EU-Project GAMBA
Gene and Stem Cell Research
On Osteoarthritis

Lay Report

Patients and Citizens assess GAMBA Basic Research on Adult Stem Cells, Gene Therapy and Nanoparticles

Update 2013

71 Participants from the Munich (Germany), Galway (Ireland) and Zurich (Switzerland) areas

Compiled by **Katharina Zöller**
Maren Schüpphaus
Sven Siebert

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Summary of the GAMBA panels' opinions

Please note: This is the summary of the five GAMBA panels in Germany, Ireland and Switzerland. G stands for Germany, I for Ireland, CH for Switzerland. PP stands for "Patient Panel", CP for "Citizen Panel". In Switzerland we had a combined panel due to the lack of participants (marked "P"). *Reactions of the GAMBA consortium in grey.*

1. The Opportunities Offered by GAMBA

1. GAMBA offers new opportunities of a cure for osteoarthritis (OA): All panels welcomed the fact that new therapeutic possibilities may be developed from GAMBA. The lay members of the panels stress that GAMBA has huge potential (GCP) and could make a contribution to increasing the quality of life of patients (GCP, IPP), e.g. via a longer period without symptoms after a GAMBA therapy (GCP) or healing the disease of osteoarthritis which to date is still not possible (GPP, ICP, IPP).

Mentioned as additional opportunities are:

- A GAMBA therapy would make possible a treatment which is less invasive as compared with those alternatives currently available (GCP, ICP) and thus provide a more gentle and lower-risk therapy for patients.
- A GAMBA therapy would be a customized therapy tailored to meet the requirements of the patient (IPP) which focuses on the power of self-healing via autologous stem cells (GPP, GCP, IPP). This also has its advantages as compared to synthetic drugs or material from donors (IPP). The use of autologous stem cells seems more acceptable from the medical and ethical points of view as compared with embryonic stem cells (GCP).
- A GAMBA therapy could make it possible for patients to live a drug free life (IPP) and thus eliminate or minimize the adverse side effects associated with medication.
- The Irish Citizen Panel sees huge potential in a GAMBA therapy for osteoarthritis sufferers – based on the level of knowledge they have at present - the opportunities outweigh the risks (ICP). In the view of the participants of the German Patient Panel (GPP) it is still too early for a final assessment of opportunities and risks.

The consortium agrees with the panels that GAMBA has the potential to one day heal OA through localized production of growth factors for tissue regeneration although the idea is to date only partially feasible. With the current GAMBA-project we are doing basic research to identify new technical approaches and look for proof of concepts.

A therapy adapted to the individual needs of a patient is appealing. We aim this therapy to be less invasive and it would promote self-healing. But we also agree that it is too early to assess benefits versus risks. We acknowledge that the use of adult versus embryonic stem cells is important as embryonic stem cells are a sensitive subject (see also chapter "Ethics").

2. It is not yet clear whether and to what extent the people most affected can profit from a GAMBA therapy: Several panels think that a GAMBA therapy would offer opportunities for young people above all others (up to about 45 years of age) and future generations (GCP, IPP, CHP), e.g. if a sports accident causes cartilage damage which could develop into osteoarthritis at a later stage (CHP). The participants' desire is for all generations to benefit from a GAMBA therapy (IPP) including those 45 years of age and above (GCP). If early diagnosis of osteoarthritis were possible – and hence a GAMBA therapy at an early stage could repair the damage before it becomes too severe and stop or prevent further degeneration of the joint – fewer people would develop severe osteoarthritis (CHP).´

3. The panel members have concrete suggestions with regard to GAMBA research:

- They recommend conducting experiments not only with young but also with older stem cells in order to test the efficiency of the stem cell therapy (GPP).

  The consortium agrees that it is necessary to use stem cells from older patients which is already done by the GAMBA partners in Rotterdam and Galway with cells from patients aged 45-80; there is conflicting evidence if these cells perform as well as cells from younger patients. In parallel, young healthy stem cells are used for research to compare the results. If GAMBA will later also work for older patients (above 50 years) is still open. The earlier the illness is detected (when the damage is still small) and the more active the stem cells are (their activity decreases with age), the greater are the chances of healing.

  When carried further, GAMBA should give priority to cartilage research as this reduces the complexity of the GAMBA approach and at the same time may lead to cartilage repair and the prevention of osteoarthritis before severe damage is done to the bone (CHP).

  OA is a complex disease. It makes sense to concentrate on cartilage damage if the bone is intact and inflammation is low which is an early stage of OA if the cartilage damage (lesion) is diffuse and progressing. But for OA with cartilage and bone damage and an inflamed joint treating only cartilage is not going to work. The GAMBA idea of temporary gene activation makes most sense when combining tissues.

- The GAMBA researchers should further explore the role of joint fluid with its effect and the interactions within the joint in mind (CHP).

  We agree, as the growth factors in osteoarthritic synovium (major part of the joint fluid) negatively influence cartilage repair. By treating the synovium (with growth factor IL10) we aim to improve cartilage repair with this anti-inflammatory therapy.

- When GAMBA is carried further, findings from epigenetics and complementary medicine should be incorporated without preconception (CHP).

  Epigenetics and complementary medicine are very interesting and important and need to be taken into consideration in the development of novel therapies which is already done by partner NUIG in Galway who looks at epigenetic changes in stem cells and cartilage research. Research into **epigenetic** influences is still in its infancy, but will doubtlessly play a role in the future. In particular, epigenetic studies may provide some insight into underlying causes of OA. Epigenetic changes that accumulate, for instance, by nutrition and/or other environmental factors, could be important to further elucidate potential triggers that may induce OA. These epigenetic changes could then be prevented. Moreover, future treatment options could involve the modulation of expression of specific genes with beneficial or detrimental effects on OA progression. The latter might be investigated in a basic research project.

  Due to the difficulty in standardization and the high variability, it is difficult to perform reliable studies in the field of **complementary medicine**; in addition, funding is still very limited in this field. Methods such as alternative medical systems, mind-body interventions or energy therapies cannot be investigated in basic research projects. However, effects of physical therapies, topical biologically based therapies, and biologically based supplements can be tested *in vitro* and could be included in a future project. The precondition is that the therapeutic agent is clearly defined; this is essential to draw relevant conclusions.

4. The GAMBA basic research project could yield important findings for other fields of medicine: The techniques or therapeutic effects on the cartilage researched in the GAMBA project may also be used with other ailments (all panels) including, for example, multiple sclerosis and diabetes (ICP) or osteoporosis (GPP, GCP), bone fractures (GCP), dentistry (GCP), rheumatism (GPP) or cancer research (GCP). This applies particularly to the therapeutic effects of the techniques employed (gene therapy, stem cell therapy, biomaterials, nanotechnology) but also to the modules of the GAMBA project (tissue engineering of cartilage and bone and anti-inflammatory measures) (GPP, GCP, CHP, ICP).

The consortium agrees that GAMBA will hopefully produce knowledge usable for other fields of medicine e.g. in the fields mentioned by the panels' participants.

5. GAMBA can contribute to a more effective prevention of osteoarthritis: GAMBA research could make its contribution to a better understanding of the disease and the molecular mechanisms within the joint (GPP, CHP) and thus not only trigger primary osteoarthritis research (GCP, CHP) but also contribute to the advancement of prevention research (GPP).

We agree that GAMBA serves to better understand osteoarthritis through the study of the synovium of OA patients and its effect on cartilage formation (chondrogenesis). In Galway, Ireland, research is done on the formation of cartilage cells by introducing mesenchymal stem cells that promote the patient's own ("host") cells to differentiate into cartilage cells. The Dutch partner in Rotterdam also contributes to OA prevention by repairing a cartilage defect due to trauma which helps prevent development of OA in time.

2. Ethical Aspects of the Fields Covered by GAMBA

1. Ethical standards and legal constraints are important "guide rails" (CHP). Research into such matters as gene therapy or into stem cells as well as experiments on animals should be conducted according to a global ethical standard (ICP). Panellists also recommend an international register of conflicting interests (ICP).

The consortium agrees that a global ethical standard for research as well as a register of conflicting interests would be ideal, although European ethical regulations at all levels are of high standard already compared to other countries. All experiments in GAMBA are approved and meet the requirements of the responsible ethical commission.

2. Ethical questions should be examined repeatedly. The Panels welcome the fact that an ethical examination of certain questions takes place immediately when research applications are filed (GPP). Lay panel members also consider the review of ethical questions to be expedient at later stages in time, particularly prior to any application involving human patients (GPP, GCP, CHP). According to a stage model for ethical assessment (Hacker et al.[1]) it would be necessary to examine the boundaries within which the GAMBA therapy seems to be ethically and medically justifiable (CHP).

Ethical issues are dealt with at regular intervals by all partners; they are discussed and decided before a project starts, assessed throughout a project and compliance reported on after the project is finished. The consortium agrees that at each stage potential ethical concerns need to be re-evaluated. This applies for both pre-clinical (animal) as well as clinical studies (which are not part of GAMBA as it is a basic research project). The hurdles to overcome before to start a clinical study are – rightly – very high. To discuss additional aspects (as outlined in this ethics chapter), the consortium recommends to pay more attention to ethical aspects at conferences and meetings and to provide courses for young scientists to create awareness.

[1] Biomedical Intervention in Humans: A Model for the Gradual Ethical Assessment of Gene and Cell Therapy. Berlin 2009 (in German, summary in English).

3. Health is more than the absence of illness. Respect for the dignity of human beings and animals must be given priority (GCP/GPP). The dignity of man demands that research be carried out in order to take advantage of possible opportunities for healing - but human beings should not be reduced to their biological and functional components (GCP). The GAMBA approach is the expression of a (too) reductionist idea of man (CHP). Being human also includes the conscious appreciation of biological boundaries and acceptance of the finite nature of life (GCP).

We are aware that the steps from cell/tissue culture to animal and then to clinical studies are huge and that finally we will need to look at the patient as an individual. A gene/cell therapy will be justified only in traumatic cases and in premature or accelerated osteoarthritis where the quality of life is (or would become) severely impaired. In a basic research project, the consortium has to focus on certain aspects and we decided to focus on stem cells and gene transfer. If the GAMBA concept turns out to become a therapy, it would be one more healing opportunity and patients have to consent in choosing this therapy.

4. Ethics committees must work within sufficient time frames and with a high degree of transparency. The persons appointed to such must be selected carefully (IPP). The committees should be made up of 50% men and 50% women, whereby health professionals should not account for more than half of members (GPP). In addition to the fields of statistics, ethics and theology as well as other representatives of society (ICP), participants also recommend the participation of at least one informed lay member to facilitate the input of other socially relevant and non-scientific ideas (GPP, ICP). Moreover, the committees must have sufficient time to fully examine applications (GPP, IPP). Decisions should be subject to peer review by members of other ethics committees (ICP).

The consortium agrees that multi-disciplinary background of the ethics committees ensure that different aspects are evaluated. On the other hand, having more than half of the people with no medical background will take more time for committee to understand and assess the status of the research field which is very important to see if it really makes sense or if it is time to move to clinical studies. Nevertheless, we agree that committees should have lay members (such as patients or interested people without specific expertise) which is already the case in the Netherlands (where probands of clinical trials participate) and in Ireland. Germany has non-medical experts such as legal and statistics experts but very rarely lay people.

Peer review of ethics committees would mean an enormous additional burden for all ethical committee, whose members work at the committees in addition to their normal job and is thus not feasible. One solution is to have a coach or trainer who can consult the committee which happens in Ireland.

The GAMBA researchers interact with the ethics committees as they sometimes call researchers in or ask a question. For a clinical trial (study with patients) the researchers have to appear at the committee to explain and discuss the study.

5. Particular attention must be paid to informed consent. The lay participants demand that the information base, the knowledge and the opinion of patients is respected by the medical professionals (IPP). On the other hand, patients may under certain circumstances have to be protected from themselves as, due to their ailment, they may be too ready to take risks and could suffer harm (GPP). The eagerness of a sufferer should not exclude the disclosure of all pre-existing conditions (IPP). Patients see here a particular duty of care on the part of the doctor and also consider it essential that they receive a comprehensive elucidation of the risks/benefits and neutral guidance (IPP) giving them sufficient time for consideration and the seeking of a second opinion (GPP). A high degree of significance should be given to the patient's responsibility for herself/himself (CHP).

The consortium agrees that informed consent is very important and information must be well understandable and based on detailed and balanced information. The consortium agrees that neutral guidance is recommended. The current regulations cover all these aspects sufficiently and it is not in the interest of the researchers to act unethically, and if they do they destroy their career and it can have a negative impact on the whole research community in this field.

6. Animal experiments are justifiable under restrictive conditions. Experiments on animals are necessary and justifiable if they are well-planned, do not commence too early and are limited to a minimum (GPP). This means they are conducted only within a limited scope and in situations where they are inevitable (CHP). Researchers should be encouraged to working towards the eradication of animal testing (ICP). Wherever possible, animals suffering from osteoarthritis should be given preference for use in GAMBA research (GPP, CHP).

The consortium fully supports the recommendation of the lay panelists that animal experiments should be carefully planned and not started too soon. The animal protection laws generally work according to the "3R" rules (replace, refine, reduce). Where possible, bioreactors are used to replace/reduce animal studies. Unfortunately it is difficult to work with animals naturally suffering from OA; due to high inter-animal variations large numbers of animals would need to be treated in order to obtain relevant results.

7. The use of adult stem cells seems more acceptable in comparison with the use of embryonic stem cells. The use of mesenchymal ("adult") stem cells as compared with the use of embryonic stem cells appears to be more acceptable from the ethical standpoint because this involves no use of biological donor material and is not harmful to third parties (GCP). The prerequisite of this, however, is tight control and regulation of international stem cell research (IPP).

The consortium agrees with the statements of the panelists regarding the use of adult stem cells compared to embryonic stem cells. We also approve tight control of international stem cell research.

8. Patenting of human cells or cell components is an ethical question which must be re-debated and pondered over from the ethical standpoint before this path is taken (CHP).

The consortium has no easy answer on this huge question. In principle we are against patenting since the cells are donated by people and this should not be a field for commercial interests. On the other hand, novel therapies like cell therapies need to be considered for protection otherwise they will not come to market.

9. The protection of data is important. The protection of the personal (patient) data must be regulated and strictly monitored (confidentiality, protection of identity and storage of genetic information) (IPP).

The consortium agrees fully.

10. Enhancement must be debated: A distinction is to be made between genetic traits and disease (ICP). The boundaries between disease therapy and pure "betterment of mankind" (enhancement) must be debated on a society level (CHP).

The final aim of GAMBA is to improve the quality of life of patients with diagnosed disease/injury and not to enhance healthy people. Certainly, "misuse" of the basic concept, should it be successful, needs to be prevented.

3. Possible Risks Involved with GAMBA

1. Gene therapies, stem cell research and the use of nanoparticles are fields of research where risks are involved (all panels). Particular emphasis is placed on

- the risk of cancer and death as a result of gene and stem cell therapies (all panels)
- the risk of an overreaction of the immune system (GPP)
- the risk of an inadvertent activation of the genes at a later point in time (GPP) and/or the problem of halting these bodily processes (CHP)
- risks regarding quality control (origin of materials) (GPP, IPP)
- risks posed by previous patient history (IPP, CHP)
- risks posed by the biomaterials (CHP) and nanoparticles used (DPP, CHP)
- the risk of dispersion of manipulated stem cells, viruses (GPP) and growth factors (CHP) in the body
- the risk of mutation of germ cells (CHP)
- the risks of infection occurring at the point of removal of the stem cells (GPP)
- the risk of a release into the environment and effects on third parties (GCP, CHP)
- risks posed by epigenetic influences (ICP, CHP).

The panels' acknowledgement that GAMBA research represents a real opportunity is allied to a very thoughtful and comprehensive list of potential risks. It is fair to say that mechanisms are in place to address many of the risks listed but scientists engaged in research in the stem cell and gene therapy fields should be made aware of the concerns expressed by the patients and GAMBA scientists will keep this list in mind as they continue with their basic research.

2. All risks known to date must be considered. Two panels (GCP, ICP) did not want to systematically list specific risks but stated all risks identified to date through research and clinical trials, such as, for example, carcinogenesis (insertional mutagenesis), undesirable immune reaction, overproduction of the gene product, abnormal mutation of target cells or the reactivation of existing viruses (see Manual p. 36). It is of utmost importance that patients be informed about the risk of cancer and death (IPP). The reliability of origin and tolerability of the materials used must be guaranteed (GPP) and has to be verified in animal experiments before an application involving humans takes place (CHP).

The consortium is aware of the potential risks and agrees that it is not possible to completely exclude the risks stated above at this stage of research; however we can minimize them to the best of our knowledge by strict quality control, (if GAMBA proceeds) by well-designed toxicological pre-clinical studies and by following the ATMP guidelines. In the preclinical and clinical phases after GAMBA, risk assessment and testing should reveal the risks. As for every medical/surgical treatment, the patient must be reliably informed about the expected risks and benefits.

3. The search for as yet unknown risks is important to the panel members is (GPP, GCP, CHP). Unknown risks are seen as the "main risks" (GPP). New findings on risks must lead to new reflections on and a new evaluation of therapeutic approaches by independent committees in order not to lose sight of undesired effects (GCP).

The consortium supports this statement recognizing that the search for yet unknown risks might not be considered often enough. The unforeseeable risks are the worst (D). Full transparency will be crucial in this respect. At this stage of GAMBA, it would be impracticable and unethical to do toxicological studies which need animal trials because the insights would be very limited. We welcome risk research which will be done later in preclinical and clinical trials.

4. Lay participants see the risk of concealment, downplaying or non-communication of risks (GCP, IPP, ICP, CHP) as negative research results for the most part are not published.

For that reason they call for the publication of research failures and risks (all panels) and a higher level of transparency regarding risks.

The consortium agrees, and to a limited extent, this is done at conferences, among consortia and at professional networks. However the communication about risks and research failures is not made easy by the system of scientific publications which encourages mainly the publication of successes and a research line that is not promising will result in insufficient data not accepted for a whole publication by the journals. Given that this project is funded by the EU and thus independent of industry funding, it is more likely that also potential negative results will be published, as long as the study design is reasonable and of scientific/clinical interest. However, in general publication of failures is still not common or not desired and transparency needs to be increased in this respect.

One solution would be a database with basic information on **research plans/settings.** One part of the consortium thinks that such a database would be valuable if the work to maintain and supervise the database is publicly funded. The other part of the consortium thinks that it would be too much effort and not feasible because of competition aspects.

5. The complexity of the GAMBA research approach results in an increase in risk**.** The panels generally find that the complexity of GAMBA, caused on the one hand by the combination of gene therapy, stem cell therapy and the use of nanoparticles and on the other hand by the aim of finding a cure against inflammation, cartilage and bone degeneration, increases the risks involved (GPP, GCP, CHP). Application of the therapy to several joints might also increase the risk of adverse effects (GPP).Effects and interactions within the GAMBA approach must therefore be examined (GCP). A plan B should be developed to make sure that growth processes (cartilage and bone) cannot only be started but also stopped (CHP). The lay participants call for the development of strategic solutions covering the remaining risks (GPP). Risks must be quantified as far as possible (IPP).

It is true that the potential of unforeseen risks is enhanced due to the complexity of the project. However, contingency planning is mandatory in every research plan and the risk management of the complexity of GAMBA is already partially covered by the GAMBA approach (through spatio-temporal control of vectors). Therefore the GAMBA research takes small steps and considers this as a technology project and not a purely translational (= transfer into clinic) one.

We agree that a method to stop the production of growth factors if required would reduce the risk of overproduction.

The next step should be defining the most promising part and see if that can lead to clinical application (still a long way to go). Additional measures would then be part of **future** research and pre-clinical and - if any - clinical trials. This presumably will enhance the level of complexity again!

6. At the current point in time the risks are justifiable. In the view of two of the panels (GPP, ICP), the risks are justifiable according to the current level of information available and – based on the information available to the panellists - the opportunities outweigh the risks (ICP). Moreover, there is no risk-free therapy; remaining elements of risks are accepted (GPP, CHP). However, the risk awareness in researchers should be raised in order to create an “open risk culture” (CHP).

7. Risk assessment is of elementary importance at every stage of the GAMBA project (GPP, ICP). Even at this (early) stage, GAMBA researchers should communicate about risks (CHP). The lay participants recommend very careful management of the use of gene vectors and nanoparticles in the phase concerning research on animate beings and restrictive regulation of such; risks must be more stringently controlled (CHP).

The consortium agrees that we should pay attention to any possible side effects at early points in research and should communicate them. A comprehensive risk assessment will be part of pharmacology/toxicology, which is not part of the current GAMBA project. This would need to be carried out before advancing into clinical testing.

8. All panels agree that comprehensive risk assessment is required prior to an application on humans at the latest.

The consortium agrees that risks must be carefully weighted (OZB/F). All data should be risk assessed and risk minimisation strategies considered with associated legislation put in place, or strengthened where it is already in existence, to ensure that there is a clear chain of responsibility.

However, focusing too much on risks in basic research applications could be a barrier for progress. The risks have to be taken into consideration but cannot be overemphazised in a research project, otherwise they become an obstacle.

The participants' concern on who decides what risks are acceptable is also thought provoking and should be of interest to regulators and legislators involved in ensuring that efforts to get novel therapies to clinical practice are regulated **appropriately.**

4. Additional Aspects and Framework Requirements for GAMBA

4.1 Osteoarthritis Prevention/Causal Research

1. Raising the awareness of the general public for prevention: The lay panel members recommend raising public awareness of the problems of osteoarthritis and their correlation with life-style, behaviour and nutrition - together with key players representing, for example, the medical profession, specialists in preventive medicine, patients' associations, government departments and others (CHP).

2. Early prevention: In addition, they recommend that osteoarthritis prevention be pursued from childhood onwards (GBF, CHP) both with a view to detecting postural deformities or defective positions as well as with a view to promoting a healthier diet in order to avoid overweight (CHP).

3. Furthermore, they call for increased causal research on primary osteoarthritis (GCP, IPP, ICP, CHP) and more research into the role of nutrition (amount and composition) in relationship to osteoarthritis (CHP).

The consortium agrees that more research is necessary to elucidate the underlying causes of primary OA, probably a complex interplay of genetic an environmental influences. Regarding factors that are known to increase the incidence of OA, such as overweight, better information of the general population would in fact be indicated. On the other hand, we cannot expect that prevention will solve the whole problem so working on new therapies in parallel is still very useful.

4.2 Research Funding

1. Sufficient funding must be provided. Participants call for sufficient funding to be provided to guarantee the independence of (basic) research (GCP, GPP, CHP). They recommend that funds be made available for osteoarthritis research on a pro rata basis for all EU member states (IPP).

2. The lay participants request parallel support for different research approaches. Important is additional research in complementary and conventional medicine regarding a therapy for osteoarthritis and a fair distribution of research funding, e.g. a minimum amount for each relevant field (GPP, CHP, IPP) not only for basic research but also for research into prevention and application (IPP) and approaches in respect of social and

psychosomatic issues (ICP). Complementary medicine must be included in research projects in general (CHP). At the same time, the causes of osteoarthritis should be researched (all panels), particularly the role played by nutrition (CHP).

The consortium agrees that different research approaches need to be financed in parallel. Regarding the integration of complementary medicine we see difficulties to start research projects including such approaches as it is important in basic research to rely on simplifying models. Complimentary medicine is a wide field (psychosomatics, immune system, metabolic ailments…).

3. There is a call for greater transparency in research policy. The lay panel members demand a higher level of transparency in research policy and funding than is present to date (GPP, ICP, CHP).

It would be ideal to have increased transparency of funding mechanisms. However, each funding body has its own specified rules and regulations. In general it involves independent reviewers and a science advisory committee. But transparency is not always obvious, therefore a difficult point to improve.

4. All results - whether positive or negative - should be published (GCP, IPP, ICP, CHP). In this context, investigative journalism is of vital importance for objective information (ICP). In cases where damage is caused in clinical trials, issues such as the preservation of evidence, care for and compensation of the participants and their families must be ensured (IPP). Possible side effects of medication resulting from stem cell and gene therapies should be clearly labeled (ICP).

The consortium fully agrees however the system makes it more difficult to publish negative results than to publish positive results. Furthermore some yellow press media may not communicate the information properly but are only eager to create headlines that sell.

5. The participants recommend a review of the methodology of trials in view of evaluation, possible instances of manipulation or the independence/neutrality upon publication, the aim being to permit greater innovation and creativity (e.g. research on osteoarthritic animals), to include complementary medicine and to allow for the selection of older participants (CHP).

The evaluation of the methodology of trials is usually done by the medical ethical committees as well as by grant providers. Peer review process makes sure that the quality of the research is excellent and fits the call criteria, otherwise the project is not funded. In addition there are guidelines for good clinical trials and the trials as well as outcome parameters need to be registered in a central data base (which will prevent that only positive results will be published) - at least for the high quality studies. As the consortium partners decide about the methodology of projects, it would be possible in a new project to design a basic research project using OA animals for the animal trials and have elderly patients as the main target group.

6. Specific Recommendations for the GAMBA Project:

- The lay panel members recommend a continuation of funding for the GAMBA project until it is completed and for auditing to take place afterwards (IPP).

After completion of the project, the consortium will be able to make first conclusions about the feasibility of the concept. Based on these conclusions, decisions will be made on how to continue with this research. The whole project is being audited by the European Commission. For a continuation the partners of the consortiums would need to apply again for funding.

- Should the target group for GAMBA mainly be comprised of young, sporty people and not solely of osteoarthritis patients (CHP), participants recommend the formulation of a tighter, clearer patient focus when GAMBA is continued.

In the early phase of the project the target group is defined broadly, since the feasibility of the general concept is investigated. Depending on the outcome, the target group may be narrowed in the way that certain modules may only be indicated for specific treatment. GAMBA is until now a technology project, looking out for revealing the most promising technologies. For further development the application can and should be more specified.

4.3 Economic Aspects

1. Basic research creates jobs: As the result of the GAMBA project, jobs will be created in research and technical support (IPP).

2. Competitive costs are important for a wide level of access to the therapy. GAMBA might also be of interest from the economic point of view and constitute a cost-effective therapy option, especially if methods can be implemented in serial productions at a later stage (GPP). The cost of the therapy should be competitive (GCP): affordable and accessible for everyone (GPP).

We agree that already at the present stage our research should aim towards a therapy that is (1) feasible to apply by the clinician and (2) cost-effective. Only then a novel treatment will have a chance for future clinical application. On the other hand, the consortium cannot assess the costs a future therapy now: it may in the end be a really expensive therapy.

3. An evaluation of the effects should be made at the present time. Even in the current phase of the basic research project, an initial evaluation of possible beneficiaries of a therapy and of the economic prospects and the financial aspects should be carried out (GPP).

The consortium disagrees in conducting an economic evaluation during a basic research state, because it is too early (GAMBA would be on the market only 15-20 years ahead) and we don't know what will be cost effective then.

