information

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