4. Particular attention must be paid to fairness of distribution. The lay panel members demand that everyone who might benefit from a GAMBA therapy in the future should indeed receive a therapy (GCP, IPP). There should be no discrimination between public and private patients (IPP).

We agree any therapy be freely available and not beyond the reach of the patients. In the experimental phase the distribution of therapy benefits will not be a problem since this will only be allowed in academic hospitals. Later it will depend on commercial interests and may be country specific.

4.4 Information, Communication, and Dialogue

1. It is important to maintain a critical view of things. The motives of everyone involved, including the ethics committees, should be open to scrutiny (GCP).

2. Scientific exchange is important and should be intensified. GAMBA is a positive example of trans-border, inter-disciplinary, and inter-sectoral cooperation (GCP, CHP). Lay participants suggest an intensification of scientific exchanges on an international level to enable an even better exchange on research approaches (CHP).

Intensive scientific exchange is organized with the GAMBA partners by respecting the boundaries of IP (intellectual property) protection through personal contacts and at consortium meetings. The communication and flow of information between the GAMBA partners, towards the European Commission, and largely also towards the "scientific community" (conferences, publications) is established and on-going.

3. Premature promises of a cure should be avoided. These run the risk of raising unrealistic or false hope in patients (GPP, IPP, ICP, CHP) and also might lead to premature pressure on researchers to produce results (GPP).

The consortium tries not to raise false promises of a cure – however scientists are confronted with the dilemma of getting funding by creating a very positive perspective – and being realistic at the same time.

4. The panelists wish for impartial elucidation of the entire therapy spectrum. This includes balanced information, including information about alternative therapies and their respective benefits and risks. Responsible patient and comprehensive advisory guidelines for doctors are necessary (GPP, GCP). The aim is informed consent via neutral advocacy (IPP) based on knowledge and trust (GCP) which respects the knowledge and the opinion of the patient (IPP).

The consortium considers this as a certainly comprehensible point of view from patients, but does not see it as a task of GAMBA.

5. Greater transparency with respect to errors, failures and adverse effects is called for. The lay members of the panels criticize the fact that in science it is difficult to publish negative research results in parallel to the successes and also to communicate critical opinions - and that there is little incentive to do so (GCP, CHP). This is something scientists should strive to achieve – also within the GAMBA consortium (CHP).

We repeat here what we stated above: In general, publication of failures is still not common or not desired; we agree that transparency needs to be increased in this respect.

6. Free access to information is very important. The participants wish for the "power of the people": the concerns of the general public must be met by scientific transparency and truth. A functional pan-European Freedom of Information Act should be installed (ICP). In order to make conflicts of interest transparent, a pan-European register on conflicts of interest should be set up (ICP).

The consortium agrees that a register of conflicting interests would be ideal. Concerning early information: If information is given too early, this raises expectations and often leads to phone calls from desperate patients hoping for new therapies, who cannot be helped.

7. The participants wish for more public relations work to be carried out. There is a call for more intense public relations work and education regarding the GAMBA approach (IPP, CHP). One single contact point should provide all the information available about GAMBA, both its successes and its failures (IPP).

The GAMBA Panels clearly showed us the need for communication of our research towards the general public. We need to consider such or similar dialogues also for future research projects. Finally the patients are our ultimate target group, and research funding is partially dependent on public money. Besides the panel, general public relations work is performed (press releases, public discussions, presentations…) and documented on the GAMBA homepage: www.gamba-project.eu

8. Dialogue at an early stage is important. Without it, the pace of research advances threatens to overrun the ethical debate and the formation of opinion in society (GPP). Communication between research, politics and the general public should be ongoing (CHP). Dialogue is a preparation for subsequent communications with the general public and promotes democratic possibilities (GPP): it transforms the affected into the involved; it makes it possible for people to form an opinion at an early stage.

9. Dialogue helps all parties involved. Researchers are given fresh food for thought and change their way of looking at things (GPP, CHP). For example, dialogue has led on the one hand to the proposal that research should be conducted not only with young but first and foremost also with older stem cells (GPP) and on the other hand to the recommendation to focus more definitely on "young, sporty people" who are a self-evident target group (CHP). The participating patients and citizens stated that they not only had learned a lot from their own personal point of view but had also gained "an insight into the difficulty of research" and appreciated the fact that their "views and opinions were taken seriously".

10. The participants wish for more dialogues like the lay panels. The views of young people in particular should be included - a youth panel would raise more attention than a panel made up of the old and sick (CHP). The participants consider the panels to be exemplary (GPP) and appreciate the fact that the researchers are facing up to dialogue at such an early stage. They advocate the establishment of additional panels with citizen participation (GPP, GCP), perhaps even as standard (ICP).

Speaking for Ireland, Switzerland and Germany, our experience of the panels has been very positive and very educational for both the research process as we move forward in our efforts to understand osteoarthritis and develop potential therapies, and the development and expansion of the ways that we disseminate our results. Engaging with interested parties other than the scientific community is critical and, from our interaction with the GAMBA panels, rewarding. We agree that such dialogue can only add to the research process and ethical standards, and ensure that the public perception of scientists and scientific output is maintained at a high level. This dialogue will increase understanding on both sides and hopefully contribute to acceptance of novel therapies based on the use of stem cell and gene therapies and nanomedicine, the concepts associated with the GAMBA project. However projects that involve panels or other “good quality” communication should be awarded by receiving proper grant money in the future. Furthermore we think that future panels should also be voluntary, because otherwise the quality of the panels might suffer.

The panels have shown that lay people can understand complex scientific issues like GAMBA – but carefully prepared presentations understandable for lay people and discussions at eye-level, where also risks, fears and societal issues can be discussed are needed. We are glad to have made the experience that we could discuss opportunities AND risks constructively: going into details in an atmosphere of trust.

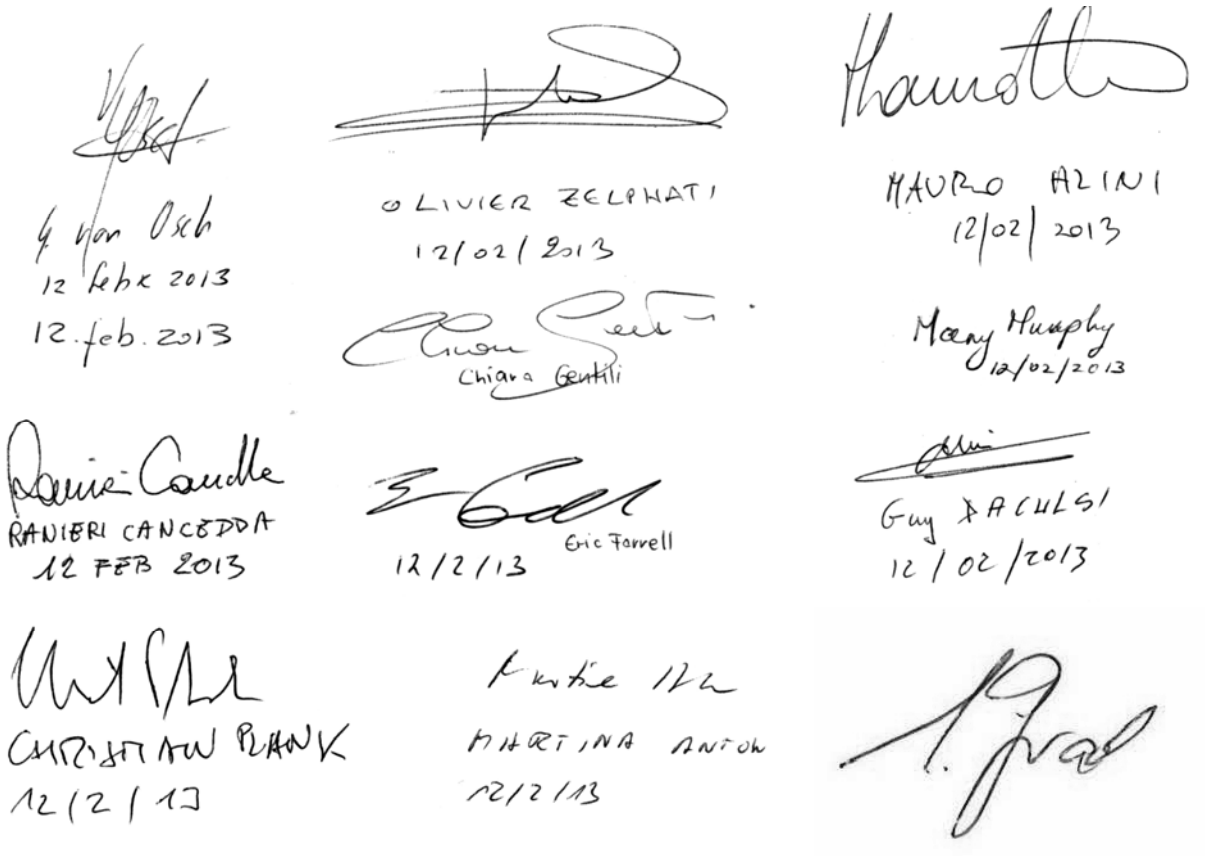
As scientists, we will continue to engage with the public, respect their opinions, avoid jargon in our communications and recognize that holistic approaches to disease are not only important but perhaps complimentary to the novel therapies that we research.

Final remarks by the consortium

GAMBA is a very early basic research project. It is true that the concept of using spatial and temporal control of relevant genes for repair of tissues damaged in osteoarthritis is novel and that GAMBA aims to provide proof of concept. We are also in agreement that GAMBA is “still a work in progress” and may not work ultimately but were pleased to read the panellists’ recommendation that research and exploration of stem cell and gene therapies, and nanomedicine should be continued but be expanded to cover aspects of social science and clear and open communication with the general public and patients.
As such we are also ready to learn from the consensus expressed by the panels on potential risks to consider and ethical aspects to keep in mind as we perform the research. We had animated discussions and we respect the reservations of the participants.

Finally, we have to sincerely thank all the participants in the panels. They challenged all the invited experts as well as the GAMBA researchers in ways we had not expected. We appreciated the tremendous work that they put into the process and we hope that the views expressed in this report will be listened to by a wider audience with this dialogue between the scientific community becoming the "norm" in the future, although we **additionally** need dialogue formats that reach more people and that are less time consuming for everyone.

For the GAMBA-consortium:



Introduction: project outline

1. The GAMBA project

In the EU project GAMBA (**G**ene **A**ctivated **M**atrices for **B**one and Cartilage Regeneration on **A**rthritis) scientists are searching for novel therapeutic approaches for osteoarthritis, which will hopefully trigger an endogenous healing process. Eight consortium members from six EU countries (France, Germany, Ireland, Italy, the Netherlands and Switzerland) are cooperating under the coordination of Dr Martina Anton and Prof Christian Plank of the hospital "Klinikum rechts der Isar" of the Technical University of Munich (www.gamba-project.eu).

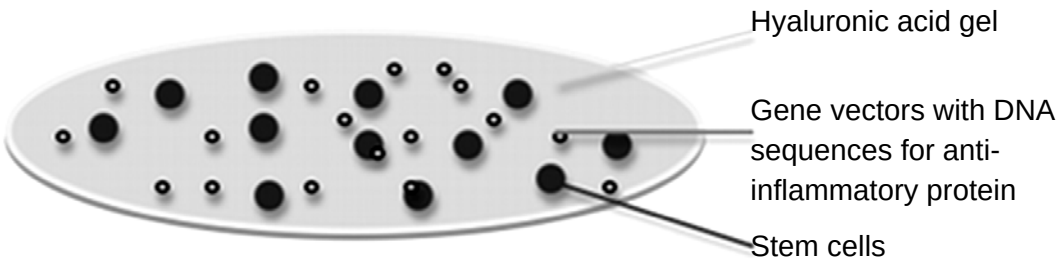
Gene vectors can transport specific therapeutic genes into the body's own stem cells, this leads to the production of certain proteins. These proteins are the therapeutic agents in the GAMBA project.

During the experimental stages GAMBA aims to identify a combination of the following healing processes:

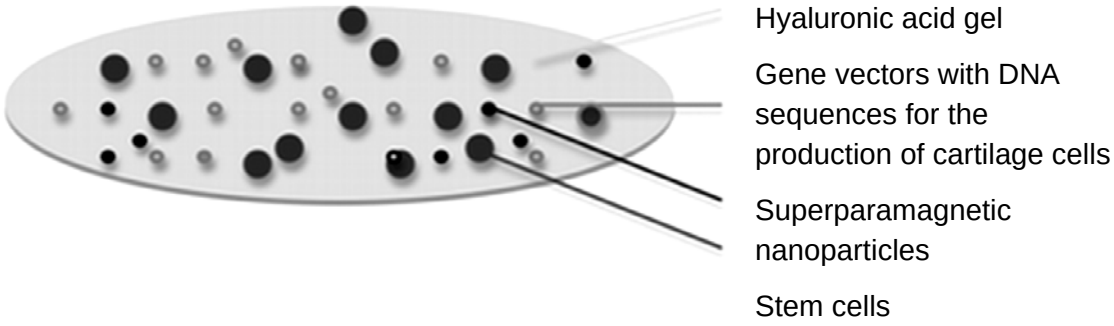
1. to **stop** inflammation,
2. to **heal the cartilage** and
3. to **heal the bones**.

With the chosen proteins (anti-inflammatory proteins, cartilage or bone proteins) the GAMBA scientists want to demonstrate the effectiveness of several different control mechanisms. To that effect they examine various combinations of matrices with stem cells and gene vectors with respective trigger systems.

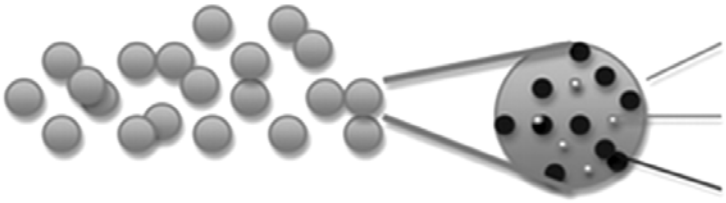
a) An option for an **anti-inflammatory,** active layer would be a hyaluronic acid gel module, which contains stem cells as well as gene vectors that react to inflammations present. This reaction then starts the production of the anti-inflammatory protein.



b) A module composed of hyaluronic acid gels with stem cells and the heat-reactive promoter is a possibility for the **cartilage-building layer**. Heat induces the expression of the DNA sequence for the cartilage protein. The heat is generated by superparamagnetic nanoparticles.



c) A **bone producing module** could consist of calcium phosphate bead lets, which contain in their pores stem cells and gene vectors for the bone protein.



Graphs: ScienceDialogue

In the lab such modules can be layered on top of each other to be able to assess the timeframe and spatial distribution of the reactions. It is not yet known what the individual modules will look like, before they have been tested in animal models. Several combinations are possible. Also it is not yet known whether they will be inserted into the joint separately, layered as gels or as a matrix.

In order to **assess the GAMBA project from a societal point of view**, so-called lay panels with patients and citizens in the three partner-countries of Germany, Ireland and Switzerland were carried out as a separate component of the project.

2. What is a lay panel?

In a lay panel, a group of 12-25 interested participants develop a joint statement on a socially relevant topic. They receive information understandable to lay people, and interview experts some of whom they can choose themselves. They are supported by a team of professional, neutral facilitators.

The term "lay panel" is derived from "citizens panel", which is a form of participation inspired by the methods of "citizens jury" and "consensus conferences". Such panels were carried out at the former Centre of Technology Assessment in Baden-Württemberg/Germany, on topics such as biotechnology, climate-friendly power supply and waste planning. The goal is to develop a joint lay opinion in the form of a "lay report".

Within the project "GAMBA lay panels" i.e. the patient and citizen panels took place between May 2011 and July 2012 on 3,5 resp. 4 days per panel (two weekends with an interval of three weeks) in Munich/Germany, Galway/Ireland and Zollikerberg near Zurich/Switzerland. The participants of the citizens' panels were partly recruited randomly. In this way we hoped to avoid recruiting only participants who are already (very) actively involved in societal debates. Another advantage of recruiting at random is that participants from differing social backgrounds can be reached.

The lay panels are a type of „microcosm", reflecting a smaller image of social reality. The whole group' assessment, and not – as in a survey – the sum of the *uninformed* individuals' opinions, is leading to the results, as they are based on intensive discussions and negotiations. The **ground rules** for the dialogue are listed in Part III.

One central element in the procedure of the lay panels is **expert input**. It sets out to inform the participants on the whole range of subject-specific technical insights and assessments. This ensures that opportunities as well as uncertainties and risks are mentioned, and ethical questions are raised.

This innovative form of discourse in professionally facilitated lay panels enables the participants to take a stand on the complex subject matter of GAMBA (gene and stem cell

therapies). They were able to advise the scientists, the EU as our sponsor, research politics and other agents in a knowledgeable and accurate way.

3. Objective of the lay panels

In the lay discourse, participants were asked to **assess** the **GAMBA field of research** from their various perspectives as patients or interested citizens. To prepare them for this, they first received an introduction to GAMBA as a field of research: in the run-up to the panels, participants received the "Manual" and "Compendium" brochures which had been written in layman's terms by the science journalist, Beatrice Lugger, in collaboration with the project team. The panels listened to presentations (on osteoarthritis, the proposed mode of operation of the GAMBA approach, possible risks and the ethical aspects of gene and stem cell therapies) and questioned selected experts directly in a hearing. Equipped with this information, they then discussed the opportunities, possible risks and ethical aspects of GAMBA, and after an extensive discussion in breakout groups and in plenary they drew up modules for submitting their opinions (see Part I).

Project leader Dr Zoeller with Irish facilitator Paula Weir (r.) and participants of the Irish Citizen Panel

4. Overview of the lay panel process

Participants prepared their "Lay Statements" in two sessions (of two days each) on the issues relating to GAMBA[2]. The **panels' first session** served to "empower" participants in the subject and methodology:

• **Day 1:** After participants had been given an opportunity to get to know each other and were provided with an outline of the schedule, they listened to an introductory presentation on osteoarthritis, were given an overview of the GAMBA research project, put their questions to the speakers and discussed the issues with them.

• **Day 2:** On the second day, participants considered GAMBA in depth with the local research teams[3]. The lay participants also listened to presentations on the possible risks

[2] A detailed account of the lay panel process is provided in Part II of the report.

[3] in Munich/Germany: Martina Anton and Christian Plank from the Klinikum rechts der Isar (University Hospital) of the Technical University Munich; in Galway/Ireland: Mary Murphy, Eric Farrell and Niamh Fahy from National University of Galway; in Zollikon/Switzerland: Sibylle Grad from AO Foundation supported by Martina Anton.

related to the GAMBA field of research and on the ethical aspects[4]. The session concluded with participants selecting experts for a hearing on the second weekend and they were given the opportunity to extend their knowledge of the individual aspects of GAMBA in terms of ethical and social factors before the second session through the creation of "ambassadorships", i.e. individual participants adopting an issue to pursue on behalf of the panel.

The **second session** (three weeks later) was wholly geared towards the development of assessments, opinions and the suggested wording of the lay report:

• **Day 3:** On the third day, those participants who had assumed a "mini-expertise/ ambassadorship" role in adopting an issue on behalf of the panel presented or discussed their results in breakout groups. Then the hearing with the experts selected by the participants took place.

• **Day 4**: The fourth and last day was used for an in-depth discussion and for the assessment of the GAMBA field of research. The patient/citizen panel members prepared modules of text covering the opportunities, risks and ethical aspects of GAMBA. Finally, two spokespersons were elected to complete the lay report and present it at the closing event.

Each day ended with a "snapshot review", i.e. a brief appraisal of the respective day. The facilitation team was flexible in addressing the needs of the individual groups, accepted criticism and suggestions and made changes. Therefore, even though the process is comparable overall, there may be minor local variations.

Discussion in breakout group

[4] In Ireland, both these presentations took place on Day 1, as the panel there met on Saturday/Sunday for organisational reasons.

Part I: Statements

1 Statements from Germany

1.1 Statement by the German Patient Panel

Foreword of the spokespersons of the German Patient Panel

As an enthusiastic follower of the "X-Men" movies for a long time I believed myself to be familiar with both mutants and genetic modifications. These movies are about people who in some cases adopt an animalistic appearance. In reality things (unfortunately) look very much more complicated. The GAMBA-project is attempting to get a grip on the problem of osteoarthritis using genetic engineering as a basis. Over two weekends organised by ScienceDialogue, I was able to experience first-hand how exhausting and tedious things become when it comes down to the details. I strongly recommend these events to everyone suffering from or at risk of developing osteoarthritis.

Dr. Gerhard Hertel

At one of the regular meetings of the Munich Osteoarthritis Self-Help Group, Dr. Zöller introduced herself and invited the group's members to attend a patient panel, the plan being to compile a lay opinion report in which patients affected by the ailment would evaluate a new and visionary therapy for osteoarthritis.

For a start, the prospect of being able to question experts about osteoarthritis is enticing. The need for information about the course of the patient's own disease is considerable. Only four of 17 participants in the panel are for the most part or entirely satisfied with their orthopaedic specialist. Therefore, many of the questions from participants after the introductory lecture by Dr. Renkawitz concerned their own "tales of woe" in relation to the ailment.

However, it soon became clear to us how complex the domain we were to deal with really is. Dr. Anton and Prof. Plank gave us an in-depth explanation of nano-particles, mesenchymal stem cells and gene vectors.

With good navigation by the ScienceDialogue team, expert hearings alternated with group work. Risks, ethical aspects, the work of ethic committees and the use of experiments on animals were subjected to just as much scrutiny as the healing potential of the new therapy.

After the first weekend we were given the opportunity to invite additional experts to join us. In "mini-expertises" we extended our in-depth knowledge of tissue cultures, stem cell research, ethical aspects of animal experiments and research ethics. During a visit to the laboratory we were allowed to peek over the shoulders of the researchers.

It became clear to us how long and exhausting the path from basic research to a model for treatment really is. And it also became evident how important it is for patients to deal responsibly with their own health and/or ailment, and how much significance must be attached to prevention.

We wish for more basic research on the causes of osteoarthritis and intensive research in the field of endoprosthesis because a prosthesis with a long life span is to date the only solution for final-stage osteoarthritis. We are cautiously optimistic about the GAMBA

research approach. We welcome the GAMBA project as basic research and hope it will help to shed more light on the clinical picture of osteoarthritis.

However, at this point in time it is premature to talk about the promise of a cure for all forms of osteoarthritis. But who knows: Until quite recently we believed that the earth was flat.

Bettina Liebstein

Tatjana Logan, Andreas Riehn, Dr. Gerhard Hertel, Bettina Liebstein at report presentation

Introduction

A good therapy for osteoarthritis must…

… be effective; it should be possible to prove its effectiveness
… protect the cartilage
… be easily understood by the patient
… be tailored to the requirements of each patient
… commence at a sufficiently early stage
… bring lasting relief (not be only a flash in the pan)
… be affordable and the costs be borne by private and statutory health insurance schemes
… have only a limited number of known adverse effects
… be easily tolerable
… be suited for all osteoarthritis patients; alternatively several therapies for the different types of osteoarthritis and target groups must be available
… be holistic in approach
… be easy to use
… involve one shot and everything is fine! (as a vision)
… take only a limited period of time (because of sick leave).

We consider the current situation for osteoarthritis patients to be unsatisfactory. The majority of osteoarthritis patients have no hope of a cure because, due to age limits, modern operative techniques such as micro fracture, autologous chondrocyte transplantation (ACT), and osteochondral transplants are available only to a small number of

patients. So currently it is at best possible to ease the pain and slow down the progress of the disease until the affected joint is replaced by an artificial joint as the only remaining therapy possible.

Therefore, this unsatisfactory situation must **be the starting point for further research.** In addition to the need for research in the field of osteoarthritis identified by us, we would like to emphasize that each and every patient is responsible for his / her own well-being and can influence the process of the disease.

We regard **prevention** as the first option when dealing with a disease. This is why we consider the recommendations of the 10-Point-Programmeme[5] for joints as ideal. However, we see a risk that preventive measures could under certain circumstances be ignored due to the availability of a therapy. Therefore we would like to emphasize: Therapy and prevention have to go together!

The GAMBA Research Approach

A standard therapy based on the GAMBA research approach is to date only a vision. GAMBA is a basic research project – and therefore it is actually not targeted at the future usability of research results. For this reason we consider a premature promise of a cure to be a risk because this may result in the awakening of unrealistic expectations and high hopes in patients and in premature pressure on researchers to produce results. Therefore we call for critical scrutiny of any promises relating to a cure. At the present point in time a basic research project calls for a cautious evaluation of the possible beneficiaries of a therapy, its economic prospects and financial aspects.

Concerning the point of time for dialogue between researchers, patients and citizens

In our view it is still far too early for final conclusions to be reached concerning opportunities and risks; many questions remain unanswered.

When applying for funding of a research project, the researchers already have to answer ethical questions on a scale we deem to be sufficient. This information is evaluated when the application is examined so that only well-founded and reasoned research projects receive financial support. Moreover, we have made our representations on ethical aspects we consider especially important in the ethics section. Furthermore, an ethical evaluation will be repeated at a later stage when questions on application (on humans and/or animals in pre-clinical and clinical research) will play a more prominent role.

We see the risk of the pace of research progress putting too much of a strain on the ethical discussion and the process of social opinion-making. Hence we emphatically welcome the fact that the researchers are open to dialogue at an early stage. The exchange of information between the general public and researchers established in the GAMBA project is exemplary in view of the maturity of the concept and the offer of dialogue at the basic research stage. This encourages society to form its own opinion at an early stage. The patient panel prepares complex topics for discussion with wider groups of interested people. Encouragement of the involvement of people affected by the disease is also an approach which advances democratization.

The researchers too learn a great deal from their dialogue with patients and representatives of society by acquiring new ideas and learning to think in new ways: for example feedback from our patient panel suggested using both young and older stem cells in research work and thus was able to exert a positive influence on research. Last but not

[5] Source: Lecture by Dr. Th. Renkawitz, Orthopaedic Clinic of the University of Regensburg, at the Bad Abbach Asklepios Clinic during a patient panel on 6 May 2011 „Die 10 Regeln der Gelenkschule“ (The 10 Rules for the Maintenance of Healthy Joints), see Prof. Dr. med. J. Grifka: „Die große Gelenkschule“ (Maintenance of Healthy Joints), Stuttgart 2010, p. 74-87.

least, dialogue has provided the researchers with contact with the realities of life, the patients' problems and questions.

The Opportunities Offered by GAMBA

Man's curiosity is the driving force behind research projects of this nature and therefore a prerequisite for society's continuing development. Basic research opens up opportunities because it creates a basis of knowledge for future applications.

The applicability of the GAMBA modules far exceeds their application in the field of osteoarthritis:

- The therapeutic effect on the cartilage can be carried over to other diseases.
- Positive and negative findings from GAMBA could be used for other bone diseases such as osteoporosis or rheumatism.
- In addition, other ailments and therapeutic approaches, such as tissue engineering for example, could also possibly benefit from experience with the techniques used in the GAMBA project and the knowledge about body processes gained from it.
- GAMBA also makes its contribution to advances in research into osteoarthritis prevention - in particular that of the GAMBA partners in the Netherlands, Ireland and Switzerland researching this field - as for example further research is carried out on certain molecular mechanisms.

We can see that GAMBA's approach to research offers the chance of a future cure for osteoarthritis. The approach could be successful.

The GAMBA approach is totally new. It examines not only bones and cartilage but also the joint environment and the inflammation processes taking place there. Stem cells and gene vectors inserted into the affected area are intended to stimulate the production of autologous proteins.

We also welcome the fact that osteoarthritis can be treated via the three GAMBA modules, thus giving rise to individual therapeutic possibilities. Stem cell therapy in particular, as an independent (autologous) therapy, provides a concept for new opportunities based on personalized medicine.

Last but not least, in our opinion basic research also provides us with the opportunity to develop cost-effective therapies: Thus, for example, it is possible nowadays in the tissue engineering sector to "manufacture" skin in serial production at acceptable prices. For gene therapy too, the assumption is that it will be possible to develop methods more cost effective than those in existence today (e.g. the use and relatively cheaper production of plasmids/non-viral gene vectors compared to adenoviral gene vectors).

Ethical Aspects of GAMBA

Ethical questions must be subjected to a critical examination in order to guarantee safety (refer to the section concerning risks) and to gain the greatest possible acceptance by the general public.

Ethics Committees

Medical ethics committees at research facilities and in clinics examine applications for research using autologous material like stem cells or for which clinical trials on humans are planned. We consider the work of these ethics committees to be very important. However, ethics committees are for the most part extremely pressed for time in their work; sometimes 10-30 minutes is the only time available to them to consider research applications. This is why we call for **sufficient time** for the ethics committees to examine applications.

The work of ethics committees is not monitored; we do not consider this to be a viable step as it would lead to a chain of applications awaiting monitoring. Moreover, monitoring is unrealistic given the abundance of applications. We do, however, endorse a **high level of transparency in the decisions** made by the committees, perhaps by publishing records while at the same time observing intellectual property rights.

The **makeup of the ethics committees** is less than optimal in our view. We call for 50 % of the ethics committees' members to be men and 50% women. Moreover, only half of the members should be medical scientists; other members should come from the fields of statistics, ethics and theology and similar. In addition we wish to see the participation of an informed layperson[6] as a layman's opinion can help to gain society's acceptance for decisions reached by committees. In other procedures the participation of laypersons is common practice (e.g. jurymen) and serves to provide input of different (non-specialist) thoughts.

Well-Being of Patients and Experimental Animals

The patients' willingness to take risks may possibly increase in proportion to their degree of suffering. For this reason, patients must under certain circumstances be protected from themselves. Doctors must exercise their duty of care with extreme diligence. To cause no harm must be given the highest priority. Risks must be assessed with extreme care.

A patient's self-interests – like the hope of a cure, pain relief and minimizing of adverse effects - are very important. For that reason, particular attention must be given to obtaining the informed consent of the patient in, for example, clinical trials. We consider informed consent to be possible once patients have been given a thorough explanation of risks and allowed sufficient time for consideration. Moreover, a second opinion should be sought.

The well-being of animals used for experimental purposes is a matter close to our hearts. We deem animal experiments to be necessary and justifiable if they are well-planned. They should not, however, be commenced too prematurely and have to be limited and/or reduced to a minimum. If possible, animals suffering from osteoarthritis should be given preference for GAMBA research.

The dignity and protection of humans and animals (according to the laws governing the protection of animals) should be given the highest priority!

Perspectives / Future

Various different possibilities for applications can result from the GAMBA project. However, we fear that certain therapies could become unaffordable in the future. A GAMBA therapy should therefore be effective, affordable and accessible for everyone.

The Risks of GAMBA

One thing is beyond dispute: There is no therapy that does not involve risks. However it is our belief that the main risk lies in those risks unbeknown to us as yet. Among others, the following risks/adverse effects of GAMBA modules exist:

- For us, the safety of origin and the tolerability of the materials used are important.
- Nanoparticles are hardly predictable in our view.
- The use of stem cells always carries a latent risk of mutation and thus of cancer development.

[6] One participant does not see the necessity to include laypersons but accepts the request made by the other participants.

- We see a risk of infection occurring immediately upon removal of the stem cells from the patient's body (infections can also spread over the whole body).
- One should not lose sight of the fact that in the GAMBA project use is made of viral gene vectors (adenoviruses). Even viruses from which the nucleus has been removed carry the risk of an overreaction of the immune system (the case Jesse Gelsinger who died in 1999 of the consequences of a genetic therapy, presumably due to an overdose of adenoviruses). The dosage is a difficult area and carries different risks. In addition to the risk of an overreaction of the immune system, direct damage to organs is also a possibility should the viruses or the manipulated stem cells spread uncontrolled throughout the body.
- Different ways are used to switch genes on and off - heat, antibiotics, or magnetic fields for example. This carries the risk of genes being unintentionally switched on at a later point in time when this is not desired.
- We also see an increase in risk if the potential GAMBA therapy is applied to several joints.
- Therefore, we call for the development of strategic solutions for any remaining risks.

The GAMBA study combines genetic therapy, stem cell research and nanotechnology. In addition GAMBA deals with three therapeutic targets: healing bones and cartilage and fighting inflammation. Because of this we also see risks arising from the **complexity of the GAMBA procedure** because risks increase as a result of the coupling of different therapeutic approaches.

Conclusions in Respect of Risks

The risks known to us at the moment are justifiable at this stage in the project. It is very probable that research will expose additional risks which are unknown to date. A new assessment of risks must be made when concrete therapies are developed. **Risk assessment is of elementary importance at every stage of the project**. Adenoviruses must be deactivated or replaced; at the moment they are merely "wrapped up" to make them less detectable by the immune system. We feel it to be expedient to carry out research into alternatives to adenoviruses (non-viral gene vectors).

Framework Requirements

Research Funding and Research Policy, GAMBA and Alternative Research Approaches

We call for **all research to be independent,** basic research in particular. We consider basic research to be very important for a society whose duty it is to support it. This is particularly true of funding: we deem the financial independence of basic research to be essential. The state must provide sufficient means to fund basic research. Existing knowledge, concerning gene therapy for example, must be developed further.

In our view a highly-developed country like Germany cannot afford to neglect basic research.

We consider the GAMBA research approach to be important but in addition we call for research on other treatments — conventional medicine and holistic and/or complementary medicine alike. One example is the influence of the metabolism on different illnesses. The conventional medical alternatives include, for example, stem cell therapies, liquid prostheses with hyaluronic acid or protein therapies.

Given the economic impact of skeletal and muscular diseases including osteoarthritis, we consider it necessary to invest more in further research work. We attach importance to a well-balanced allocation of research funding, e.g. a minimum amount for each relevant field.

We have also held discussions on transparency in research policy and funding, which is in our view insufficient. However, we do not consider complete transparency to be feasible here.

Economic Aspects

The three therapeutic GAMBA modules,

1. an anti-inflammatory layer,
2. a cartilage-forming layer, and
3. a bone-forming module

offer a broad field of application and in consequence make it economically interesting.

Conclusion

GAMBA offers the opportunity of one day healing some forms of osteoarthritis (refer to the "opportunities" section). We welcome the GAMBA project under the prerequisite that risks are always carefully and thoroughly assessed (refer to the "risks" section). A repeated ethical evaluation will be necessary once GAMBA is ready for use on humans (refer to the "ethical aspects" section).

Participants of the German Patient Panel

Bauer, Irmgard
Bichlmaier, Annelie
Bruckmayer, Georg
Csontos, Gabor
Dolezik, Brigitte
Hertel, Gerhard Dr.
Hlevnjak, Ivanka
Kostrzynski, Petra
Levens, Helen
Liebstein, Bettina
Preuß, Sigrid
Reiter, Gerlinde
Richter, Elisabeth
Thesen, Monik

Participants of the German patient panel

1.2 Statement by the German Citizen Panel

Forewords by the Spokespersons of the German Citizen Panel

According to Wikipedia, apart from being the family name of various different personages, "GAMBA" can also mean either historical string instruments, places in Angola, Gabon or Costa Rica, an administrative district in Tibet or, as "Gamba Osaka", a Japanese football club. For me and 25 fellow residents of the Munich region, in January and February 2012 the term meant "Gene Activated Matrices for Bone and Cartilage Regeneration in Arthritis". Oh, I see. Genetic research. The last time I had concerned myself with genetic research was when I was reading a thriller by Michael Crichton, and the relevant genes in that case were those of dinosaurs which became extinct more than 65 million years ago. And now it is genetic research relating to osteoarthritis in two legged mammals of the species Homo sapiens. I had few expectations from the specialist point of view but the invitation aroused my interest first and foremost because there were plans to establish a citizen panel. Citizen panel? The word "citizen" has after all been made intensive use of since 2010, especially in combination with another term describing strong emotions and an impulsive and aggressive reaction. The irate citizen. The word of the year 2010 (chosen by the Association for the German Language). However, the citizens described as irate citizens were naturally not – upon proper examination - motivated by anger but rather by the desire for participation. And now I was being asked to participate.

When the invitation to participate in the GAMBA citizen panel arrived in the mail, I initially assumed this would be a discourse between scientists and several hundred “laypersons” - people without a scientific background. When it emerged that we, the participants, a team of about 25 people with different professional backgrounds, were to evaluate a research project in the field of genetic research on stem cells for osteoarthritis, I had my doubts about the significance of a lay opinion report of this kind with respect to the number of participants and their capability of forming a judgment without any or with only very little in-depth knowledge. I was to learn that this was not the case: A framework was built up based on the common ground existing between all participants, their interest in GAMBA and the ethical and moral ability of judgment of each participant. As a first step, the experts held lectures to provide us with the basic knowledge required and the answers to the questions "how? what? why?". Allocated to small groups, we were able to continue to absorb the new information and to ask further specialist as well as ethical and moral questions.

To a large extent many of the participants knew of genetic research only from the media and were accordingly uneasy and sceptical, particularly regarding the term "stem cells". The term stem cell with its negative connotations (many thought instantly of embryonic stem cells) was neutralized in the course of our information collection sessions. Many experienced a moment of enlightenment when they learnt that the genome in its entirety is present in every cell of the human body. Most cells can only execute specific functions. However, every human being - regardless of age - has his or her own stem cells which can be influenced genetically to form cartilage or bone tissue - a central theme of osteo-arthritis research.

Many liked the possibility of autologous material being used for this research. Many others were fascinated by the idea of the researchers to use "cut" viruses, to a large extent rendered harmless as a "means of transport" in order to gain access to the stem cells. Nevertheless, in spite of the fascination of the matter, we all continued to be sceptical as to the controllability of this method and the as yet unidentifiable risks involved. The discussion moved deeper and deeper in the direction of ethics and morality. Those among us who had been enthusiastic became more thoughtful and recognized potential hazards. Those among us who had had great misgivings and had been extremely hostile to the whole idea became somewhat more optimistic and started to see possible opportunities. The discussion and in the long run the evaluation too remained very positively controversial. My

concern that the intention was to ”synchronize” our opinions on the part of the participants hence proved to be unfounded.

All in all, I have perceived the formulation of the lay opinion report to be a democratic process and I believe that the communication between citizens (for whom research is being performed) and researchers is growing ever more important and must be cultivated.

Andreas Riehn (Paragraph 1)/Tatjana Logan (Paragraphs 2-5)

Preamble

GAMBA is a basic research project with the aim of researching into a therapy for the treatment of osteoarthritis. This future therapy is intended to impede inflammations and to heal cartilage and bone.

Patients understandably and justifiably wish for mobility and freedom from pain to enable them to participate in everyday life. Due to a change in lifestyle in Germany and many other EU-countries, a large number of people are overweight and take too little exercise. Because of this and the increase in life expectancy, the number of osteoarthritis patients is growing. GAMBA could possibly provide new therapeutic opportunities and the hope for a longer and more active life.

A programme of additional therapies for osteoarthritis might be developed from GAMBA at a later stage, in parallel to such therapies as acupuncture, a change of diet and joint replacement. We welcome therapies like GAMBA which strive to find a cure for osteoarthritis. However, we also consider it important to find alternatives to somatic gene therapy, like better joint replacements and prostheses (refer to 2.5 Framework Requirements). Prior to commencing treatment the patient must be informed comprehensively about different therapeutic options. This applies to both positive and negative consequences. The guidelines concerning advice by doctors should be all-inclusive.

The Opportunities Offered by GAMBA

Opportunities are possible positive results but are not a guarantee. Realistically first applications of a possible GAMBA therapy are to be expected in 15-20 years at the earliest. Thus results relevant to patients will only be attainable after a very long period of time involving a great deal of work, money and effort (and possibly suffering as well). It would be desirable to speed up the “findings” process.

The aim of GAMBA is to ease and cure osteoarthritis. In more specific terms this means: easing pain, regenerating damaged cartilage and bone and improving movability. The GAMBA method focuses on activating self-healing. In addition, there is the prospect of a long phase of remission (absence of symptoms).

We consider the use of adult stem cells as autologous material from the patient to be medically and ethically more acceptable as compared to embryonic stem cells.

- Medically because cartilage and bone developed from these stem cells are of better quality than material bred externally or using chemical materials.
- Moreover, autologous material is more easily tolerable since it is not rejected. This means fewer risks for the patient.
- Ethically because the use of autologous adult stem cells as in GAMBA does not require third parties to donate biological material and therefore eliminates possible harm to third parties (donors).

From today's point of view, the planned minimally invasive procedure seems to be more gentle and seems to carry fewer risks since a major operation with the risks involved is not required.

The intended aim is to achieve competitive therapy costs.

Additional Medical Opportunities

GAMBA's intention is to provide insight into the mode of operation of different research approaches and a combination of these:

- Genetic therapy (switches, adenoviral vectors, lipids (non-viral vectors)),
- nanotechnology (form and function of iron oxide nanoparticles), and
- stem cell research.

Insight of this kind could be used in other medical fields like dentistry as well as for other disease patterns like osteoporosis, fractures and even cancer.

GAMBA would be of even greater interest the higher the bar could be raised with respect to a patient's age limit (with previous bone replacement therapies the age limit is about 45 years). Although some experts see definite opportunities in this sector, it is at present still uncertain as to whether this will be possible. We would like to see research also being carried out on therapies for osteoarthritis for people above the age of 45. The general ageing processes, however, cannot and should not be stopped.

We see a chance of GAMBA also creating the impetus for research also to take place in the field of primary osteoarthritis (unrelated to external causes).

Comments on the Social Opportunities of a Citizen Panel

The project provides an opportunity of informing the general public about a potential new treatment. We consider it important to provide good and balanced information allowing people to form their own opinion and to assess the risks involved. Patients and other interested parties should be in a position to reach an informed decision thanks to an increase in public vigilance. Responsible patients should be in a position to make decisions not out of fear but based on knowledge and trust. For this reason trust-building measures are required which could also lead to a decrease in anxiety.

More information and transparency make the citizens feel responsible and open up an additional option when a decision is being made on osteoarthritis therapy. This results in everyone involved - doctors and patients in particular – acquiring greater knowledge and more options for action.

Further Opportunities

GAMBA is a positive example of transnational cooperation: the project is international, interdisciplinary and intersectoral.

We also see GAMBA as the opportunity for German and European scientists in the GAMBA research sectors to gain greater recognition and appreciation, enabling them to assume a leading role in research.

It is our wish that additional research funding be approved. We advocate additional panels involving public participation.

Ethical Aspects of the Fields Covered by GAMBA

We consider it to be very important to allow time and space for ethical discourse on the topics covered by GAMBA. To this end, light should be shed on and a scrutiny made of the motives of all participants, including those of the ethics committees.

We ask ourselves: How can ethics, as a complex and wide-ranging domain, provide guidance and food for thought? Ethics should furnish guidelines for social decision-making.

Despite the wide range of opinions within the group, ranging from ethical innocuousness to clear-cut misgivings and the limitations of GAMBA, there is a basic consensus of opinion

concerning respect for life and human dignity. On the one hand human dignity demands research and possible healing as defined by basic research but — on the other hand — human beings must not only be reduced to their biologically functional components in defining the term "health" — health is more than the absence of illness. Within this area of conflict the GAMBA Citizen Panel has deemed the following points to be important aspects:

- The mature patient should not be absolved from personal responsibility for his/her own health by the possibility of a therapy with GAMBA. A loss of personal responsibility or even the refusal to assume personal responsibility because there is an available gene therapy as a cure-all would be a development in the wrong direction. Encouragement of personal responsibility includes focusing the patient's awareness on preventive and alternative measures, thus advancing and strengthening his/her self-efficacy via personal positive experiences in this direction. Personal responsibility should be promoted during childhood and adolescence as early as the kindergarten stage and, for example, pursue the central objective of avoiding or reducing overweight (overweight is seen as one of the fundamental factors influencing osteoarthritis).
- Important for us in this respect is the conscious perception and acceptance of biological limitations and finally respect of the finiteness of human life.
- There is consensus in the group concerning
  - the safeguarding of the dignity of animals and
  - the utilization of research results of other medical/scientific sectors.
- There is also consensus on the demand for fair distribution. In view of limited financial resources, the following should be examined and considered in this context:
  - Who would benefit from a later GAMBA therapy so that all those GAMBA would be of use to also profit from the therapy?
  - How and for what therapy approaches should research funds be deployed so that new therapy opportunities for all patients result and can be used (more) meaningfully?
- Also important for us is the impartial consideration and presentation of alternative therapies (also see Preamble).
- Desirable would be the joint development of research projects by patients/sufferers and specialists from different fields of science and the involvement of all interested parties in the research process.

In conclusion we would like to ask the recipients and readers of the report: Does this final consensus by our group reveal a collective social basis of values worth maintaining? And if so, how should this be done and how – as we asked at the beginning of this chapter — could time and space be generated for ethical discourse?

Risks of GAMBA

Risk research is essential. In case of new therapy approaches both effects and interferences must be considered. Findings from gene therapy have already proved that possible negative effects can be[7]:

- Undesirable insertion into the genome (insertional mutagenesis = cancer formation caused by gene insertion in unfavourable locations and cell degeneration)
- Immune reaction
- Overproduction of the gene product
- Abnormal cell mutation in the target cells
- Infections caused by viral gene-taxis
- Reactivation of existing viruses
- Dispersion of gene-taxis throughout the body

[7] Cited from "GAMBA Manual for Citizen and Patient Panels", Chapter 4.2, p. 36

- Insertion into the genetic makeup of ovules and sperm cells
- “Interferences” (interplay with other active substances)
- Disruption of protein balance
- Therapeutic gene is incomplete
- Virus attacks on immune cells.

These side effects can, among other things, lead to cancer development. In earlier clinical studies side effects occurred and people died (J. Gelsinger 1999).

The interferences of technologies with stem cells, magnetic nanoparticles and gene therapies have not been studied in sufficient depth. Through the interplay between the technologies and the greater complexity, the overall risk is higher than the sum of the individual risks. The same applies to the interaction between bone and cartilage structure and anti-inflammatory measures in the 3-fold GAMBA approach.

Any potential inadvertent impact on the environment, future generations and other third parties must be taken into consideration and researched extensively. We have a responsibility to the environment.

The objective should be the identification, regulation and control of interactions and side effects. We demand: Findings on risks must prompt a new reflection and a reappraisal of therapy approaches by independent committees and be well communicated so as to guard against the risk of our losing sight of undesired effects (avoid tunnel vision!).

We see the problem that, although known risks are currently rated as low, the occurrence of an emergency could have serious negative effects which are not really assessable. Furthermore, researchers might possibly shy away from searching for additional, as yet unknown risks so as to “let sleeping dogs lie” (also see communication and transparency of failures in scientific research in the “Framework Requirements” chapter).

We see the softening of the frontiers of gene therapy in the direction of germ line therapy and enhancement (amelioration of the human condition outside of therapies), the so-called “slippery slope”, as a further problem. To prevent this foresight it is important to promote continuous reflection — including reflection on an ethical level, where possible right at the very start of a project (also see the chapter on Ethical Aspects). However, we can also see that the German demand for intensive ethics discussions is a competitive disadvantage internationally. Notwithstanding, the suppression of ethics discussions is also a risk because in future there could perhaps be a lack of acceptance for a technology.

Framework Requirements of GAMBA

It would be desirable to apply the GAMBA research results on stem cell and genetic research to different clinical pictures (also see Opportunities).

Competitive therapy costs are important to us.

Communication between Research, Politics and the General Public – Including Communication about Negative Results

Our demand is that there must be communication between research establishments, politics and the general public at each phase of a research project.

Negative research results must be published. The status quo is, however, that the publication of negative research results has a negative impact worsening the chance of further funding.

The willingness to look at issues critically must be strengthened by intensive secondary research before and after the project. We also see the danger of a cover-up of negative effects in clinical studies, in industry for example.

There must be greater fostering of application research.

An open question on the part of the group to the recipients and readers of the report regards how we can become responsible citizens or how and where the general public can learn to take responsibility for their own actions.

Participants of the German Citizen Panel

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B., Clara
G., Hiltrud
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Kling, Wilhelm
Logan, Tatjana
Merlin, Ulrich
Mieth, Kristin
Puschkeit, Jaana
Raith, Wolfgang
Riehn, Andreas
Roßmeier, Anton Josef
Schaal, Nicol
Scherr, Margitta
Strasser, Andreas
Twele, Stephanie

Participants of the German citizen panel

1.3 Statement by the German GAMBA Researchers on the Lay Panel Opinions

GAMBA is a basic research project on the subject of osteoarthritis which, although target-orientated, is nevertheless far from clinical studies or even clinical applications. For this reason it is by nature difficult, as panellists outline in their report, to make a final evaluation of the potential therapeutic opportunities over the risks and the economic and ethical aspects. Even we as scientists often find it difficult to make this projection of the future. The question asked time and again in the panel meetings was: "What if the GAMBA concept does work?" Our mission in GAMBA is first of all to show that the concept does work. However, we are consciously facing up to questions on opportunities, ethics and risks at this early stage in order to learn from participants and also to be equipped for future discussions.

Opportunities

We see an opportunity in the basic idea of controllable and strictly restricted localized production of growth factors for tissue regeneration aimed at reducing possible side effects caused by growth factors. At present these approaches, however, are only partially feasible.

Ethics

We totally support what patients say about the importance of informed consent for participants in clinical studies which must be based on detailed and balanced information provided by physicians.

As researchers with a therapeutic objective we are the further our work progresses, dependent on experiments on animals. We fully support, however, the comments of patients that these should be carefully planned and not started too soon.

It is worth noting that both reports particularly highlight the personal responsibility of the patient not to rely on a therapy but to act pre-emptively and supportively himself/herself.

However, while on the one hand patients emphasize the individualization of medical practice, participants on the Citizen Panel call for "fairness of distribution", viz. accessibility for everyone.

Risks

We have always endeavoured not to promise a cure. We are ourselves aware of the known risks of the individual components; in contrast to the participants, however, we are also (more) aware of the route prescribed for testing procedures which – if followed properly – should and can expose additional risks. All of the risks mentioned will have to be examined in toxicological studies. In this context we again point out that non-viral vectors hold fewer risks than adenoviral vectors (but here, too, the risk does not equal zero). However, current investigations show that non-viral vectors are still not effective enough, hence the two-tier approach in GAMBA.

In principle we agree with the statement made in the citizen report "Due to the interplay between technologies and their greater complexity, the overall risk is higher than the sum of the individual risks".

Naturally the unforeseeable risks are the worst risks. In this context in particular we too would welcome the performance of risk research.

Framework Requirements

We, too, hold the view that basic research should be independent. For this reason we are grateful to our sponsors, the EU (but also the DFG (German Research Foundation) and the BMBF (Federal Ministry of Education and Research)) for enabling us to carry out this basic research. This research is naturally project and purpose-orientated but we are not compelled to produce positive results as tends to be the case under industrial research conditions. The day to day reality of research work, however, teaches us that we must do all we can to produce publications, i.e. to inform the scientific world of our results in order for us to be in a position to continue our research work and keep our staff employed. In principle it is to be assumed that conventional medicine and tissue engineering approaches receive by far the highest share of research funding. Based on our exchanges with patients on the subject of holistic approaches we see the necessity for such approaches. However, basic research must initially always fall back on simplifying models. That is why we see difficulties in starting up — and being granted funding for — the relevant research projects due to the extensive character of the field (influence of psychosomatics, the immune system, metabolic illnesses ...)..

Conclusion

In conclusion we would once again like to formally express our appreciation for the dedicated commitment of the participants in both panels in Munich. Panels of this kind give us - as (natural) scientists - the opportunity to discuss our project with the general public. This is also a never-ending challenge. We as scientists have also learned from the panels: Not only that every patient has his/her own story but also their wish for us to concern ourselves not only with adult stem cells from young donors but also to test the GAMBA approach on the stem cells of older donors, since operating techniques practiced until now have been reserved solely for younger patients ...

We have held animated discussions. We respect the reservations of participants and it will give us pleasure should we have been able to awaken enthusiasm in one panellist or another for our research work.

Dr Martina Anton/Prof Christian Plank, Klinikum rechts der Isar TU Munich, coordinators of the GAMBA project

Facilitator Maren Schüpphaus with Prof Christian Plank and Dr Martina Anton

2 Statements from Ireland

2.1 Statement by the Irish Patient Panel

Forewords by the Spokespersons of the Irish Patient Panel

Being given the chance as an osteoarthritis person to participate in the start of a research project was exciting, as patients are usually only consulted at clinical trial stages. So we approached the weekends with a high degree of curiosity. After all, this was a new departure: an opportunity for patients to be listened to, of being consulted at the very start of a research process. Patients like us who often have a feeling of isolation coping with a long term chronic illness that is often dismissed as part of the ageing process. It is good to have a voice to air our frustrations regarding the lack of progress in the prevention of osteoarthritis and in identifying a non-drug related cure.

Basically, the group from all walks of life learnt so much from the presentations and the expert panels with whom we could engage and share our knowledge. The panels and team were so professional, inclusive, and enthusiastic and that was infectious. The process that came to building the lay report, which is our collective opinion on GAMBA, was fascinating and it stretched us in a good way. Furthermore, it left us with great reassurance that the future research is in safe hands. The report shows the importance of the scientific community engaging with the public as well as the need for peer advocates to translate the scientific terminology to the public.

Wouldn't it be wonderful, if not in this generation but in the next, if osteoarthritis patients would be pain, drug and surgery free with a better quality of life by using their own cells that have been researched in this project to self-heal?

Jacinta Leech

Jacinta Leech and Stephanie Mahon during workshop

Arthritis has been a part of my life for the past 20 years approximately. I have managed to keep some level of control through diet and supplementation-but lately, unfortunately, I am losing the battle.

Arthritis is an extremely frustrating illness-with very little known about its origins. Available treatments appear to just delay surgery rather than cure. I work in the area of complementary medicine. When I first saw the information about GAMBA, it was a quote from Mary Murphy, from REMEDI, that caught my attention. Her statement that 'we want to encourage the body to heal itself' appealed to my belief in the body's untapped ability to work with illness. Stem-cell therapy is something that I have a lay-man's interest in-so the idea of finding out more about it, along with finding out more about osteoarthritis, had me jumping at the opportunity to participate.

Turning up to the first weekend, I have to admit I was feeling some apprehension, especially after reading through the information booklets sent out to us. I was concerned it might be somewhat over my head, as it is quite some time since I studied science at school! I think all of the participants were feeling the same. However, we all agreed that to have the opportunity to be included and consulted with, to have our opinions taken on board in a serious way and to have our frustrations listened to made us all dig in and work hard to produce the best report that we could.

The various experts who presented to us were excellent and extremely informative, explaining things in a very easy to understand way. They answered all of our questions and allayed the fears of some of the participants. Our facilitator, Paula Weir, is an amazing woman. She coordinated, juggled, moved people on without being obvious and managed to reign in and clarify some of the 'science' for us! Credit has also to be given to the participants, who gave up their time and travelled distances to be involved. To the last, we all worked hard. I don't think any of the participants could believe what we had achieved at the end of the process.

The process itself was a very positive experience for all of the participants and, I believe, for those involved with GAMBA also. It showed the importance and benefits of the scientific community engaging with the public in such a way. I believe we learned a lot from each other. It would be wonderful to see more of this in the future-especially when related to medicine.

We all agreed that we came away from the process enlightened, invigorated and reassured that GAMBA was a good organisation, with good ethics and with good people involved. Our only regret was that, unfortunately, we may never benefit from this research, but we are confident that future generations will.

Stephanie Mahon

Note to the reader: "The ideal osteoarthritis therapy" is the result of a brainstorming session. Therefore, respecting the spirit of brainstorming, all contributions have been included, however some have been put into context in the footnotes.

An ideal osteoarthritis therapy …

... reduces inflammation, swelling and pain
... reconfigures joints
... works instantly
... is non-invasive
... gives full mobility
... has no side-effects
... makes you feel good and pain free
... is natural
... is proven to work
... relieves pain without risk
... is based on full early information
... is long lasting
... is cheap
... is freely available
... can be got online
... is instant and retrospective
... undoes damage
... improves your sex life[8]
... involves sunshine[9]

Preamble

GAMBA may be a **new and innovative way forward** in the prevention, the treatment and the eradication of osteoarthritis (OA). If GAMBA gets to the therapy stage, it should be available to ALL patients: there should be no discrimination between public and private patients.

We like that **GAMBA researchers** are seeking and **listening to the views of osteoarthritis patients**.

The question arose "what type of humans do we become if our life is without suffering", as most forms of OA are currently accepted as a natural part of the aging process. Our group touched here on a philosophical discussion that was considered to be important and noteworthy however not a topic of debate for GAMBA.

Having met the GAMBA team we are confident of their ability to bring this research to a successful conclusion.

[8] This comment was not made flippantly or tongue in cheek, but in a heartfelt way indicating the impact that a successful therapy would have for those living with osteoarthritis.

[9] The almost miraculous effect of moving to a warmer climate has been experienced by many participants. For example, for one participant a month spent in South Africa was practically pain free. Climate therefore was seen as a key to a reliable therapy.

Opportunities of GAMBA

GAMBA offers an **opportunity for self-healing** using the patient's own stem cells to carry the gene vectors.

Patients would therefore not have to rely on synthetic drugs or other donors as stem cells are a natural component of the body. GAMBA might one day become an **individual therapy** adapted to the needs of the individual patient.

GAMBA gives **hope for a better quality of life**. We **hope** that **all ages will benefit**. GAMBA should not just be for the old and totally infirm. Future generations could also benefit.

If GAMBA is successful, less resources might be needed for the treatment of osteoarthritis. The budget could then be spread out to the wider community.

Patients could **live a drug free life**. Associated **side effects** of drugs on the whole body system could therefore be **avoided or minimised**.

Through its research, GAMBA offers **opportunities for employment** (i.e. researchers, technicians etc.).

Ethical Aspects of GAMBA and related fields

We see ethical aspects in the following areas of GAMBA and related fields:

- **Data Protection**: Data protection must be regulated and strictly adhered to. We demand that there be structures in place to protect confidentiality, identity protection and storage of genetic data.
- **Clinical trials**: All testing agents should be held responsible and accountable for any negative outcome to the participants. In the event of negative consequences, participants should be "taken care of" in all circumstances; this includes the participants' family and financial compensations.
- **Communication between the patient and the medical professional**: We want the patients' information base, opinion and knowledge to be respected by the medical profession.
- **Informed consent**: All participants must be made fully aware of all risks/benefits leading to informed consent. The patient/professional dialogue is essential with NEUTRAL advocacy.
- **Ethics committees**: A careful construction and selection of personnel involved in ethics committees is necessary. In addition, sufficient time should be given for full consideration by ethics committees (maybe 90 day time frame for assessing a project is sometimes too short).
- **Regulation:** Tight control and regulation must be observed in all international stem cell research.
- **"Hype" / False promises:** It is essential to us that scientists do not overpromise or even make false promises to avoid unrealistic expectations.
- **Funding:** We want to see a fair distribution of funds between basic research and prevention as well as the research on current treatments: we would like to see 40-50% of the research funding to be spent on osteoarthritis prevention and cure. We recommend that the research should be funded until the completion of the project which should then be fully audited.
- **Embryonic stem cells:** Although not part of GAMBA (where only adult stem cells are used), we discussed the use of embryonic stem cells in other research projects in depth. We demand that absolute consent MUST be obtained by both the donor and the beneficiary of embryonic stem cells.

Risks of GAMBA

Researchers should be able to **quantify the risk** before human involvement in a trial starts. It is of utmost importance that p**atients be informed about the risk** of cancer and death.

We are concerned that important **information about risks** and possible side effects is **withheld**. **Negative research results** should be **published**.

We demand the **traceability** of the origin of the **DNA** structure and the **adenovirus** along with a quality assurance.

There is also a risk that, if informed consent isn't clear enough, **trials may collapse** at an advanced stage. In ethics committees, we see the risk that the lack of knowledge due to the novelty of gene therapy could interfere with progress of the research project.

To avoid conflict of interest, we find it essential that the **roles in clinical trials are clearly separated**: the researcher, the doctor and any company financing the trial or taking advantage of it should not be the same person. In addition, research funding should come from different sources, not just pharmaceutical companies.

We see a risk of **reduced interest in conventional treatments** when a gene therapy is available.

As the risk is always on the patient (in clinical trials as well as when a therapy is on the market), **guarantees** should be in place for the patient (see also "ethical aspects"). At the same time, GAMBA should endeavour to ensure that the eagerness of the suffering person to participate in the treatment does not outweigh the **necessity of full disclosure of pre-existing health conditions**.

We see the risk of **rogue research and medical tourism** by dubious stem cell companies which should be avoided as far as possible. At the same time, we trust in our scientists/ researchers.

Other aspects regarding GAMBA and related fields

While we support GAMBA and its research, we are awaiting the **answers for the cause** of osteoarthritis. It is important to us that the causes of OA are researched in parallel to new treatment options.

Regulation, compliance control and standards need to be in place from the outset. We also demand that firm regulation be applied to all commercial investors.

All osteoarthritis research funding should be equally available to all countries that require it on a pro rata basis from **central EU funds**. All countries – be they big or small – should be given support.

A continued **dialogue with the public** and participants of trials should ensure regulation and compliance. Biological and ethical issues should be monitored by experts AND lay people. There should be **peer advocates** to translate scientific jargon to the public.

There must be a multi-media exposure to **promote and create awareness of GAMBA**. We want a **1-stop shop** for GAMBA related information: A "centre of excellence" should deliver a comprehensive overview of the GAMBA project dealing with successes and failures in order to ensure transparency.

Finally, we recommend that **humanism behind all science** is maintained – otherwise, "what's the point"?

Participants of the Irish Patient Panel

Conole, Helen
Cullivan, Nancy
Darcy, Gwen
Farrell, Monica
Finn, Mary (Maudie)
Gannon, Anne
Gannon, Geraldine
Leech, Jacinta
L., Therese
Mahon, Stephanie
Morris, Evelyn
Mullins, Anna Pauline
Newell, Jimmy
O'Farrell, Una
Ruane, Tom
Ryan, Patricia
Ryan, Patrick

Participants of the Irish patient panel

2.2 Statement by the Irish Citizen Panel

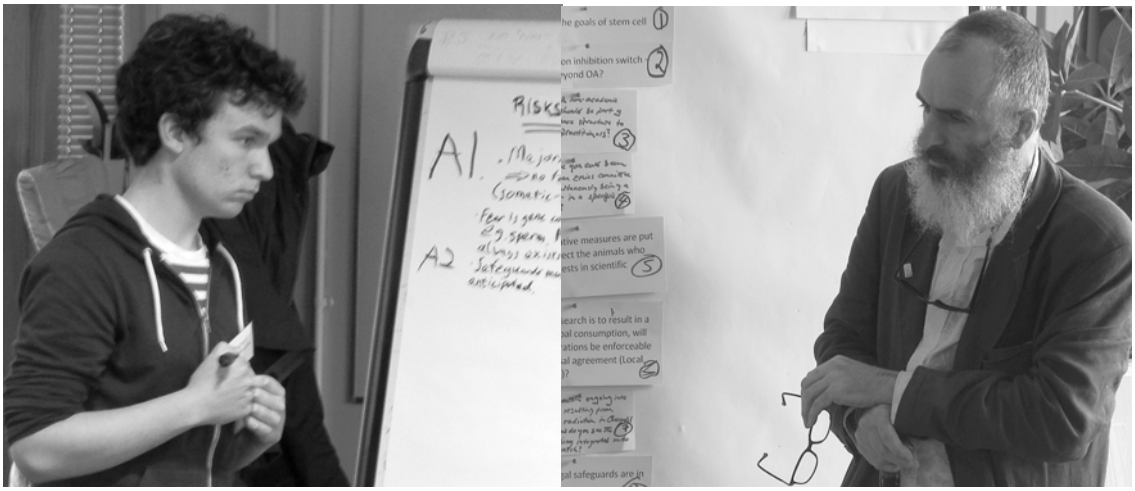
Forewords by the Spokespersons of the Irish Citizen Panel

GAMBA is an important part of science and mankind's struggle against age-related degenerative illness. The citizen panels associated with GAMBA act as a means to connect the scientist and the layperson. Like many others on the panel, I felt that the panels were not only educational, but empowering, as they allow the layperson an input into scientific advances and research.

Such approaches to public outreach in the future could be very beneficial in improving public sentiment towards and spurring interest in medical science and advancement, while also being beneficial to the researchers by offering them viewpoints from outside their own professional sphere.

I was delighted to be part of the citizen panel and certainly, when I first signed up, I did not expect it to be such an experience. While the thought of writing an entire report with a group of strangers on a topic that was somewhat alien to me seemed a daunting prospect at first, we soon found ourselves working as a functional team with the help of the wonderful facilitators. I am proud of the report produced, and I think it fairly and accurately reflects the informed thoughts and attitudes of the citizen panel in relation to GAMBA, gene therapy and stem cell research.

Richard Prendiville



Richard Prendiville and Padraig Mac Donnacha during workshop

I decided to participate for several reasons. Foremost, the panels were/are a unique opportunity to discuss significant social and scientific issues. It was/is important to discuss and to learn from the various perspectives proffered, regarding a *form* of a science in its infancy, and to seek to ensure collectively, that adequate safeguards are in place, to offer the necessary protections for its future beneficiaries, and of course any victims of malpractice.

We, collectively, discussed methodologies to seek to correct past failings in medicine and its practitioners, and in doing so, raised issues of responsibility; personal and collective, issues which have been found to be in urgent need of revision, and to be subject to robust and binding legislation, so as to ensure accountability. This process was undertaken utilizing the Principle of Subsidiarity and the Socratic Method, and this allowed for a general ethical consensus to be achieved by the participants of the panel in Galway, Eire.

I found the panels to be conducted in an open and totally honest environment; one where every consideration was afforded to the views of the participants. I found the panels to be

both educational, and a social platform in which misconceptions regarding the topics discussed could be corrected- where necessary- by virtue of compelling scientific data, and reasonable, courteous persuasion.

Padraig Mac Donnacha

Achieving best possible outcomes in science for society[10]

- Safety
- Efficacy
- Reliable results
- Quality control for lab practice
- Potential for future development
- Global availability
- World governing body
- Proper funding
- Collaboration
- Transparency
- More openness with public
- Science as knowledge
- Early diagnoses
- What the scientist would wish for self

Preface

“The health of the nation is the wealth of the nation”.

We feel that there is a moral obligation to future generations to explore gene and stem cell therapies as well as nanomedicine. GAMBA is a research in its infancy. Although gene therapy may not have widespread positive results for a long time or at all, it still must be fully explored. We suggest an openness to acknowledge that GAMBA is still work in progress and not necessarily a viable solution – yet.

Introduction

The panel is aware of the differing opinions as expressed by experts in this area. They chose two of them as examples:

"It remains to be seen what we can do if genetic nature becomes malleable to us." "Counting on genes, to account for what ails us, may cause us to dither while waiting for answers we don't yet have, and squander those we do, along with the clear and present opportunities to promote health through better living those answers provide. How nature might one day hone the cutting edge of biomedical advance, in other words, might blunt our application of nurture"(Katz, D.).[11]

In the midst of such diversity of opinion expressed by experts the panel has arrived at considerable consensus as a group of interested citizens.

Genetic research has a long way to go, particularly with multifactorial diseases and our understanding of epigenetics[12].

Stem cell therapy has been widely used for decades in the form of bone marrow transplantation, for example.

[10] “Achieving best possible outcomes in science” is the result of a brainstorming session.

[11] http://tinyurl.com/cftrblr

[12] Epigenetics is the molecular switching on and off of genes that seems to influence health considerably.

To find out more about the causes and potential cures of OA, we recommend the investigation into arthritis-free animals and people with comparable conditions and characteristics such as age.

Social impacts (like economics, belief systems etc.) need to be explored besides the natural science basics.

Opportunities of GAMBA

"The panels are an opportunity to explore all opportunities".

As the population ages, regenerative medicine will become crucial to healthcare **and as world population increases the need for research becomes acute.** GAMBA is an important step towards that. This research promises a less invasive, safer treatment. Based on the information we have, the benefits of GAMBA outweigh the risks. Therefore we see a huge potential for osteoarthritis sufferers.

We appreciate that the technologies researched in GAMBA will have applications outside OA therapy such as M.S., diabetes etc. GAMBA is also an opportunity to make the funding criteria for scientific R&D transparent to the public.

Possible Risks of GAMBA

The risks for GAMBA can only be fully realized when animal and human trials commence. Nevertheless, continuous policing of the risks involved in the GAMBA research project is required. We have the impression that people working on the GAMBA project have considered the risks involved in a responsible manner.

On the other hand, we cannot ignore the fact that certain risks have occurred in basic research or clinical trials in the past. Among them are:

1. Gene therapy risks[13]:

- "Insertional mutagenesis": Integration of the therapeutic gene in unfavourable locations + malignant cell degeneration (cancer)
- Pathological cell mutation of the target cells : Defence reaction of the cells against the therapeutic gene
- Unwanted integration of the therapeutic gene into the genome: The therapeutic DNA sequence is passed on to all daughter cells
- Overproduction of the gene product: Too many proteins at once (overdose)
- Undesired immune response: Body reacts defensively to the foreign matter
- Infections through viral gene vectors: Not all disease causing parts of the virus were removed
- Reactivation of existing viruses: Through contact with other viruses gene vectors turn into disease triggers
- Dispersion of the gene vectors in the body: Undesired distribution of the therapeutic DNA sequences in the body
- Integration into the genetic makeup of egg and sperm cells: Gene vector is integrated into reproductive cells
- "Interferences": Drug interactions
- Disruption of the protein balance: Increased production of a protein that has several functions within the cell
- Therapeutic gene is incomplete: Segments with unknown functions are missing
- Virus attacks immune cells: Scavenger cells are infected.

[13] Cited from "Manual for the GAMBA patient and citizen panels", p. 36. Download: http://www.wissenschaftsdialog.de/Manual%20GAMBA%20web.pdf

2. Risks of proteins as growth factors[14]

- Proteins stray from target area with unknown side effects
- Overdosing of bone producing growth factors leads to undesirable ossification of the cartilage
- Overdosing of cartilage producing growth factors leads to less elastic and less hard bones.

3. Risks of stem cells[15]

- Stem cells can be the original source of a tumor as tumors are most likely derived from disregulated stem cells
- Stem cells are not processed fast enough and specialize too quickly
- Stem cells in the joint interact with blood forming cells in the bone marrow with unknown side effects
- Adult stem cells can also trigger an auto-immune response[16].

4. Risks of nanoparticles[17]

The nanoparticles used in GAMBA are iron oxide nanoparticles used routinely for MRI scans. Nevertheless, there remain certain risks:

- Nanoparticles tend to surround themselves with specific proteins; this could lead to an undesirable exchange with other proteins in the surrounding area.
- Nanoparticles can spread in the body and accumulate in organs such as the liver.

Although it is unclear yet if any of these risks will apply to GAMBA and there are risk minimization strategies underway in the GAMBA project like the "spatio-temporal control mechanisms" (see Manual p. 38 f.), **a full risk assessment including quantitative data analysis must be performed should GAMBA proceed**. In addition, all possible side effects of drugs resulting from stem cell and gene therapy research should be clearly labelled.

We should try to incorporate anticipating and preventive legislation to minimize risks. Oversight is necessary in the ongoing process to hold people responsible. There must be a standardized quality control mechanism in the EU and globally.

Another risk is to ignore or play down risks in the pursuit of results. Finally, we see the problem of who decides which risks are acceptable.

Ethical aspects in the GAMBA field

Ethics are essential considerations to be factored in the GAMBA project:

- Ideally, there should be a global ethical standard for animal research, stem cell research, gene therapy etc. We encourage the research community to working towards the eradication of animal testing.
- All results in research be they positive, negative or inconclusive should be published.
- Bias can cause unrealistic expectations and this needs to be borne in mind by the GAMBA researchers.
- To avoid conflict of interest, vested interests which could influence scientific results negatively, should be laid open. We encourage a pan-European register of conflicting interests to which researchers and drug companies should contribute.
- As stated in the risks chapter, all possible side effects of drugs resulting from stem cell and gene therapy research should be clearly labelled.
- We demand more transparency as regards funding of research programmes.

[14] "Manual" p. 39
[15] "Manual" p. 40
[16] Original card from citizen panel; this risk is not listed in "Manual", therefore included here.
[17] „Manual" p. 40

- We want more research into the psychosomatic influence on the body.
- Furthermore, it is important to distinguish genetic trait and disease.
- Ethics committees should be composed of members who represent society including a wider range of lay people. The decisions of the committees should be peer-reviewed by other ethics committees' members.
- Investigative journalism is vital for objective information.
- We demand "people power". Public concern must be met with scientific transparency and truth. A fully functional pan-European Freedom of information system should be installed. Ireland is currently utilizing a limited Freedom of Information Act.

Final remarks

The GAMBA project and the patient and citizen panels, carried out by ScienceDialogue, are an opportunity to engage with the wider community. The patient and citizen panels are an opportunity to counteract misinformation in public perception. We wish that citizen panels should become the norm to encourage trust through dialogue between the public and experts.

Participants of the Irish Citizen Panel

Hogan, Margaret
Horan, James
Mac Donnacha, Padraig Antoine
Mulkearn, Mervyn
Nealis, Denis
O'Gorman, Ultan
Onions, Olwyn
Prendiville, Richard
Sandouly, Gilles
Sumption, Mary

Participants of the Irish citizen panel

2.3 Statement by the Irish GAMBA researchers on the Lay Panel Opinions

It is interesting but not unexpected that the major outcome from the patient participants was essentially a plea for us as researchers/scientists and the research medical community in general to listen and respond to their views of the ideal therapy. The take home message, although personalized, is remarkably similar to the "best possible outcomes (for GAMBA) in science for society" generated by the lay participants in the citizen panel. Both panels recommend that proven efficacy with minimal risk (safety) is critical for therapeutic development in general and GAMBA in particular. We agree with their views that it is important that scientists produce reliable and comprehensive early research data before any translation to a therapy and that any therapy be freely available and not beyond the reach of the patients.

We acknowledge that the panels' view that GAMBA is a very early basic research project is correct. It is true that the concept of using spatial and temporal control of relevant genes for repair of tissues damaged in osteoarthritis is novel and that GAMBA aims to provide proof of concept. We are also in agreement that GAMBA is "still a work in progress" and may not work ultimately but were pleased to see that these clear words of caution were mitigated by the opinion that research and exploration of stem cell and gene therapies, and nanomedicine should be continued but be expanded to cover aspects of social science and clear and open communication with the general public and patients. We feel that the open communication between researchers and the panels did get the point across that gene therapy may not have application for a long time but must be fully explored; however, we are more than willing to acknowledge that GAMBA does not provide a viable solution to osteoarthritis "yet".

As such we are open to the suggestions on what the opportunities of our research may be and ready to learn from the consensus expressed by the panels on potential risks to consider and ethical aspects to keep in mind as we perform the research.

Opportunities

The panels' view that regenerative medicine and the need for research in the area is an opportunity to develop less invasive but safe treatments that promote self healing is interesting and GAMBA researchers will continue to strive to advance our understanding of osteoarthritis and how gene and/or stem cell therapy can mitigate any aspect of this chronic condition. The idea of GAMBA leading to a therapy adapted to the individual needs of a patient is also appealing and another chance to take the GAMBA concept further should it work.

Risks

The fact that the panels' acknowledgement that GAMBA research represents a real opportunity is allied to a very thoughtful and comprehensive list of potential risks in both reports is both interesting and very instructive for all researchers. The list and the associated prioritisation emphasized by the targeted use of words such as "demand" or the phrase "of utmost importance" in the patient report, for example, represents the basis of a framework that translational and clinical research needs to comply with. It is fair to say that mechanisms are in place to address many of the risks listed but scientists engaged in research in the stem cell and gene therapy fields should be made aware of the concerns expressed by the patients and GAMBA scientists will keep this list in mind as they continue with their basic research. Of particular interest is the consideration that **"Negative research results** should be **published"** to reduce risk.

We agree with the recommendation from the lay panel that all data should be risk assessed and risk minimisation strategies considered with associated legislation put in place, or strengthened where it is already in existence, to ensure that there is a clear chain of

responsibility. Their concern on who decides what risks are acceptable is also thought provoking and should be of interest to regulators and legislators involved in ensuring that efforts to get novel therapies to clinical practice are regulated appropriately.

Ethical Aspects

We support all the comments and suggestions of the participants and consider that the ideal would be a global ethical standard for research, development of a register of conflicting interests for scientists and industries and increased transparency of funding mechanisms and researcher response to public concerns. It has always been a concern of GAMBA scientists that we do not create unrealistic expectations and also agree with the patients that it is essential to perform research into the causes of osteoarthritis as we also try to develop novel therapies based on existing knowledge of the disease.

It was interesting that the citizen panel considered the publication of negative results and attention to bias as ethical issues but both panels focussed on the composition of ethics committees and the provocative ideas of oversight or peer-review of committees and the development of "neutral advocacy" in the dialogue between patients and professionals.

Summary

Our experience of the panels has been very positive and very educational for both the research process as we move forward in our efforts to understand osteoarthritis and develop potential therapies, and the development and expansion of the ways that we disseminate our results. Engaging with interested parties other than the scientific community is critical and, from our interaction with the GAMBA panels, rewarding. We agree that such dialogue can only add to the research process and ethical standards, and ensure that the public perception of scientists and scientific output is maintained at a high level. This dialogue will increase understanding on both sides and hopefully contribute to acceptance of novel therapies based on the use of stem cell and gene therapies and nanomedicine, the concepts associated with the GAMBA project. As scientists, we will continue to engage with the public, respect their opinions, avoid jargon in our communications and recognize that holistic approaches to disease are not only important but perhaps complimentary to the novel therapies that we research.

Finally, we have to sincerely thank all the participants in the panels held in Galway. They challenged all the invited experts as well as the GAMBA researchers in ways we had not expected. We appreciated the tremendous work that they put into the process and we hope that the views expressed in their reports will be listened to by a wider audience with this dialogue between the scientific community becoming the "norm" in the future.

Prof Mary Murphy, Dr Eric Farrell, REMEDI, National University of Ireland Galway

3. Statements from Switzerland

3.1 Statement by the Swiss GAMBA Lay Panel

Foreword by the Spokespersons of the Swiss Lay Panel

As someone with manifold interests – particularly in the field of science and research – and also an osteoarthritis patient of several years' standing (knee, secondary) I came across the advertisement for the GAMBA project Patient Panel while job-seeking on the AO Foundation's website. Interested and curious, I instantly registered, knowing that this would presumably not bring any improvement as far as my own personal ailment was concerned but that I could do my bit for future patients. Moreover, I expected a valuable and unique experience.
The complex research approach with its interdisciplinary fields was particularly impressive and challenging, just as the spectrum of topics we had to deal with in our panel. I also admired how the team of facilitators guided our heterogeneous and not always easy to manage group (patients and lay participants) in a competent and target-oriented way through the process. Taking these factors into account, the period of time expended here is comprehensible and acceptable.
In spite of my history as a patient and my diligent preparation (reading up on the topic before the first weekend), I personally gained some surprising insights and changed or rather substantiated my opinion, e.g.:

- Healing not at any price but rather prevention and alternatives or respectively acceptance particularly in the context of a higher life expectancy and the resultant increase in the afflictions accompanying old age
- to give greater consideration to alternative medicine and thus to qualify faith in studies or respectively to reconsider the mechanisms involved in compiling and communicating studies
- basic research does not focus on ethical aspects.

This occurred on the one hand thanks to the designated experts and the experts we selected ourselves and on the other hand as a result of the subsequent group discussions and presentations. I would have liked to dedicate even more time to the topics dealt with and the compiling of the opinion report; in our panel, for example, we had practically no time to broach the issue of research funding. Nevertheless, I am proud of what we accomplished as we were after all able to address some concrete aspects, and we are convinced that these will be taken into account and exert a certain influence not only on the GAMBA project but also on other projects.

Through my participation in this panel I have met interesting people, have been able to take part in an exciting process and have gained an unique insight into the field of research. I would be happy to participate actively in a panel of this kind on a future occasion. Many thanks!

Manfred Zuber and Krista Berz[18]

[18] Krista Berz supports this text written by Manfred Zuber. From her view it provides a coherent impression of the experience of most of the participants in the panel.


Dr Sibylle Grad receives the lay report from the spokespersons

Opportunities

Opportunities offered by GAMBA for osteoarthritis therapy

GAMBA offers a new opportunity for osteoarthritis therapy but is not a panacea: In our estimation, a therapy based on the approach used in the GAMBA project would co-exist alongside other therapy approaches in the future. For this reason, people affected by osteoarthritis should not set their expectations too high.

GAMBA is an opportunity for certain kinds of osteoarthritis. We see a great potential for the repair of small and medium defects of cartilage and bone.

In particular we see the chance of contributing to the prevention and prophylaxis of secondary osteoarthritis with GAMBA: injuries in the joint caused by accidents in particular could be healed by means of a therapy based on the GAMBA approach so that early intervention could prevent future osteoarthritis. It is probable that young people with sports injuries above all would benefit most from GAMBA – an interesting market if one thinks of professional sports like soccer or leisure sports like skiing. The large group of older osteoarthritis patients currently affected who are suffering from primary osteoarthritis could profit from a GAMBA therapy if an early diagnosis of osteoarthritis were possible. Then less severe damage could be treated at such an early stage that the further degeneration of the joint could be slowed down or possibly even stopped and fewer people would be affected by severe osteoarthritis than is the case at present.

GAMBA can also contribute to deepening and defining knowledge about osteoarthritis; however, GAMBA will above all else presumably provide more in-depth knowledge about tools and the interaction of modules.

The concurrent spatial and temporal control of active substances in the patient is an interesting approach in GAMBA. Therefore we would welcome a continuation of this research with a view to minimising risks and achieving a more specific effect of the individual therapy modules (anti-inflammatory substances as well as growth factors for the formation of cartilage and bone cells).

Here we particularly see opportunities should future GAMBA research give priority to cartilage research as this would reduce the complexity of the GAMBA research approach and early repair and prevention work could be carried out before damage occurred to the bone.

Opportunities offered by GAMBA beyond osteoarthritis therapy

GAMBA is a basic research project. In basic research it is also possible to gain insights which were unplanned but can be used for other fields of research.

- We see opportunities for a reciprocal scientific progress if researchers involved in basic research develop a better exchange of findings with osteoarthritis researchers and therapists.
- We ask the GAMBA researchers to research more closely the nature and functions of synovial fluid since this is very important for healthy cartilage. Synovial fluid seems to play a subordinate role in the GAMBA project.
- GAMBA could offer methodical findings about how interdisciplinary cooperation between different research groups can succeed: for example how a close exchange of information on successes and failures between ever more specialised researchers can lead to joint partial successes (and publications).
- The exchange of findings from risk research on stem cells, gene therapies, bio-materials and nanoparticles is a great opportunity for the GAMBA researchers.

Inclusion of New Sciences

We see additional opportunities in the impartial incorporation of new sciences. We recommend including findings from epigenetics and complementary medicine should GAMBA be taken further.

We consider communication and the exchange of ideas between different interest groups (researchers, public interest groups, osteoarthritis sufferers and lay persons) good and valuable. We see in this an opportunity for GAMBA if this is continued and possibly intensified.

Ethical Aspects in the Fields Covered by GAMBA

Ethical requirements and legal constraints are accepted as guide rails. Confrontation and effort concerning ethics are necessary and helpful.

Although osteoarthritis is not a life-threatening disease, we hope for the most intensive research and problem solving.

Ethical questions posed by the current research project

We welcome the fact that experiments on animals are conducted only to a limited extent and in situations where they are inevitable.

We approve of the fact that GAMBA aims at curing injuries caused by accidents and degeneration processes and therefore focuses on helping the patient.

Relevant ethical questions concerning the future of the GAMBA project:

We deem a re-evaluation of ethical aspects to be relevant for the future:

First and foremost, it is necessary to check whether, according to the ethical stage model of the Munich Institute Technology – Theology – Natural Sciences (TTN)[19], Stage 2, GAMBA can be assigned to the category “to a certain extent ethically and medically justifiable”. The application of a GAMBA therapy would to some extent be irreversible and would involve “cell proliferation in the body”. According to the stage model, the limitations of employment of a future GAMBA therapy would have to be deliberated and it would be necessary to decide whether the risk is “justifiable and normally controllable”.

[19] Hacker J. et al. (2009): Biomedical interventions in humans. A model for the gradual ethical assessment of gene and cell therapy. Berlin

Secondly, GAMBA research pursues an approach focusing on genetics when it comes to human beings and the healing of their illness. It thus symbolises the increasing influence of genetics on medicine. Here we see the danger of genetic reductionism, a view of pathogenesis which is too narrow. Projects like GAMBA confront us with the question of whether this development is desirable and appropriate – also in the light of the complexity of interdependency which is becoming more and more familiar to us.

The patenting of human cells or cell parts is an ethical question which should be discussed and pondered on once more before this path is taken. On the one hand, we accept that without patents there is less incentive for investment– on the other hand, we are concerned about elements of human life and/or human cells being patented.

The results of the GAMBA project could also lead to new technical possibilities for creating human tissue. If, for example, it were possible to grow nasal cartilage inside the patient, this technique could be used for accident victims or in plastic surgery. A social discussion is required on the extent to which these new technologies and use of these are desirable. Where does the boundary lie between therapy/healing of diseases and a pure enhancement of mankind? Is it necessary to formulate restrictions for undesired applications here?

The Risks of GAMBA

Research of risks and risk management

GAMBA is a project with manifold risks. We recommend promoting the risk awareness of researchers and practicing tighter risk control. This entails the establishment of an open risk culture in which the researchers maintain an intensive exchange of experiences not only internally but also externally. In particular, we consider the publication of failures and risks to be very important. We need greater transparency in risk research; to this end we also recommend research aimed at seeking additional risks which are unknown to date.

With GAMBA, risks of complexity are already limited and minimised by a procedure involving taking one (small) step at a time. We accept that an element of risk can never be excluded completely! This applies in particular to risks posed by

- incidences of release into the environment, i.e. nanoparticles or gene constructs (even in closed laboratory systems there is the remaining risk that security measures fail)
- the nanoparticles used
- the gene vectors used
- and last but not least an accidental alteration of germ cells (e.g. due to accidents in the research process)

Individual risks of GAMBA

Our recommendation to GAMBA researchers is that they develop a plan B with mechanisms to stop the reactions activated in the body in case the phasing out of the processes does not function properly. We see the risk of the control of growth factors not being sufficiently manageable.

With regard to the gene vectors used we would like to point to the following risks: the risk of cancer, an uncontrollable protein-synthesis or the integration of gene sequences into the genome (even though with an estimated probability of 1:1,000,000).

We approve of using adenoviruses instead of retroviruses because with adenoviruses integration into the genome and thus a spread throughout the body via cell division is very unlikely. However, an element of risk remains.

Additional areas of risk

We recommend that the previous toxicological impact on a patient and any resulting influence on his/her individual patient history and therapy development be factored into the reckoning.

We recommend that toxicological influences caused by the materials used (vectors, stem cells, nanoparticles, bio-materials) be taken into account as early as the animal experiment stage. Moreover, we recommend research into and consideration of epigenetic influences. The risks inherent in nanoparticles, too, should be more closely researched. We recommend extremely careful management of the use of nanoparticles and gene vectors at the stage of research on living beings or even restrictive regulation of such since very little research on risks for humans and the environment has been carried out as yet.

Framework Requirements of GAMBA

Should GAMBA, which is up to now a basic research project, be continued, we recommend the formulation of a tighter, more clearly defined patient focus. Hence, in our view, mainly young, sporty people who develop osteoarthritis as a late effect of a joint injury are part of the GAMBA target group and not paramount all osteoarthritis patients. A focus of this nature means that the basic research project can be continued in a more target-oriented way.

Causes and Prevention of Osteoarthritis

We think the causes of osteoarthritis are being overlooked by research – here, further research is needed. We recommend

- more research into the causes of primary osteoarthritis: The role of genetic predisposition on the one hand and environmental influences on the other hand should be subjected to improved research . This would allow for early intervention and more effective prevention in case of previous genetic problems.
- more research into the role of nutrition (amount and composition of nutrition) due to major regional differences in the global distribution of osteoarthritis
- the inclusion of complementary medicine into research projects in general as well as in the continuation of the GAMBA project.

Prevention and personal responsibility– in parallel to research on new therapies and approaches to healing – continue to be important. We recommend that osteoarthritis prevention should be pursued from childhood onwards, both with a view to the diagnosis of postural deformities or defective posture and with a view to healthier nutrition as a means to prevent overweight. Responsibility for oneself does not only encompass prevention concerning a person's own self but also providing information to offspring. We appeal to sufferers to do as much as they can to avoid falling victim to osteoarthritis.

Internal communication

Internal communication within the GAMBA project should be directed to a greater extent via failures and errors, including inter-scientific communication within the global research community as a whole.

External communication

We recommend more intense public relations work and "education" of the general public concerning the GAMBA research approach, even though it is difficult to communicate GAMBA in a comprehensible fashion as the project contains very complicated content matter. We think it is possible to improve media work, to more satisfactorily incorporate the perceptions of young people for example: in our opinion, a youth panel would also raise more public interest than a panel made up of only the old and sick.

We recommend raising greater awareness in the public with regard to the problems of osteoarthritis and its relationship with lifestyle, attitude and nutrition – together with players like the medical associations, the Rheumatism League, the departments (government ministries), the cantonal preventative medicine professionals and the Swiss National Science Foundation for example.

Better communication – in particular regarding press relations and inclusion of young people – also increases the chances of funding.

Public and private funding

We see research funding as a topic worth discussing. Within the framework of the project, on the one hand we did not have enough time to discuss this issue and on the other hand we lacked sound information. We would for that reason like to briefly touch on the following aspects – which contain some potential for conflicts – with a few arguments of our own:

We would like to see sufficient funding of basic research, also incorporating funding by private sponsors or foundations. Here a watch should be kept on possible conflicts of interest between researchers and pharmaceutical companies – also with an eye on the future use of results (of patents for example) for the benefit of society.

Research work

We suggest intensifying scientific exchange on an international level. In our opinion, the aim is

- to allow for increased exchange of experiences on a global scale
- to reduce or if possible to eliminate competitive thinking and double-tracking in order to get quicker and less expensive results.

We recommend reconsidering the methodology of studies (with regard to evaluation, manipulation, and independence/neutrality)

- in order to achieve greater innovation and foster creativity. Would it be possible, for example, also to use animals suffering from osteoarthritis instead of healthy animals in experiments?
- in order to reduce the risk that studies with negative results are not published („publication bias“)
- in order to be able to include approaches to be found in complementary medicine
- in order to include not only adults of 50 years of age on average as test persons in osteoarthritis studies but also people of 70 years of age or above.

Social debate on the acceptance of ageing-related restrictions

We consider a social debate on our handling and our acceptance of the restrictions involved in the ageing process to be expedient and necessary.

Participants of the Swiss Lay Panel

Berz, Krista
Bonaldi, David
Hauser, Ingrid Katharina
Hauser, Rudolf M.
Hlavicka-Abt, Beatrice
Huber, Barbara Beatrix
Kruker, Elfriede
Mungo, Nella
Schmid , Erika Lydia
Van Orshoven, Frank
Zuber, Manfred

Participants of the Swiss lay panel

3.2 Statement by the Swiss GAMBA researchers on the Lay Panel Opinion

Opportunities offered by GAMBA

We highly appreciate that the participants acknowledge the great potential of GAMBA especially for small and medium size defects. This is relevant not only for young patients, where the therapy could help to prevent the development of post-traumatic osteoarthritis (OA), but also for progression prevention of early stages of OA. The fact that the participants also recognize the opportunities to gain more basic knowledge about the potential and limitations of such novel therapies shows that they well understand the concept and the importance of basic research projects.

The participants recommend giving priority to cartilage research. In fact the cartilage part is generally more difficult to heal than the bone part, and we agree that more emphasis could be put on focal chondral lesions. However, solutions should also be available for osteochondral defects. Due to the modular approach of GAMBA, lesions that only affect the cartilage are also included.

There was a particular interest in further exploring the role of the synovial fluid. This is partially addressed by the anti-inflammatory therapy, as inflammation negatively affects the function of the synovial fluid. It is generally expected that in a regenerated joint the function of the synovial fluid is also restored; nevertheless, the lubricating ability should be assessed during the GAMBA experiments.

We generally agree that findings from epigenetics and complementary medicine also need to be taken into consideration in the development of novel therapies. At present they go beyond the scope of the project; however, assuming that the GAMBA concept will be successful, new findings from other areas may certainly be implemented.

Ethical aspects

With respect to ethical standards, we would like to emphasize that all GAMBA experiments are approved and meet the requirements of the responsible ethics commission. Furthermore, the local, national and European ethical regulations are of high standard compared to other countries. We agree that at each stage of the project, potential ethical concerns need to be re-evaluated. This applies for both pre-clinical (animal) and clinical studies. The hurdles to overcome before the start of a clinical study are – rightly – very high; this would be performed by other teams/companies after the concept has been proven successful.

Regarding the statement that the GAMBA approach is the expression of a (too) reductionary idea of man, we are aware that the steps from cell/tissue culture to animal and then to clinical studies are huge and that finally we will need to look at the patient as an individual. It is important to note that we do not pursue infinite joint health and treatment of a normal course of ageing; therapy will be justified in traumatic cases and in premature or accelerated osteoarthritis where the quality of life is (or would become) severely impaired. In terms of a future treatment we agree that all relevant information should be given to the patient in a form that is well understandable. Furthermore, we highly appreciate the panel's opinion that a high degree of significance should be given to the patient's responsibility for herself/himself.

Regarding animal studies we fully support our animal protection law and generally work according to the "3R" rules (replace, refine, and reduce). Where possible, bioreactors are used to replace/reduce animal studies. Unfortunately, it is difficult to work with animals naturally suffering from OA; due to high inter-animal variations large numbers of animals would need to be treated in order to obtain relevant results.

Finally we clearly support the statement that “misuse” of the concept for "enhancement" absolutely needs to be prevented. The final aim is to improve the quality of life of patients with a diagnosed disease/injury.

Possible risks

We are aware that we cannot completely rule out all the risks raised by the panel; however, we can minimize them to the best of our knowledge by strict quality control, awareness of new findings, and well-designed in vitro and pre-clinical studies. As for every medical/surgical treatment, the patient must be reliably informed about the expected risks and benefits.

The panel mentions the possibility of concealment, downplaying or non-communication of risks. Given that GAMBA is funded by the EU and thus independent of industry funding, it is likely that also potential negative results will be published, as long as the study design is reasonable and of scientific/clinical interest. Unfortunately, publication of failures is still not common or not desired and transparency needs to be increased in this respect.

We appreciate that the importance of a "plan B" is recognized by the panel. Contingency planning is mandatory in every research plan. The potential of unforeseen risks is certainly enhanced due to the complexity of the project, and we are required to make decisions during the course of the running project if necessary.

Framework requirements

Public awareness of OA prevention and causal research are crucial issues for the panel, which is highly appreciated. Regarding factors that are known to increase the incidence of OA, such as overweight, better information of the general population would indeed be indicated. On the other hand, we also agree that more research is necessary to elucidate the underlying causes of primary OA, probably a complex interplay of genetic and environmental influences.

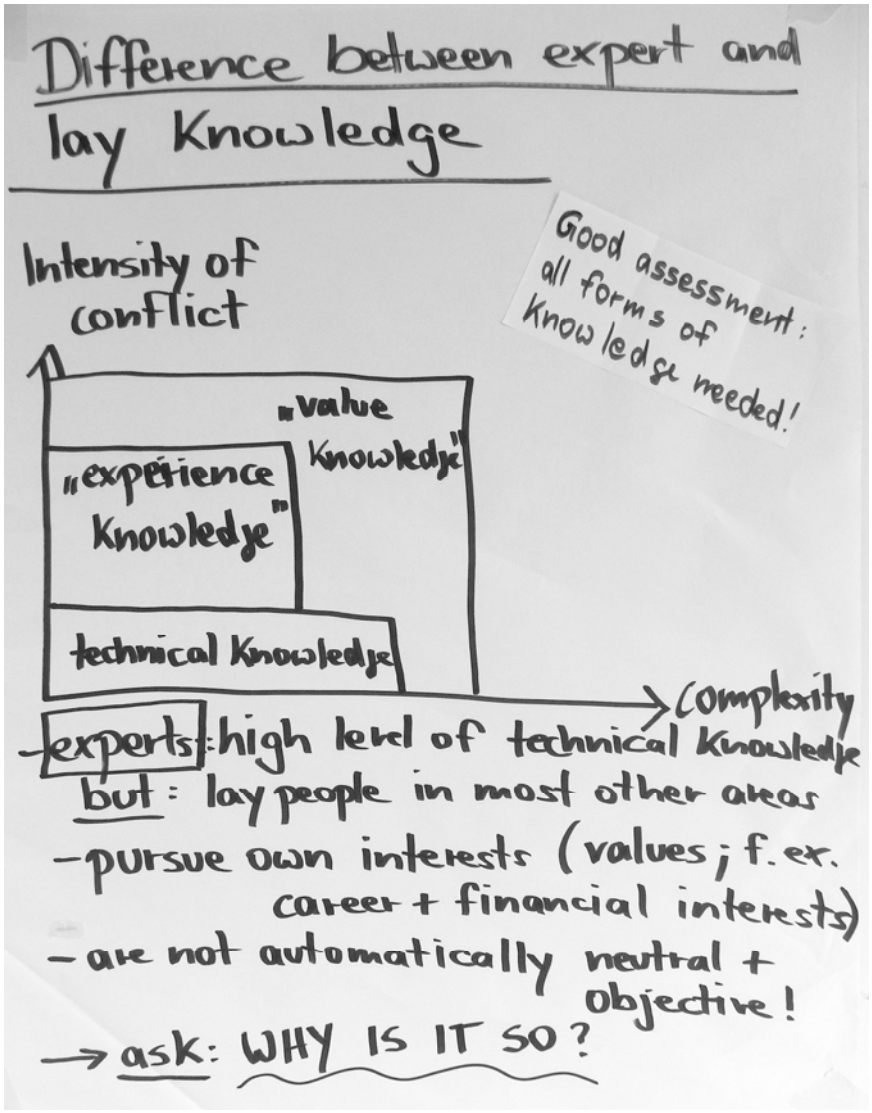
Concerning the focus on a specific patient group, we would like to note that in the early phase of the project the target group is defined broadly, since the feasibility of the general concept is investigated. Depending on the outcome, the target group may be narrowed in the way that certain modules may only be indicated for specific treatment.

Complementary medicine and epigenetic findings should definitely also be investigated, although this would go beyond the scope of GAMBA. Due to the difficulty in standardization and the high variability, it is challenging to perform reliable studies in the field of complementary medicine; in addition, funding is still very limited in this field. Research into epigenetic influences is still in its infancy, but will doubtlessly play a role in the future. In particular, epigenetic studies may provide some insight into underlying causes of OA.

The communication and flow of information between the GAMBA partners, towards the European Commission, and largely also towards the “scientific community” (conferences, publications) is well established and ongoing. We agree that politicians should also be informed early about potential new approaches and concomitant new ethical questions in order to be able to prepare ethical guidelines accordingly. The GAMBA Panels clearly showed us the need for communication of our research towards the general public. We need to consider such or similar dialogues also for future research projects. Finally the patients are our ultimate target group, and research funding is partially dependent on public money.

Dr Sibylle Grad and Prof Dr Mauro Alini, AO Research Institute Davos

Part II: Information on the Lay Panel Process



Poster: Introduction to the panels by project leader Dr Zoeller

1. Concept of the Project

The total duration of the GAMBA "Lay Panel" sub-project was from August 2010 to November 2012. The first nine months involved preparation of the panels including compiling the Manual and Compendium[20]. The first panel held was the Munich Patient Panel in May 2011 and the last were the Citizen Panels in Ireland and Switzerland in June/July 2012. The closing event in Munich took place in April 2012, the Irish and Swiss closing events in November 2012.

1.1 Preparation of the Panels

The first module in the preparatory stage was the researching of scientific and general information for the participants. The German ScienceDialogue Team (see Part III) carried out research in major specialist and lay media (see list in Part III). Using the so-called research database, to which approx. 700 publications were added during the research period, the scientific journalist and chemist Beatrice Lugger, aided and supported by the project team, created the so-called Manual and Compendium, each easy to read in order to be comprehensible for lay panellists and containing the most important information related to the project.

In parallel the programme and the facilitation concept for the three and a half or four-day panels were developed, experts for lectures and hearings contacted (see list in Part III) and the quest for participants for the Patient Panel begun (cf. Chapter 1.4).

1.2 Implementation of the Panels

A lay panel like the Patient Panel or the Citizen Panel is an innovative method of participation designed by the ScienceDialogue team combining elements of the established methods Citizens' Panel or Jury[21] and "Consensus Conference[22]". In the lay panels, over two weekends, interested parties develop a "lay report" on a clearly defined topic, requiring the weighting of social, ethical, cultural, economic, ecological and legal questions. A particular element of the Citizen Panel is the random selection of participants; this prevents participation solely by persons who are highly committed already[23]. This allows for the potential of the "interested but silent majority" to be reached. Many people participate in a lay panel who, unless invited to give a qualified opinion, would hardly even consider taking up a request to participate.

A lay panel carried out by ScienceDialogue must satisfy the following quality criteria:

- **A qualified information base:** Of utmost importance is the multi-perspectivity of information input, for example based on balanced information brochures in lay language (for GAMBA, Manual and Compendium), presentations on opportunities, risks and ethical aspects, a hearing with experts selected by the participants themselves and input developed by the panellists.
- **Openness of results:** Participants must be able to influence the information process by selecting experts and by performing their own investigations, and they alone determine the content of the recommendations.
- **A clear mandate**: From the very outset it is clearly defined what will be done with the results. The researchers are present as partners in dialogue and hear for themselves to the arguments and concerns of the lay panellists. At the public event held at the conclusion of the panel, they and other addressees from the fields of research and politics give their response to the lay report (see part I).

[20] http://www.wissenschaftsdialog.de/index.php/download (in German and English)
[21] http://www.jefferson-center.org/index.asp?Type=B_BASIC&SEC=%7B2BD10C3C-90AF-438C-B04F-88682B6393BE%7D
[22] www.peopleandparticipation.net/display/Methods/Consensus+Conference
[23] However, random sampling was not possible in Ireland since the country does not have valid data available from a residents' register (see Chapter 1.4).

- **Methodical empowerment**: Impartial, experienced and methodically competent facilitators support the participants' capacity to work as a group, strengthen the self-confidence of participants and their ability to assume the functions of lay assessors.
- **Transparency** evolves from informing participants about goals and procedures of the dialogue with its creative leeway and its boundaries. The process is documented openly (on flippcharts/pinboards or via computer and beamer) which supports the process of information gathering and the finding of intermediate results. The procedure of the dialogue is also transparent, i.e. concerning the selection of the participants or the way decisions are reached. The participants of the lay panels develop a so-called "lay report" (refer to Chapter 2 regarding the programme).

The participants of the lay panels develop a so-called "lay report" (refer to Chapter 2 regarding the programme).

1.3 Post-Panel Processing

At the close of each panel, the project team draw up a draft copy of the **lay opinion** using the modules compiled during the panel sessions. The draft is subsequently agreed upon with the participants and approved by the spokespersons.

In Germany the **closing event** took place immediately after the last German panel: Multiplicators from the fields of science, business, politics and society were invited to the "Klinikum rechts der Isar" in Munich to attend the handover of the lay report to the researchers and a representative of the EU on 25 April 2012. At this closing event, the project manager, Katharina Zoeller, gave a presentation outlining the project before the spokespersons of the panels presented the main results and handed these over to the GAMBA consortium. Similar events have also been taking place in the autumn of 2012 in Ireland and Switzerland.

1.4 Selection of Participants

Germany

For the **Patient Panel**, an invitation was issued to interested parties by way of letters to orthopaedic specialists in the Munich area, requesting them to draw the panel to the attention of patients concerned and display project flyers (refer to Part III) in their waiting rooms. In addition, a visit was paid to the Munich group of the German Osteoarthritis Forum, advertisements were run in local advertising broadsheets and press releases sent out, two of these appearing in local advertising broadsheets. Additionally an article appeared in the "MRI News" published by the Klinikum rechts der Isar. Attention was also drawn to the panel by way of notices in shops in the neighbourhood of the clinic. 17 patients (out of 20 registered) appeared on the first day and 16 came back for the second weekend.

For the **Citizen Panel**, letters were sent out to a total of 4,000 people from those suburbs neighbouring the Klinikum rechts der Isar, the addresses taken at random from the Munich residential register. Under strict observance of data protection regulations, these are made available to public institutions like the Klinikum rechts der Isar for purposes of social research. 25 citizens (out of 28 registered) started on the first day, 17 came back for the second weekend.

Ireland

The Irish panels were to a large extent prepared by Christine Ritter in Galway. She undertook the following measures to find participants for the **Patient Panel**:

- Letters to 22 consultants and notices on boards in local clinics
- Link on the Arthritis Ireland website, Facebook Arthritis Ireland, national and regional (Galway)
- Notices on boards in 34 pharmacies, 8 health food shops and 3 libraries in Galway and suburbs and in the drop-in centre of Age Action Ireland

- Radio interview with the director of REMEDI, Prof. Frank Barry (Galway Bay FM radio)
- As a follow-up to this interview, a 3-day appeal to interested patients on Galway Bay FM during the local news broadcast
- Article in the Galway City Tribune "Galway osteoarthritis researchers seek help of sufferers", January 27th 2012
- Article in the Galway Independent (print edition) "Osteoarthritis Researcher looking for insights", February 1st 2012
- Appeal on the NUI Galway website
- Institute-wide e-mail campaign
- Appeal on boards.ie (sub-forum "long-term illness")
- Article on irishhealth.com.

17 patients (out of 20 registered) appeared on the first day and all of them came back for the second weekend.

In order to draw public attention to the **Citizen Panel** and find participants, the following activities were undertaken:

- Letters to 8 patients who were unable to participate in the Patient Panel
- Letters to 30 county councillors and 14 city councillors
- Letters to 25 secondary schools in Galway City and Galway County
- Letters to 20 active retirement groups in Galway City and Galway County
- Letter to the local Green Party group
- Letter to the Literacy and Debating Society NUIG
- Notices on boards in 3 libraries
- Letter to the Galway City Community Forum (galwaycityforum.ie) requesting for publication
- Letters to the Students' Unions NUIG and GMIT => NUIG SU then sent an e-mail to every student and mentioned the Citizen Panel on Twitter and Facebook
- Display of approx. 30 posters campus-wide
- Additional search for candidates via volunteergalway.ie
- Notices on boards in 5 convenience stores close to the university
- Radio interview with the spokeswoman of the Patient Panel, Jacinta Leech, and Mary Murphy, the project leader for Ireland
- Advertisement in the Galway Advertiser.

Out of 20 registered people, 14 people appeared on day one, ten of them staying until the end.

Switzerland

In Switzerland the Patient Panel and the Citizen Panel had to be combined since not enough participants registered for the Patient Panel although numerous marketing activities had been undertaken:

- Publicity measures in practical courses run by the AO Foundation in Davos (150 medical practitioners and medical students)
- Letters to 67 orthopaedic specialists, 65 rheumatologists and 20 physiotherapists in the Zurich area, including follow-up mail or letter
- Posters and flyers in the "Züricher Höhenklinik" in Davos
- Schweizer "Rheuma-Liga" (the major rheumatism and osteoarthritis association in Switzerland): Announcements on the website and circulation of flyers at local meetings and training courses in the Zurich area
- Press releases and phone calls to the major Swiss newspapers in the Zurich area
- Advertisement in a regional advertising broadsheet and a paid article in the "Zolliker Bote"

- Distribution of posters and flyers in public buildings such as day centers for the elderly and leisure centres, in shops and pharmacies
- Contact with doctors personally known to members of the team.

After only 12 patients had expressed their definite willingness to participate, the panel was cancelled. Some of those interested subsequently took part in the Lay Panel three months later.

For the Lay Panel (patients and interested lay persons combined), letters were sent out additionally to 3,300 households in communities surrounding the congress venue of Zollikon near Zurich as well as the repeat of promotional activities in the public sector and at the "Rheumaliga". Nevertheless, on this occasion, too, only 15 people definitely registered. We decided that the panel would go ahead. 11 people appeared on the first weekend and all of them returned on the second weekend.

1.5 Socio-Demographic Data on Participants

Germany
We had 20 registrations for the Patient Panel, 17 people appeared on day 1. One person withdrew after the first weekend for personal reasons. Two participants remained up to the opinion-compiling stage on the last day but no longer wanted to be involved in this. Thus the patient report was compiled by 14 people. Of 28 people who had registered for the Citizen Panel, 25 appeared on the first day. Unfortunately six of them were taken ill prior to the second block (presumably as a result of the very cold February weather in Munich), two were prevented from attending due to job-related appointments at short notice so that 17 people prepared the statement on the second weekend. Altogether 31 people in total drew up the two German votes; one Citizen Panel participant subsequently distanced herself - unfortunately without giving her reasons, despite being asked several times – from the report that had received unanimous approval during the panel session.

Ireland
20 patients had registered for the Irish Patient Panel. 17 appeared on the first day, all of them remaining until the close. For the Irish Citizen Panel we had 20 registrations with 14 people appearing on the first day. Three participants did not come back on the second day (unfortunately without giving their reasons); one further person withdrew for the second weekend for personal reasons so that 10 people compiled the draft report.

Switzerland
For the Swiss Lay Panel (patients and lay representatives combined) we had 15 registrations one week before the panel was due to meet; in the week before the panel convened, two participants withdrew for health reasons. One participant did not show up. At the end of day 1, one participant excused himself from attending on day 2 of the panel because he was in severe pain –prior to the second panel session we all tried to figure out whether it would be possible and expedient for him to rejoin the panel for the second weekend – but it was no longer possible to contact the participant in question. All 11 participants from the first weekend returned on the second weekend. One participant had to withdraw prior to the final report-compiling phase for job-related reasons, but he rejoined the reporting process. Hence the Swiss report was prepared by 11 assessors.

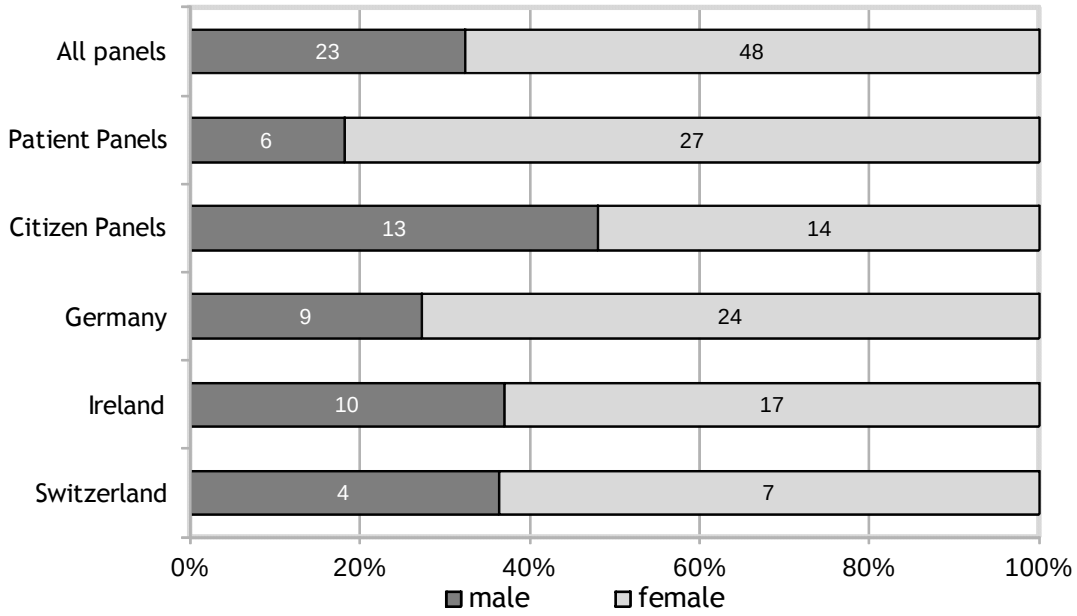
Participants Panels

	Participants	Report-compiling	Questionnaire submitted
Patient Panel D	16	14	16
Citizen Panel D	17	17 (16)[24]	17
Patient Panel IE	17	17	16[25]
Citizen Panel IE	10	10	10
Lay Panel CH	11	11	11
Total	71	69	70

Gender Distribution

Osteoarthritis is an ailment affecting more women than men. This is also reflected in our panels: In the Patient Panels, four out of five participants (81.8%) were females, in the Citizen Panels there was a nearly balanced relationship (13 male/14female); overall a good two thirds of participants (67.6%) were females. Germany had the largest quota of female participants (72.7%) as compared with Ireland and Switzerland.

Composition of Participants in the GAMBA Panels by Gender (All Panels, n=71)



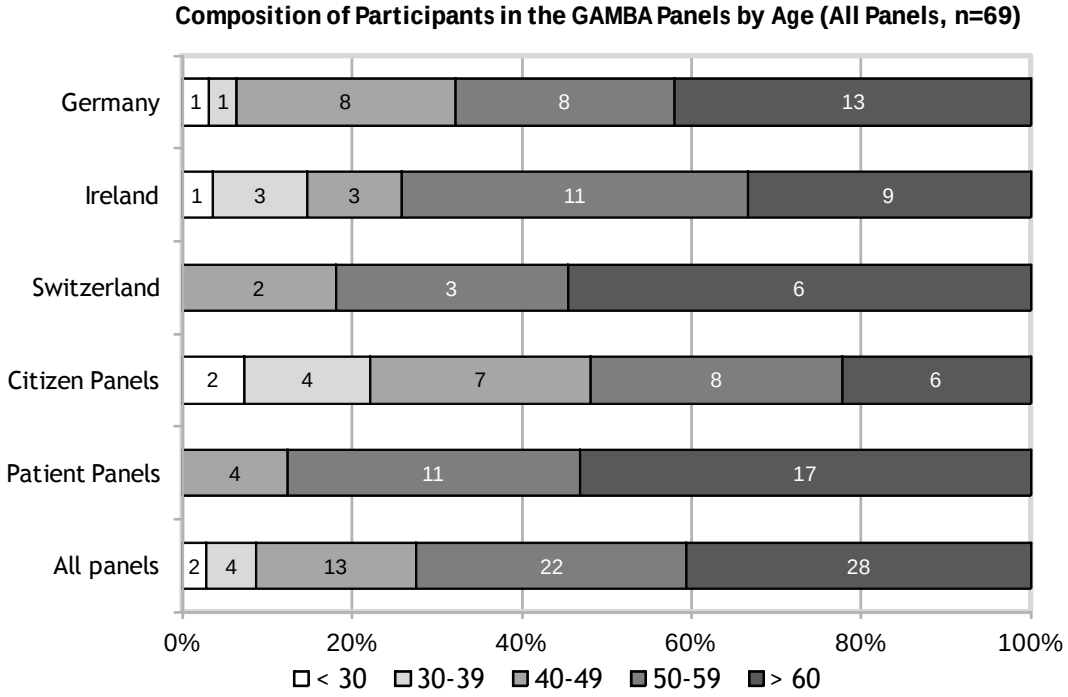
Age Structure within the Panels

Our youngest participant was 19 years old, the oldest 82. Most participants, i.e. 28 or 41%, were over 60 years of age (see fig. following page). In the Patient Panels, more than half of participants (17 people) were over 60 years old, nobody was under 40. In the Citizen Panels most participants were between 30 and 49 years of age; here only six were over 60, two on the other hand under 30 years of age [26].

[24] One female participant subsequently withdrew from report compiling activities without giving her reasons, although she had been involved in drafting the report.

[25] One Irish participant could hardly read and write and hence could not hand in his questionnaire. Due to shortage of time, no other participant was able to assist him, which would also have been difficult due to the need for anonymity.

[26] Two participants did not divulge their age so in this graph there are 69 nominations.



Educational Background of Participants

As is to be expected when dealing with a complicated biological/biochemical subject, the educational background of the participants – at least in **Germany** - was above average: over 60% of the German participants were academics, in the German Citizen Panel almost 80%. Around 40% of the participants in the German Patient Panel have served an apprenticeship.

The educational background of participants in **Ireland** is mere conjecture since the Irish team regarded it as inappropriate to ask about educational qualifications. Upon examination of information on profession (see below), however, it is apparent that the percentage of academics in Ireland was lower than in Germany.

In Switzerland, just under half (5 participants) have an academic qualification/degree, two each have a university entrance diploma (in Switzerland: "Matura") or have completed technical college education. Two people gave no details.

Professions

Participants **in all panels** provided the following details on their professions:

Germany: Consultant (Medicinal Products), Economic Engineer, Flight Attendant, Geologist, Lawyer (2), Legal practitioner (Administration), Nurse, Painter, Portfolio Manager, Product Manager, Psychologist (2), Sales Manager, Student (2),Technical Employee

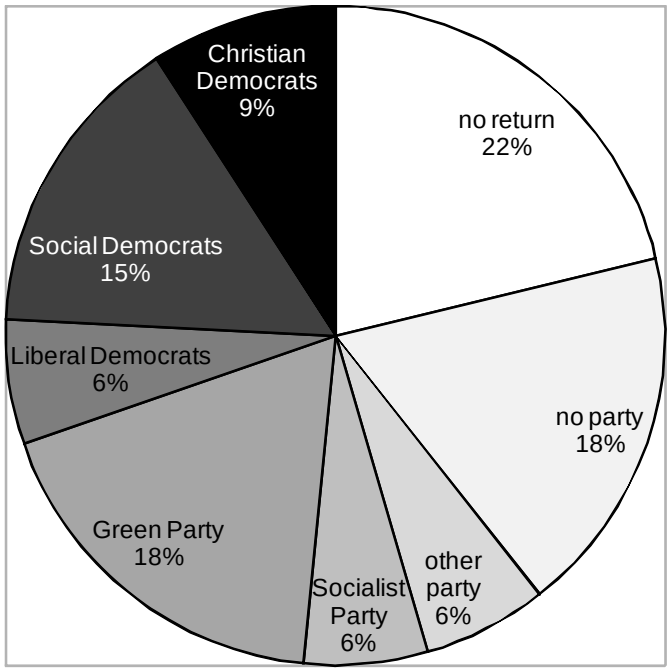
Ireland: Author, Community Development Employee, Laboratory Supervisor, Medical Attendant (3), Medical Student, Medical-Technical Assistant, Nurse (2), Office Employee, Production Manager (electronics), Psychotherapist, Retiree (3), Sales Assistant, Sales Manager, Social Worker, Stay at Home People (3), Taxi Driver, Unemployed (3)

Switzerland: Businessman, Economist, Freelancer (scientific coaching/innovation management), Industrial Engineer, IT Consultant, Medical Attendant, Publicist, Real Estate Administrator, Retiree (2), Sales Manager/Tourist Guide.

Political Views of the Participants

In **Germany** participants were questioned on their party preferences for the next parliamentary elections. The number of non-voters and the %age of those who gave no information here – 15 nominations – is almost exactly as high as the number of those who did state their voting preference (18 nominations). There is much diversity with regard to party preference among those participants who provided information[27]:

If next Sunday parliamentary elections were held, which party would you prefer?
(GAMBA panels Germany 2011/2012)



In **Switzerland** it was not possible to evaluate the results since only 3 of 11 people gave details of their voting preference (all three centre or centre/right). Five participants said they would not go to the polls (this coincides with the number of non-Swiss panellists), three gave no details.

In **Ireland** the Irish organisation team considered it inappropriate to ask about party preference. Instead of that we mentioned the names of figures who can be classified as leaning to the left, centre or leaning to the right[28]. Here 55% of nominations were from people with a leaning to the left, 35% with a leaning to the right and 10% "centre" (list of people in Part III).

Panels Ireland	Leaning to the left	Centre	Leaning to the right
Nominations	29	5	18
Percentage	55%	10%	35%

[27] CDU/CSU: Christian Democrats; SPD: Social Democrats; FDP: Liberal Democrats; Grüne: Green Party; Die Linke: Socialist Party

[28] The question was: On the following people, which 2 or 3 do you identify with and/or respect and/or admire most -- please select your options by circling the relevant name: Tendency "left": Joe Higgins T.D.; Gerry Adams, T.D.; Nell McCafferty; President Michael D. Higgins; Tony Gregory. Tendency "right": Kevin Myers; Michael McDowell; Hildegaarde Naughton; Declan Ganley; Shane Ross, T.D. Tendency "centre": Joe Duffy; Pat Kenny; An Taoiseach Enda Kenny. We listed only the names without the indication of the political tendency. 2.5 names on average were checked here.

2. The Lay Panel Programme in Detail

The panel programme was split into two blocks which took place three weeks apart. The first block served to introduce participants to content and methodology, the second to give a deeper insight as regards content, with experts selected by the participants themselves and intensive discussion on preparation of the modules for the report.

2.1 The First Block

Day 1:

Panels commenced with a brief word of welcome from senior university representatives (in Switzerland by the representative of the AO Foundation). They thanked participants for their interest in GAMBA and expressed their excitement concerning the results of the deliberations and the views of the lay panellists.

In order for participants to then get their bearings regarding the background of the panels, the project leader Dr Katharina Zoeller (Germany, Ireland) or respectively the deputy project leader Maren Schuepphaus (Switzerland) gave a short presentation introducing the project. The participants learned something about the reason for and the background to the project and the purpose of scientific dialogue for setting up a channel of communication with the general public at an early stage. In addition, they were given an outline of the entire course of the project (panels in Germany, Switzerland and Ireland), the planned closing events, the team members and the course the panel sessions would take.

An important element for the formulation of the lay report and for participant orientation were four central questions which the facilitation team introduced at the beginning of the panel meeting and took up on time and again in the course of panel sessions:

- What do you like about GAMBA? What opportunities do you see?
- Which ethical aspects are significant in your view?
- What risks do you see and how should these be dealt with?
- What should the political sector use public money to fund, what not?

The introduction of participants to each other, which is also of importance for the group process, was performed by means of a so-called sociogramme involving two questions. Participants took up position within the room in such a way as to signal

- the extent to which they had concerned themselves with bioethical issues in the past (in several gradations ranging from “never” to “intensively”) or
- the extent to which lay people are capable of evaluating the ethical aspects of new technologies (in gradations ranging from “very easily” to “not at all”).

The facilitator interviewed participants so that they could hear each other’s names for the first time and obtain a clear picture regarding the interests of individual panellists in the panels and the positions they held on the questions asked in the sociogramme.

An introductory presentation on osteoarthritis served to give a detailed illustration of the clinical picture of the ailment, its diagnosis and the therapies currently available – ranging from lifestyle changes right through to state-of-the-art operating techniques and joint replacement. The respective lecturers are listed in Part III.

Then, in randomly arranged breakout groups, participants had the opportunity to collate what in their view were important findings gleaned from the lectures and to pose further questions to the speaker. In this way it was possible to close gaps in understanding, clarify certain issues and gain a more in-depth insight into individual aspects.

Later followed the adoption of the “Panel Rules” (see part III) as well as a digression into the evaluation competencies of lay participants and experts with regard to socially significant issues – in order to define the limits of expert knowledge on the one hand and

to strengthen participants in the adoption of their role as "lay assessors" on the other hand[29].

Subsequently, participants were given a first outline of the GAMBA research project by the GAMBA partners:

- in **Germany** by Dr Martina Anton and Prof Christian Plank, Institut für Experimentelle Onkologie und Therapieforschung (Institute of Experimental Oncology and Therapy Research), Klinikum rechts der Isar, Technical University of Munich (and GAMBA coordinators)
- in **Ireland** by Prof Mary Murphy, Dr Eric Farrell and the Ph.D student Niamh Fahy, REMEDI, National University of Galway
- in **Switzerland** by Dr Sibylle Grad, Forschungsinstitut AO Stiftung (AO Foundation research institute) and Martina Anton, Institut für Experimentelle Onkologie und Therapieforschung (Institute of Experimental Oncology and Therapy Research), Klinikum rechts der Isar, Technical University of Munich.

At the close of each day, in a short feedback session, participants gave facilitation team their feedback on how the day had gone and suggested improvements.

Day 2:

On the second day the individual research team concerned gave an in-depth presentation on the GAMBA project (details of the GAMBA research approach, in particular with respect to the use of stem cells, gene vectors, bio-materials and the concept of temporal and special control). Additionally, the programme included two further presentations on ethics and risks (the speakers on these topics are listed in Part III)[30]. For all presentations participants – in randomly arranged breakout groups - analyzed important findings for use in further work to be done on the report and formulated questions they addressed to the expert. The facilitator first asked the group spokespersons to give a brief description of their findings and then bundled the questions asked by the groups together by content so that answers and discussions could, for the most part, be handled in subject blocks. This permitted a more favourably structured discussion between participants and experts as compared with classical question-and-answer settings.

In the afternoon, participants selected experts for a hearing to be held on the second weekend: They amassed open questions for an appraisal of GAMBA and selected a mix of different experts based on two-page profiles (see Day 3).

The facilitator encouraged participants to form one team for each expert and, with the support of the facilitator, to be solely responsible for questioning the experts. It was only in the German Patient Panel and in the Swiss panel that the facilitation team took over facilitation duties and documentation of expert input at the request of the panel.

All those open questions brought up by the participants – both during the first block and any supplementary questions submitted between the two blocks – were structured by the facilitator with the competencies of the chosen experts in mind, and these questions were passed on to the experts in order for them to prepare their responses. In addition to overlapping questions addressed to all experts, the facilitator also allocated some questions to several experts when these could be answered from different specialist angles – i.e. in order for participants to form a picture of possible differences in viewpoint, determination of focal points or the way in which individual experts make their

[29] see flipchart copy at the beginning of part II.

[30] In Ireland these presentations took place on the very first day due to the changed timings (Saturday and Sunday from 10.00 to 18.00 hours instead of Friday evening and Saturday).

evaluations. In Ireland, from all the questions submitted, participants themselves selected those they wanted to ask individual experts to answer.

Furthermore, participants were given the opportunity to deepen their insight into individual aspects of GAMBA relating to ethical and social issues prior to the second panel block by "ambassadorships". To this end they were given a list of links to "lay-friendly material" (see Part III) and were also able to do their own supplementary research. The facilitator volunteered support here (by telephone, per e-mail or in person) although this was not taken up on.

Laboratory Visits

Participants of the German and Irish panels had the opportunity to have a look at the GAMBA scientists' research laboratories[31]. They were given a short briefing on the laboratory visit including safety requirements by Dr. Martina Anton (Germany) and Dr. Eric Farrell and Niamh Fahy (Ireland). Additionally researchers had prepared laboratory experiments showing cells in differing stages of growth.

German Citizen Panel participants in the laboratory

2.2 The Second Block

The **second block**, in addition to the hearing, concentrated on the preparation of evaluations, opinions and suggested formulations for the lay report.

Day 3:

First of all – again via sociogramme – a tie-in was made with the first weekend. The objective was to encourage exchanges between participants about what they had (not) liked about the first weekend and why. Then the facilitator interviewed participants in order to "dig deeper". In a second step, participants were asked, for example, for feedback on how secure they felt at present about their own ability to form an opinion – and what might be required to assist them in being able to form an opinion for themselves.

Those participants who had prepared an ambassadorship presented this to the panel (German Patient Panel, Irish Panels) or discussed their results in work groups (German Citizen Panel). These were used to formulate initial aspects on GAMBA for the report.

[31] In Switzerland, this was not possible as the panels took place in Zollikon near Zurich while the laboratories of the AO Foundation are in Davos.

Then the hearing with the experts participants had selected took place. Here the facilitator reacted with flexibility to the interests of the participants and, for example, issued invitations to six instead of the three to four experts intended to attend the Patient Panel. A list of the experts selected by the panels is to be found in Part III.

Day 3 closed with the evaluation of the content of the hearing.

Day 4:

The fourth and final day was reserved for in-depth discussions on the issues discussed as well as an evaluation of the GAMBA topics, with lay panellists preparing text modules on the opportunities, risks, ethical and other aspects of GAMBA.

At the beginning of this last day, the facilitator asked participants in some panels (the German Citizen Panel and Irish panels), simply to change their perspectives and to give some thought to what person within the GAMBA project environment they would like to be: The "role-play" revealed that there are differences of interest, preferences of opinion and future expectations with respect to **GAMBA** and led to an exchange of views among participants.

The process of drafting the report began with an evaluation phase in which participants, on their own or in pairs, evaluated all material, results and information available so far: This led to the generation of notes from each participant concerning points they considered to be of importance for inclusion in the chapters on Opportunities, Ethical Aspects, Risks and Framework Requirements which were collated and structured in the group work that followed.

The objective of the final work phase in breakout groups was for participants to develop their keywords into concrete formulations and recommendations, the intention being to elaborate the participants' opinions or the spectrum of opinions as well as the content of and arguments for their recommendations and demands, thus developing a draft for the plenary assembly. Here the facilitator made sure that, for every chapter, one participant continued to work on the same chapter to guarantee a transfer of results from the first group to the second[32]. All other participants switched at random with the result that each chapter was developed by around half of the participants. At the conclusion of the breakout group phase, participants studied a synopsis of the results set out on pin-boards and had the opportunity to use red-dot stickers to signal the need for clarification and/or the existence of differences of opinion on suggested formulations.

In the plenary assembly the facilitator called up these marked cards, in order to first of all clarify why these stickers had been added – and then either to make a consensual amendment to the formulation or – should agreement not be possible - to document dissent within the group. A flip-chart record was kept of the discussion. One participant in the German Patient Panel had a different opinion from the rest of the group on one point[33]; her views were documented in a footnote in the report. Otherwise all of the groups reached a consensus in approving their report.

[32] In Switzerland, due to the small size of the total group and their capacity to work, the subjects of "Opportunities and Ethics" and "Risks and Framework Conditions" were initially prepared in parallel in two breakout groups in each case. Then the group discussed and approved the subjects "Opportunities" and "Framework Requirements" in the plenary assembly. The subjects of "Risks" and "Ethical Aspects" were dealt with in work groups but without remixing the composition of participants.

[33] She saw no need for the presence of lay participants in the ethics committees (see comments of German Patient Panel in Part I).

After low-key celebrations and the reimbursement of expenses, panellists elected two spokespersons (and deputies) for each panel to complete the lay report and hand it over to the researchers at the closing event. In addition, they completed a final evaluation questionnaire. The panel sessions came to a close with a perspective on final editing of the report and coordination of this with participants, the joint closing event for the Patient Panel and the Citizen Panel with hand-over of the report accompanied by short statements.

3. Panel Evaluation from the Viewpoint of Participants

Each participant was given a questionnaire for evaluation of the lay panels at the end of the second block with time to complete this questionnaire. The questionnaires for the German panels were also completed by those participants who did not want to participate in the reporting process (two members of the Patient Panel) as well as the participant from the Citizen Panel who distanced herself retrospectively from the Citizen Panel without giving reasons for doing so. Thus, in total, 33 people from Germany completed the questionnaire. In Ireland there was one participant who could neither read nor write; since completion of the questionnaire was supposed to be anonymous, none of the other participants was able to assist him - as had usually been the case during the panel sessions. Here we have 26 questionnaires. In Switzerland all 11 participants completed the questionnaire, thus **70 questionnaires** (from 71 participants in total) were available for evaluation.

3.1 Motivation for Participation

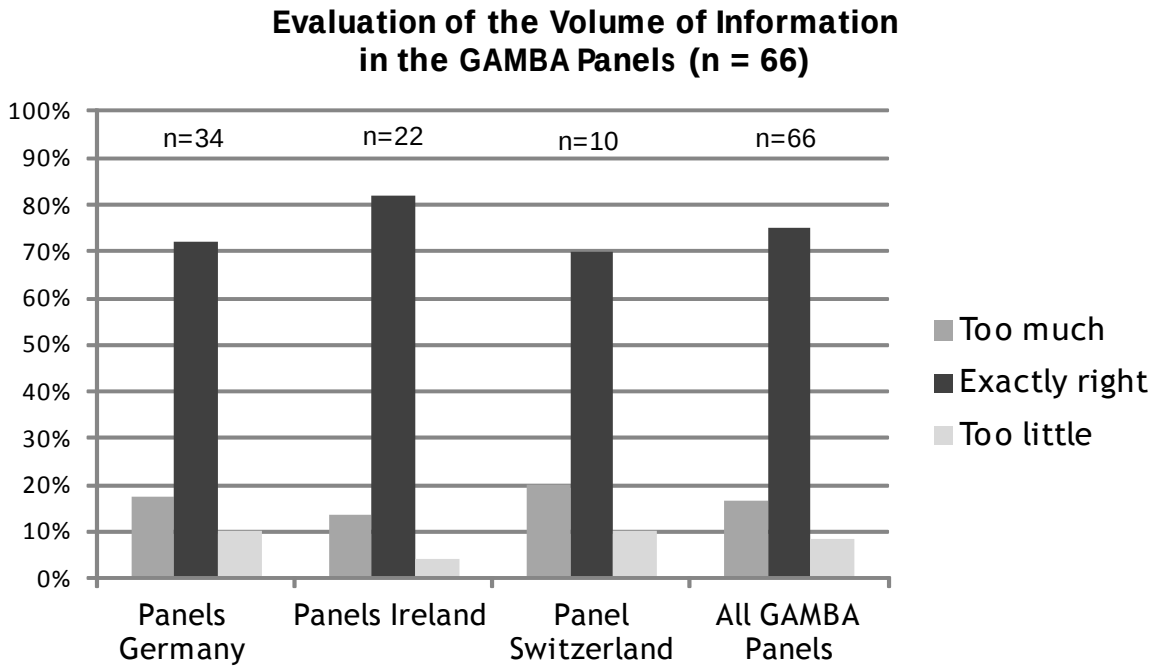
In the case of the (open) question regarding participant motivation for the **Patient Panels**, in first place was an interest in learning about the illness and the potential opportunities of a cure: “Interest in a cure for osteoarthritis because I am a sufferer myself” or “Interest in possible therapies for the future”. One Irish patient said: “I had nothing to lose and a great deal to learn”, another said: “I wanted to make my contribution to the development of a new treatment”. One person also had a very concrete interest in patient participation, another in “co-determination/helping to shape policy”.

In the case of the **Citizen Panels**, the centre of interest was gene and stem cell therapies: Mentions here ranged from “curiosity” and “importance of the issue” to “interest in healthcare”. Some participants also specifically mentioned the issue of ethics as a reason for their participation. Just as important was contact with researchers (“How do scientists think and communicate?”). Mentioned in addition as motives for participation were “the chance to practise a certain degree of co-determination”, “having a voice” or “the once in a lifetime opportunity as a member of the general public to be asked my opinion early on”, also described as “performance of civic duty”.

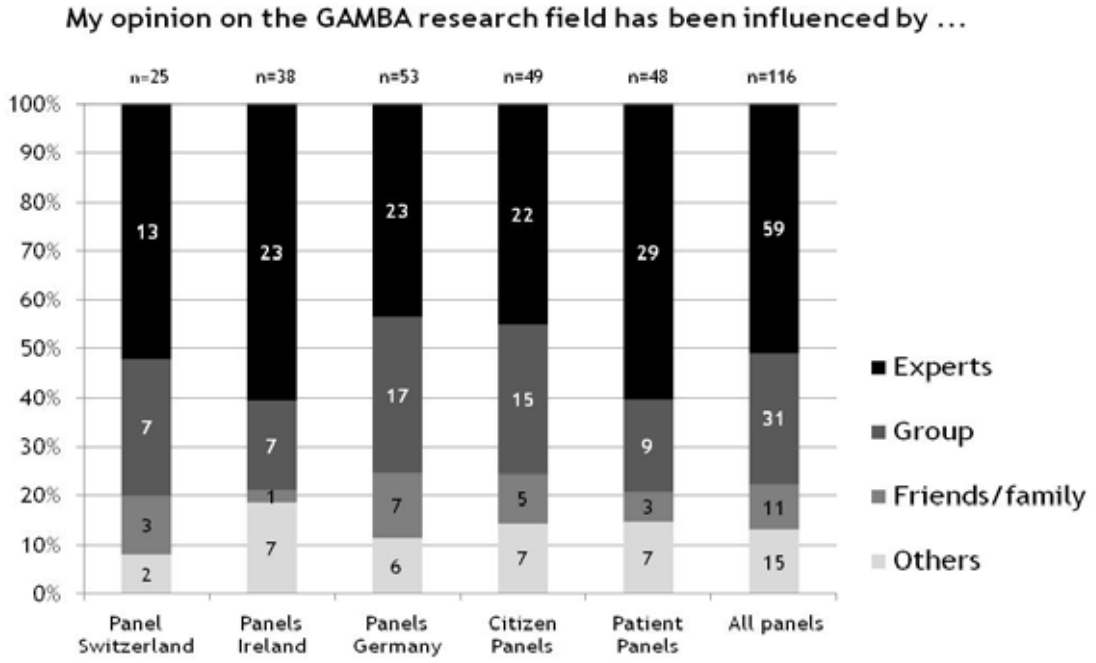
3.2 Evaluation of Dialogue Content and Working Method

With respect to the **adequacy of the volume of information provided in helping participants to form an opinion,** 75% of panellists (49.5 nominations[34]) were of the opinion that they had been given “exactly the right amount” of information. 11 people (17%), the majority of these patients, thought there was too much information. There were 5.5 nominations (8%) for “too little information”. 82% of the Irish rated the volume of information provided as adequate; the highest percentage of all panels (see graph following page).

[34] Some “ticks” on the evaluation sheet – intentionally or not – were placed between two points on the scale, resulting in “half marks” being given.



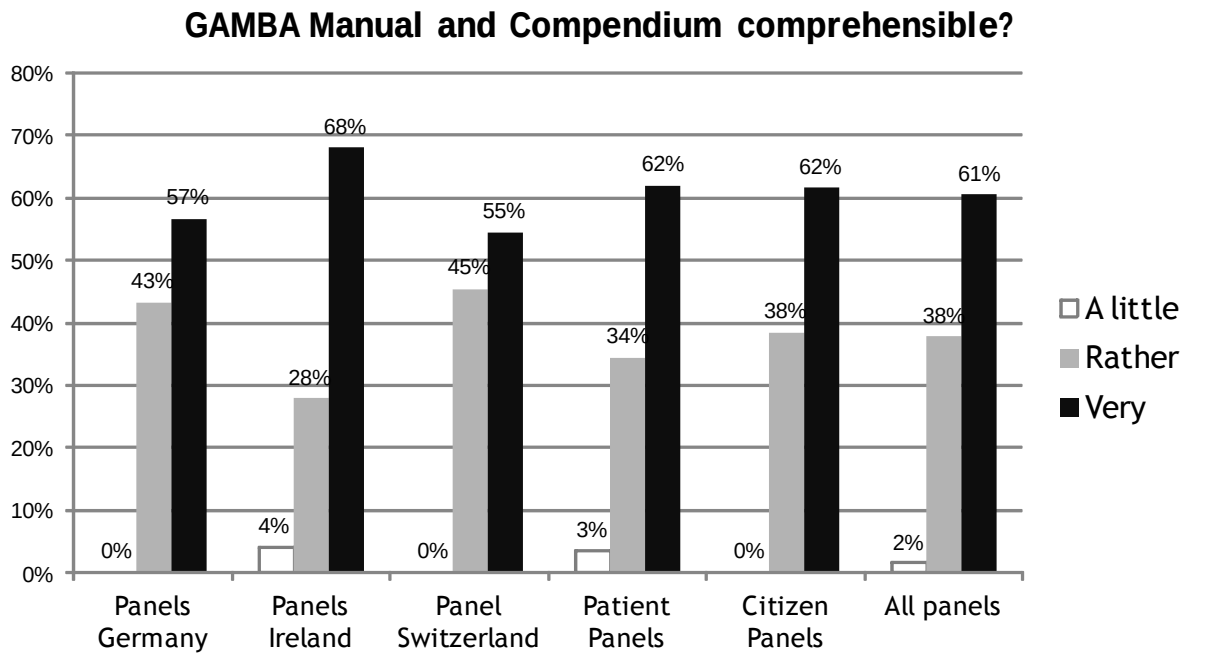
The **position held by participants with respect to GAMBA** has been influenced above all by the experts (51%) and by the group itself (27%) (multiple nominations were possible here). Other influences were through "conversations with friends/family" (9%). Additional factors mentioned as influencing participants (13% of nominations) included "Manual", "individual panellists", "other sources of information such as the Internet" and "personal dealings with the issue". What strikes is that patients (60%) feel that the experts have had a greater influence on them than citizens do (45%)[35]. The Irish participants (60%) judged themselves to be influenced more by the experts than the Swiss (52%) and the German lay panellists (43%).



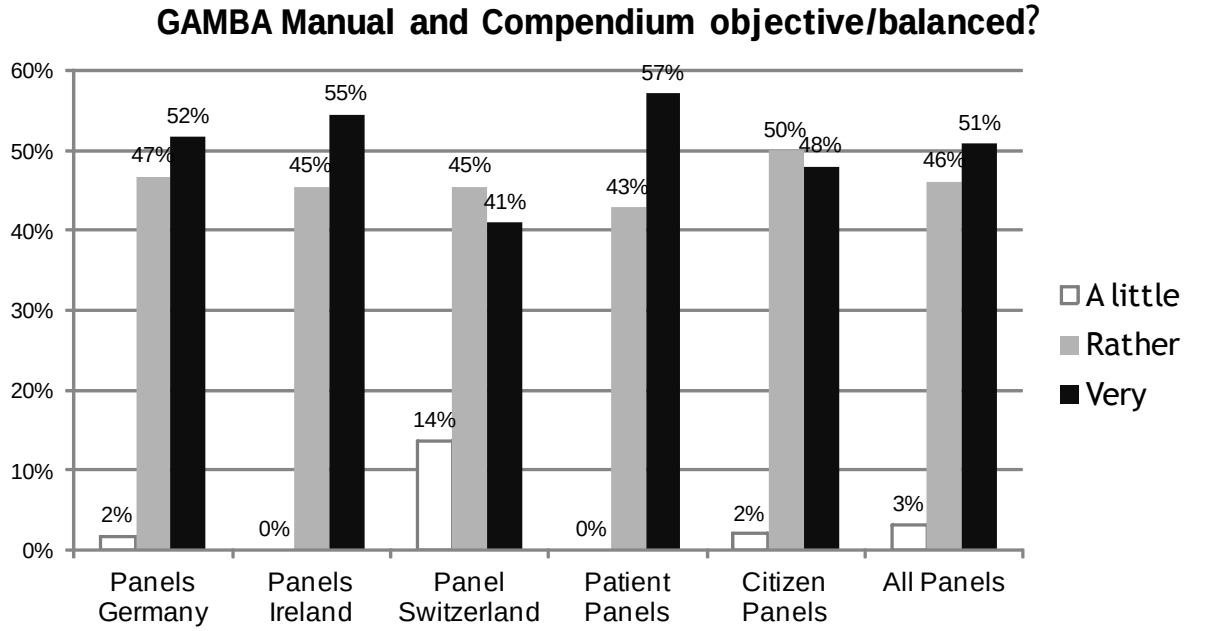
[35] The information for Patient and Citizen Panels respectively – **including for the following graphs** – applies only for Germany and Ireland since a combined panel was held in Switzerland.

Evaluation of the Information Brochures

The information brochures "**Manual and Compendium**" were sent to participants two to three weeks before panel meetings commenced. The majority of participants found the brochures "very" (61%) or "rather comprehensible" (38%), with Ireland achieving the best results here with 68% of nominations for "very comprehensible"[36].

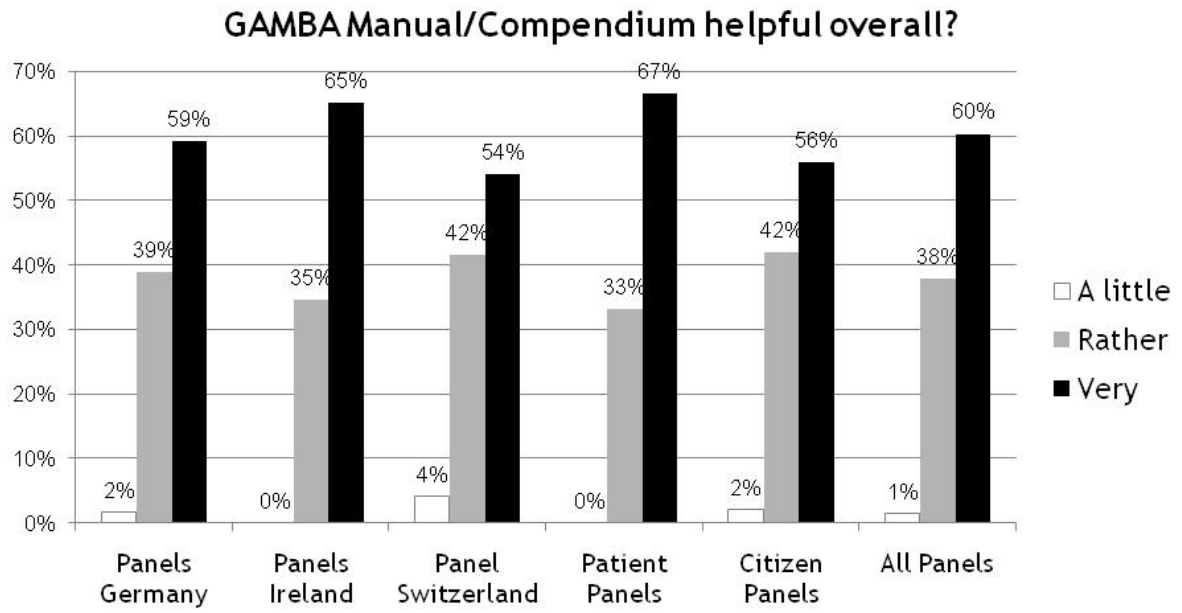


The majority of lay panellists found the information brochures also "very" (51%) or "rather objective/balanced" (46%). Here, too, all countries achieve more or less similar results, only in Switzerland there were 1.5 ticks (14%) for "balanced a little".



[36] The sum of some columns can be more or less than 100% due to rounding differences.

60% of participants described the brochures as "overall very helpful", 38% thought they were "rather helpful". One vote in total (0.5 votes each from the German Citizen Panel and the Swiss Lay Panel) was given to "a little helpful". About two thirds (67%) of the patients found Manual and Compendium "very helpful" compared to 56% of the citizens. Of all countries, the Irish panellists judged the brochures most helpful (65% "very helpful").

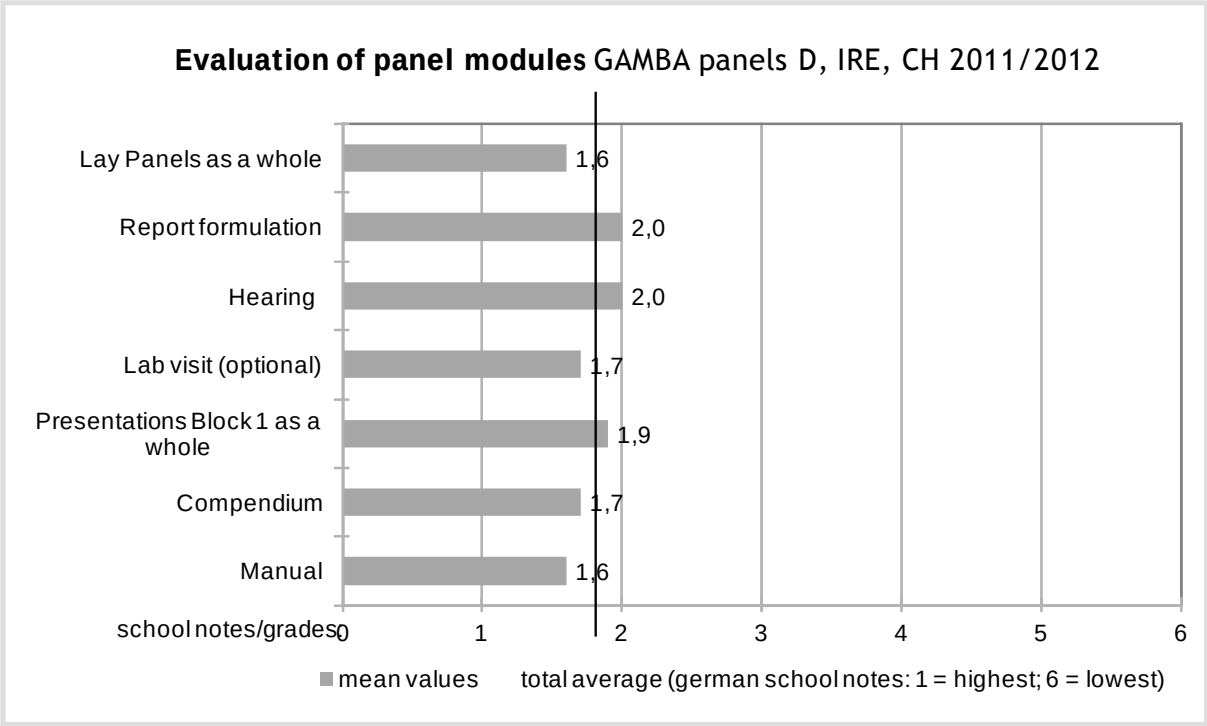


The **work units for the panels** were rated using German school grades (1 = highest, 6 = lowest)[37]. Here participants predominantly gave the grades 1 and 2: 31 participants gave the lay **panels as a whole** the grade 1, 27 the grade 2, grade 3 was given six times, resulting in an average grade of 1.6. **Manual and Compendium** got average grades of 1.6 / 1.7. The **laboratory visit**[38] was likewise predominantly given the rating "very good" averaging in 1.7 (see graph following page).

The **presentations** on the first weekend were predominantly rated as "good" (27 nominations); there were 22.5 votes for "very good" and 9.5 "satisfactory" votes. Two participants felt the quality of the presentations to be only "adequate" (grade 4 – average: 1,9). 19 lay panellists rated the **formulation of the report** as "very good", 32 as "good", grade 3 was awarded eight times, grade 4 on four occasions (average: 2.0). The **hearing** achieved an average grade of 2.0 (19 times grade 1, 32.5 times grade 2, 8.5 times grade 3, four times grade 4), although one participant awarded a grade 6 without giving his reasons for doing so.

[37] In Switzerland "6" is the best school grade but the grades were reversed for the evaluation to achieve standardization.

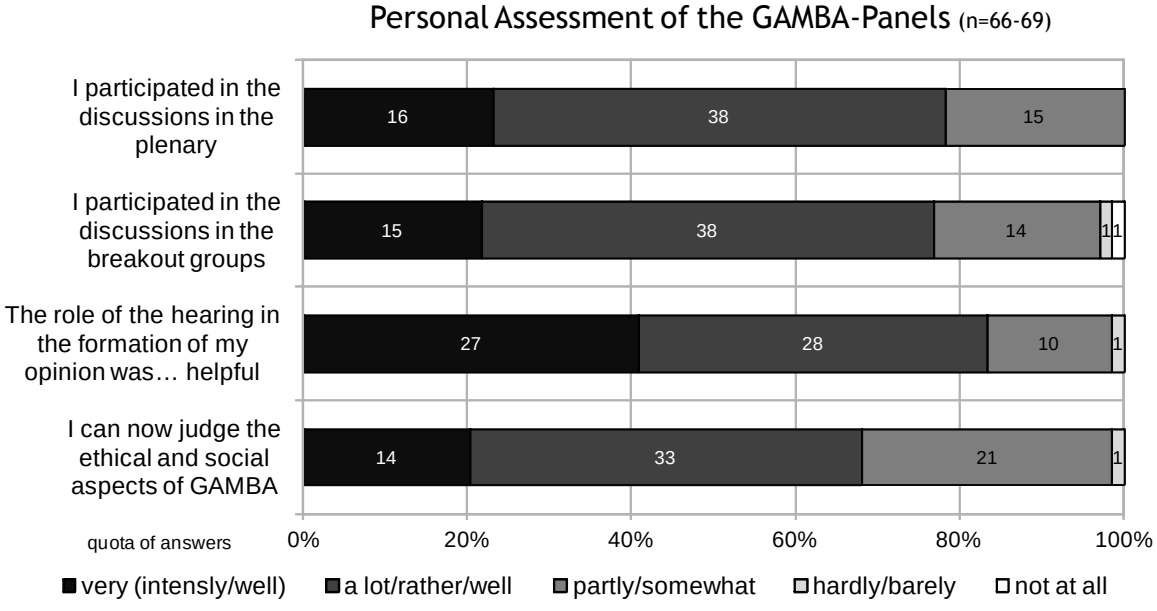
[38] The laboratory visit could not be offered in Switzerland since the AO Foundation is located in Davos but the panels were held in Zollikon near Zurich. In Germany some panellists did not participate in the laboratory visits which were offered as an option between the two weekends.



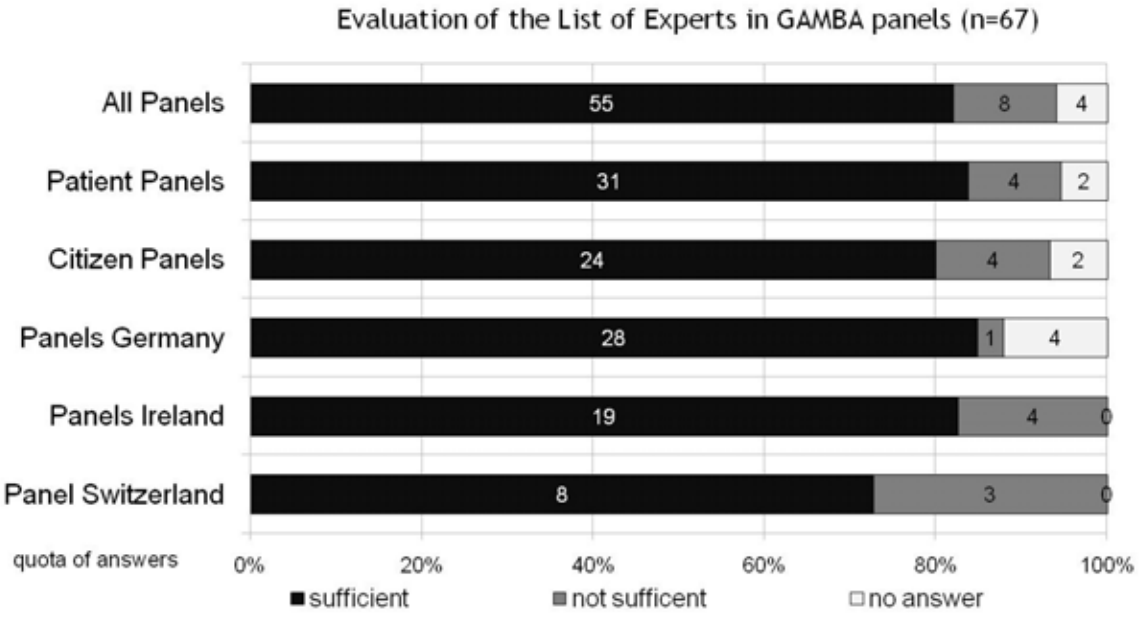
As far as **participation in discussions in the group** as a whole (plenary) is concerned, more than half (55%) participants stated that they had "participated a lot"; 23% had even participated "very intensely", 22% had "participated partly". **In the breakout groups**, participation was as follows: 22% of the panellists said that they had "participated very intensely", 55% had "participated a lot". 20% felt they had "participated partly", one each checked "hardly" and "not at all".

With almost 41 % an equal share of respondents considered the **hearing** to be "very helpful" to them in forming an opinion, 42% found the hearing "rather helpful", 15% checked "somewhat helpful". One person judged the hearing as "not very helpful", nobody found it "not helpful at all".

At the end of the dialogue, 48% of respondents were of the opinion that they could now judge the **ethical and social aspects of GAMBA** "well", around20% are of the opinion that they could even award the rating "very well". 30% were for "somewhat", one respondent said he/she could rate these aspects "barely".



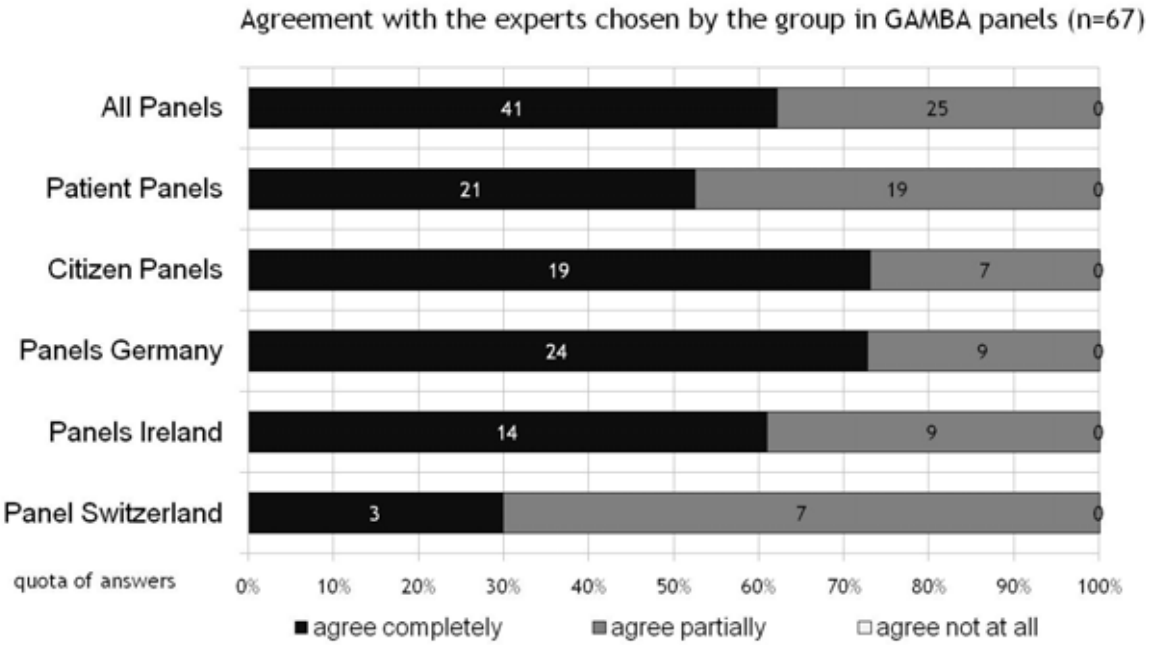
Overall 82% of participants (55 nominations) found the number of experts to choose for the hearings (see Part III) "sufficient"[39]. Here, too, the quota in Germany and Ireland is over 80%. Those who checked "I would have liked to hear additional speakers" mentioned among others: a representative from the field of politics, an additional ethics specialist, someone from the field of complementary medicine, a nanotechnology expert, a financial expert, a representative from the field of commerce, an expert on social aspects, an expert on pain therapy as well as on other osteoarthritis treatment methods.



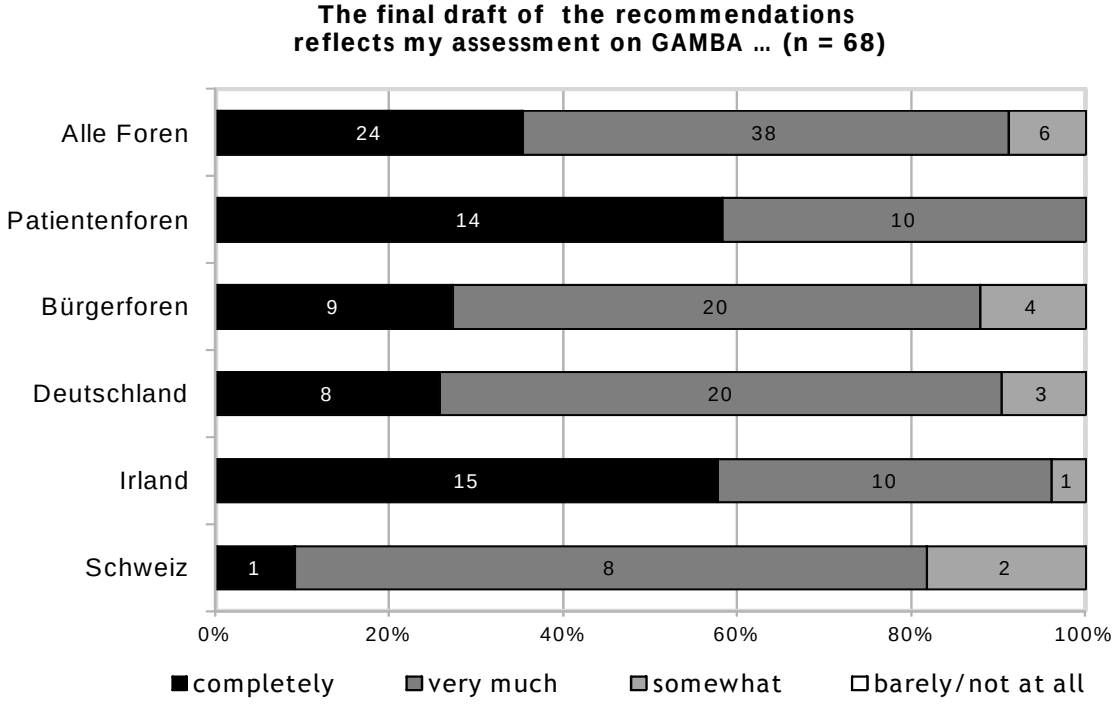
62% of participants (41 nominations) "agree completely" with the selection of the group for the hearing, 38% (25 nominations) "agree partially" (see fig. following page). The German participants and the citizen panels were the most satisfied with the selection of the group (73% "agree completely"). With patients, only just over half of participants agree completely with the selection of the group, in Switzerland only 30% (seven nominations)[40], the rest nominated "agree partially". Here, nobody checked "agree not at all" (see graph on following page).

[39] Unfortunately, in spite of great efforts, we were unable to cover all sectors in all countries since the experts had to make themselves available to the hearings although they could be informed only three weeks in advance whether they had been selected to take part. The list of experts from the individual countries is to be found in Part III. **Our thanks again at this point go to all the experts who made themselves available to the Panels.**

[40] The Swiss participants, when asked by the facilitator immediately after the selection process, expressed agreement with the selection of the group – the fact that the evaluation ex-post is a great deal worse presumably relates to the very divergent evaluation of the four experts.



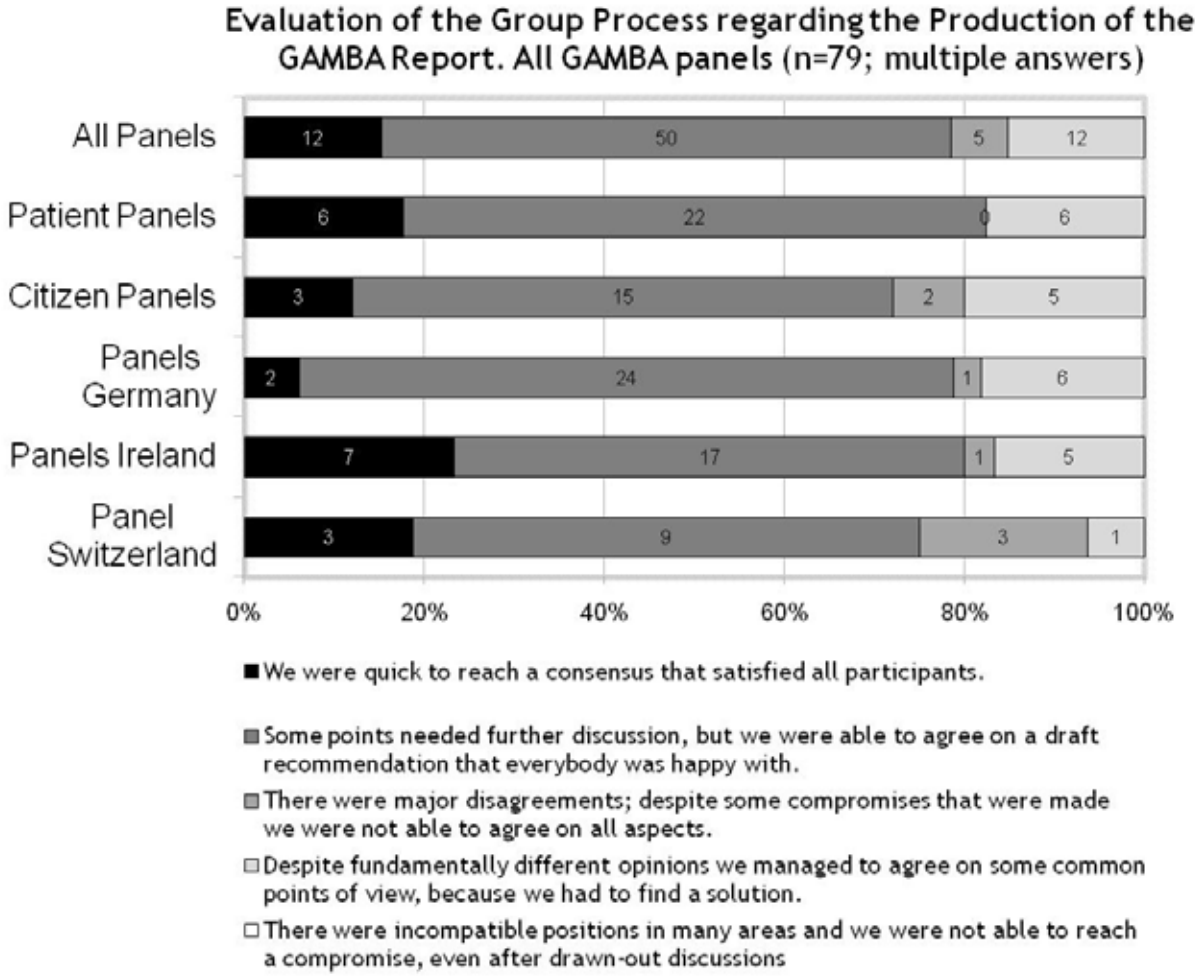
Most participants **feel the draft report reflects their opinions**: 35% (24 nominations) checked "completely", 56% (38 nominations) "very well" and 9% (6 nominations) "somewhat". Nobody checked "barely" or "not at all". The patients and the Irish panellists identify themselves most ("completely") with the draft report, at 58% each.



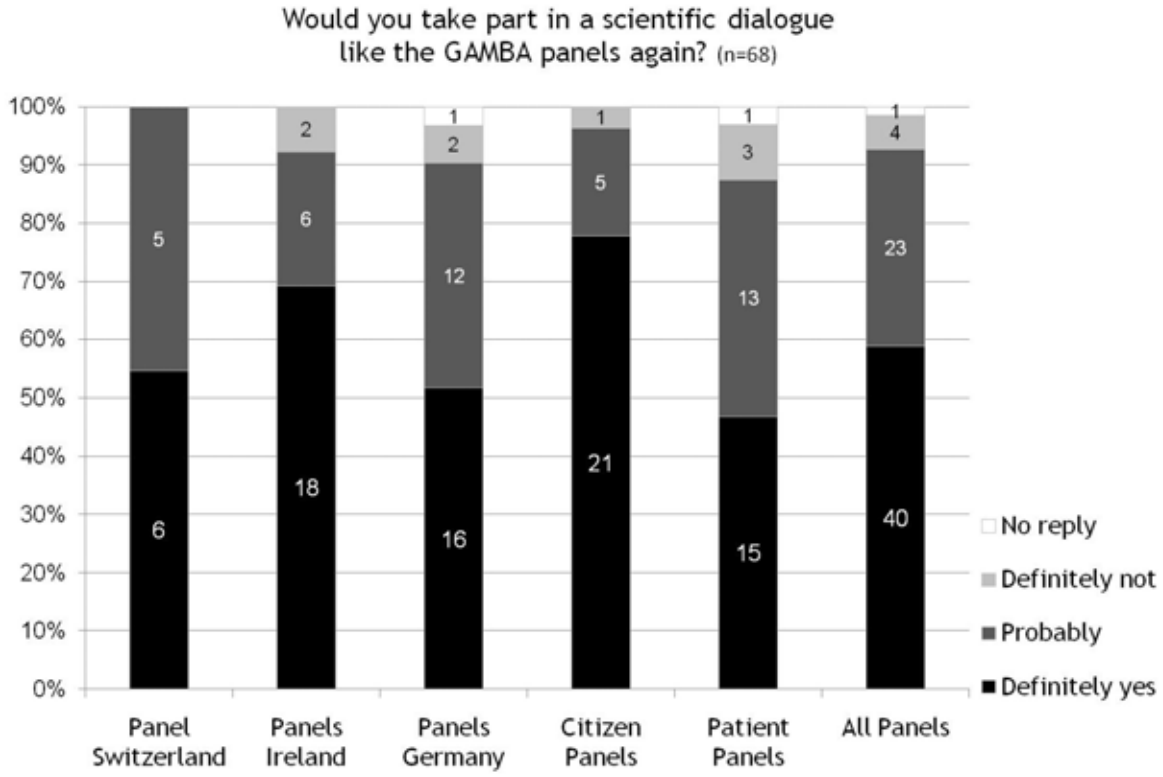
More than three quarters of nominations[41] reveal satisfaction with the **process of drawing up the draft report** (see graph on following page): "We were quick to reach a consensus that satisfied all participants" (15%) or respectively "Some points needed further discussion, but we were able to agree on a draft recommendation that everybody was

[41] Some participants checked several options here.

happy with" (63%). 15% of crosses are for "There were major disagreements; despite some compromises that were made we were not able to agree on all aspects". Five crosses (three of them from Switzerland) were made against the assertion that "Despite fundamentally different opinions we managed to agree on some common points of view, because we had to find a solution". Nobody checked the statement "There were incompatible positions in many areas and we were not able to reach a compromise, even after drawn-out discussions". By comparison, the patients, at 83%, are more satisfied with the result than the citizens at 72% (check against "quickly reached a collective result" or "after need for discussion … in agreement on a recommendation satisfactory for everyone").

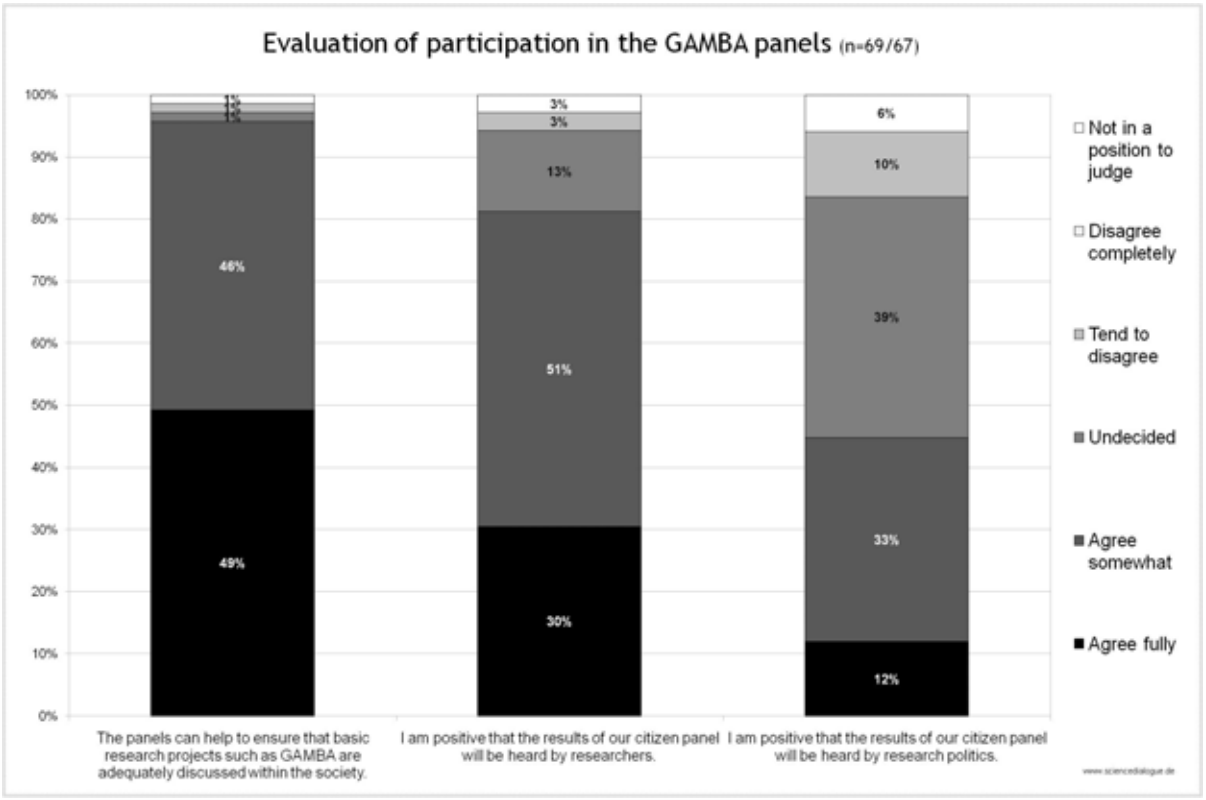


In reply to the question of whether they would **again participate in a scientific dialogue** like the GAMBA panels (see graph next page), 59% answered "definitely yes", 34% "probably". Four people (three of them patients) indicated "definitely not", one patient gave the reason "too challenging / does it make sense?". Citizens (78%) are more convinced than patients (47%) that they would want to take part in a scientific dialogue on a future occasion - which is presumably due to the problems caused to patients by their osteoarthritis (i.e. joint stiffness after a longer sedentary period, or a lower level of physical resilience) or due to the older age of the patients. In a comparison of countries, the Irish panellists are most convinced that they would want to take part in another scientific dialogue: all 10 members of the Irish Citizen Panel would want to participate again.



Asked for **reasons for renewed participation** panellists mentioned that the panel had been "very informative", that panellists "had learned a (very) great deal", that they had "an interest in future research" and "that it had been fun and had provided fresh food for thought". As well, the panel had been a "pleasant change" and provided "informative brain calisthenics". One participant believes: "Everyone has a responsibility to support scientific achievements and to see that they are understood by non-scientists", another says: "I found the whole process fascinating". Some participants also highlight the fact that dialogue of this kind "is important from a basic democracy viewpoint" or that "civic participation is important" and that "I have the feeling that I can contribute further to a scientific debate".

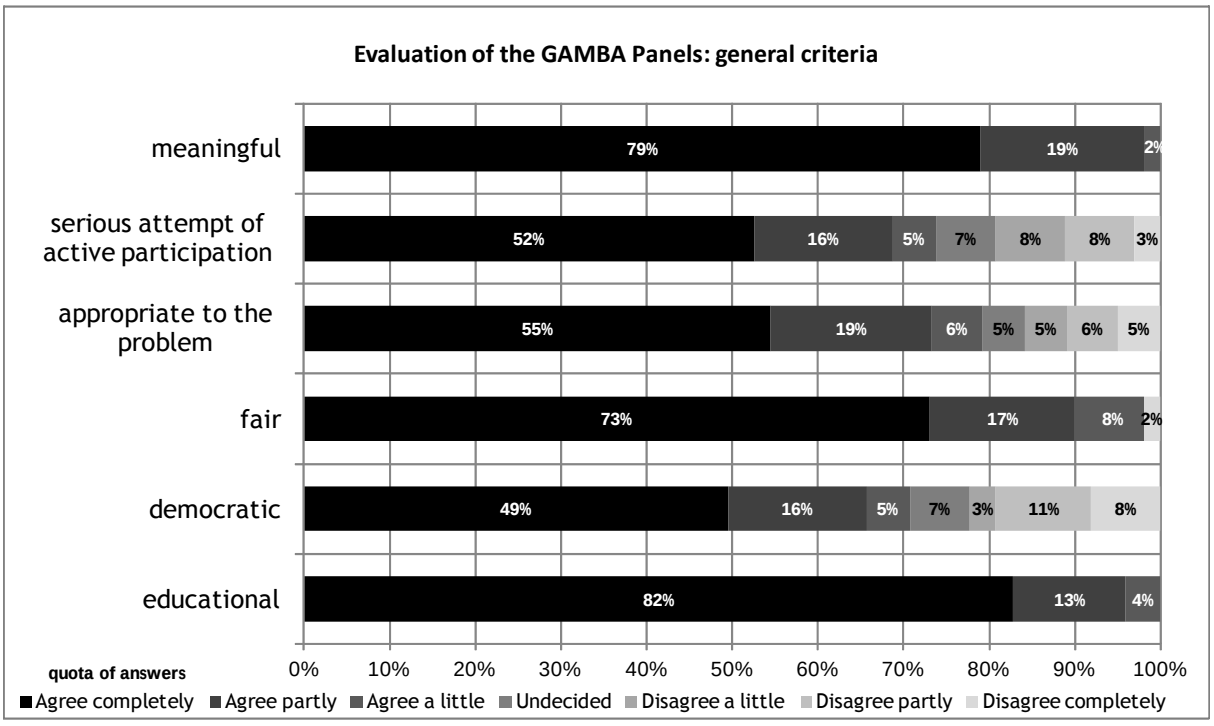
When questioned on the **meaningfulness of the panels** in contributing to discussion within our society, 95% hold the view that "the panels can help to ensure that basic research projects such as GAMBA are adequately discussed within society" (49% "agree fully"/46% "agree somewhat"). Participants are more sceptical about whether their concerns are heard by the researchers: 81% agree with the statement "completely" (30%) or "somewhat" (51%) that "I am positive that the results of our Panel will be heard by the researchers", 13% are undecided, 3% "tend to disagree". Most sceptical panellists are regarding the statement that "I am positive that the results of our Panel will be heard by research politics": 45% "agree fully" (12%) or "agree somewhat" (33%), 39% are undecided, 10% "tend to disagree". Nobody checked "disagree completely" (see graph next page).



3.3 Overall Evaluation

When asked about overall evaluation of the panels, all respondents described these as "meaningful" and "educational" . 98% of participants describe the lay panels as "fair". 80% of the participants thought that the panels were "appropriate for the problem". 74% believe the panels to be "a serious attempt of active participation"; however, 20% of participants had serious doubts regarding co-determination and checked "play ground"[42]. 71% of participants consider the panels to be "democratic"; 23%, however, saw the panels as "authoritarian/undemocratic" (as a counter-pole to "democratic"); here, time pressure was the point most critizised. And apparently we could not please everyone: questioned on what they had not liked about the panels, some even commented that discussion had in part been "too excessive" and verbose speakers "had not been brought to a halt" (see graph next page).

[42] It is not, however, clear to what extent lay panellists had a negative understanding of the term "play ground" since many who had otherwise given the panels a very good rating marked this option.



When questioned about what **they had particularly liked about the lay panel**, participants mentioned first and foremost the dialogue itself, the information, the atmosphere/teamwork, the organisation/facilitation and the fact that they had been taken seriously:

- **Dialogue**: "The dialogue with medical practitioners, researchers and lay participants"; "meetings with scientists", "discussion with experts" and "the very patient and informative researchers"; "speakers and researchers (were) frank and represented different opinions"; "be able to disagree and arrive at a consensus".
- **Information**: "Manual and Compendium"; "the hearing"; "we were given very good and comprehensive information"; "the diversity of information/comprehensive information"; "educational regarding stem cell therapy"; "the competence of the specialist lectures and the diversity of the experts".
- **Atmosphere/teamwork**: "The open discussion, the fairness in dealing with each other"; "pleasant, friendly, respectful atmosphere", "the good collaboration of everyone concerned", "the group process" or "good group dynamics"; "wonderful group"; "we respected each other's views"; "the collaboration with each other's opinions to form a consensus".
- **Organisation/facilitation**: "Professional facilitation", "good organisation"; "constant involvement of participants via diversified activities"; "well coordinated"; "very professional"; "very well organised and hosted".
- **Being taken seriously**: "Our views and opinions were taken seriously"; "participants were given value to their opinion"; " "the feeling that I am contributing in a positive way to GAMBA research"; "17 people from all walks of life who had never met before came together and produced this document".

Participants **did not like**

- **Time pressure**: "The time pressure we were under in parts"; one participant evaluates the panel as "over-loaded"; "not enough time"; "days too long";
- **Difficulties of understanding**: "Some people came with expectations of getting something different out of it" or "had no clue as to what the exercise was about";
- **Problems with information supplied**: "The abundance of information"; "too over-loaded"; "too many speakers", but also: "even more perspectives"; "lack of financial information";
- **Group dynamics aspects**: "Dominant fellow patients"; "the constant interference of a co-patient"; "difficult and passive participants";
- **Ineffective discussions in some cases**: Several people mentioned "windmill discussions" and the fact that "some speakers were not interrupted in their flow"; "There was a tendency to stray off topic"; "ineffective and too much group work".

Questioned on **recommendations for the future,** participants wish, among other things, for:

- At the start: Make sure all panellists do really know why they are here
- Reading assistance[43] for the Manual and Compendium
- More presentations by experts
- Videos of presentations by experts to enable these to be viewed over again
- Advance videos of experts for hearings to aid selection
- More time for presentations
- More work groups
- Encourage panellists to explore more between weekends
- Limit time allowed for speaking in discussion groups, tighter discussions
- More creativity techniques, more open methods
- Fewer organisational instructions
- More time but shorter days, "toning down"
- More specific participant selection, perhaps by testing ;-)

However, some also think: "Do something similar next time, too", "more of the same", "carry on like this!"

[43] e.g. an explanation at the beginning of panel meetings as to why the brochures are arranged as they are.

4. GAMBA assessment of the lay panel from the perspective of the dialogue team

In order to comprehensively evaluate a high-quality dialogue, the assessment should ideally be carried out from three perspectives (cf. Mohr 2009):

1. According to the goals and criteria of the scientific dialogue partners or sponsors of the dialogue.

2. From the perspective of the participating laypersons

3. Based on normative quality criteria.

In the report that follows we present the views of the dialogue project team with regard to these three perspectives.

4.1 The aims of the project

The objectives of the sponsoring institution, the European Union, with regard to the role of the public is kept very general: „FP7 is working to develop a better relationship between scientists and European citizens. The … program will encourage activities to promote greater public engagement and dialogue in order to involve citizens … in research and science policy“[44].

Therefore we will rather focus on the goals, which the project consortium had set. These are:

a) To discover what patients and interested laypersons find interesting about GAMBA, how they assess the project (see 4.2) and what recommendations they can make for researchers, scientists, politicians and society (see also summary and part 1).

b) To test qualified scientific dialogue as an instrument of communication for the researchers, and to infer recommendations for the scientific community with regard to engendering in laypersons a general understanding and balanced view of the early stages of research, as well as to gain their feedback.

a): What are laypersons interested in?

Most of the participating laypersons had no developed knowledge regarding the GAMBA project's field of research. Some participants worked in healthcare, had occupied themselves more closely with their osteoarthritis or ethical questions or brought with them a certain amount of background knowledge.

The expert presentations[45], like the Manual and Compendium, aimed to provide the laypersons with a multi-perspective, qualified knowledge base. From the start of the dialogue there was the opportunity to continually expand the knowledge base at all times:

- through question & answer sessions and discussions with invited experts at the four main presentations (on osteoarthritis, GAMBA, ethics, risks);
- through the introduction of new questions, which were responded to during the dialogue by the invited experts, the researchers present, research done by the participants themselves or the facilitators. Prior to formulating the lay report final questions were clarified with the GAMBA researchers.
- through the careful choice of experts for the hearings, for whom Individual question catalogs were developed based on the accumulated questions

[44] ftp://ftp.cordis.europa.eu/pub/fp7/docs/wp/cooperation/cooperation-intro-wp-201301_en.pdf, p. 5
[45] The experts had been informed upfront by the facilitation team that their presentation should give an overview, ought to be in lay language, and should be balanced regarding arguments.

The questions posed by the laypersons made the following clear:

When provided with the time and space, laypersons will continue to pose questions intensively as long as they believe they have not understood the contents of the presentation

- Laypersons have a desire to know the exact way in which a therapy such as GAMBA aims to function, and to place this within the context of their total knowledge about the illness: causes, target groups / beneficiaries considering various characteristics of the ailment, therapies in both conventional and complementary medicines, preventive medical care, risks, reversibility, time resources, impact on quality of life, costs / profitability.
- Laypersons ask questions about the background of the research situation: the origin of the research idea, competition or cooperation between researchers, the current situation in the research, working conditions, vested interests, how ethical questions are tackled, funding of research.
- Particularly in assessing risks and ethical aspects, laypersons question responsibilities, vested interests, and the credibility of the involved parties including researchers and the regulators, but also the responsibility of the patients themselves.
- In this regard laypersons also see connections for example with other ethical discussions such as those dealing with embryos or organ donation. Furthermore, transparency of information is important.
- Laypersons would like to discover the personal attitudes of the researches, for example with regard to ethical questions, such as what would cause them to discontinue their research or if they would use the therapy themselves, and questions regarding their own motivation („Why are you doing this?“).
- The laypersons are interested in personal and social change processes, which may be influenced by the research results: enhancement, acceptance of illness, perception of humanity and the role of genes, or dealing with illness / health in an aging population.
- Laypersons also question the relevance of the panels and the results gathered from the dialogue, particularly who was funding the dialogue.

What did the laypersons recommend?

The recommendations of the laypersons which are displayed in detail in the summary as well as in part one are founded in all countries on similar basic ideas (see table 1).

Patients evaluated GAMBA as being somewhat more closely related to practice then other laypersons do. As a result the evaluation of opportunities is very similar, whereas specific improvements are mainly mentioned by patients. The basic risk assessment is also the same. While non-patients tend to focus more on the social problems, patients are more likely to emphasize personal risks. When regarding ethical aspects it becomes clear that the laypersons in the citizen panels tend to argue more basic principles, whereas in the patient panels participants focused more on the patient's perspective. In most recommendations differences between patient and citizen panels are only limited to the wording. The Swiss panel was a mixed panel consisting of 8 patients and 3 non-patients and is therefore presented as a comparison.

Table 1: Recommendations of laypersons in the GAMBA panels

Area	BF	PF	CH*
Opportunities			
Important findings for other fields	**x**	**x**	x
Improvement/healing	x	x	x
Individually through the use of the body's own stem cells	x	x	
Special opportunities for those under 45 years	x	x	x
Less invasive	**x**		
Fewer side effects than with medication		x	
Experiments recommended with older stem cells		x	
Better understanding of osteoarthritis and its prevention		x	x
Risks			
Gene therapy, Stem cell research and nanoparticles are risky	**x**	**x**	x
Before human application comprehensive risk assessment is necessary	**x**	**x**	x
Danger of risks being concealed	**x**	x	x
Risks are justifiable or opportunities outweigh risks	x	**x**	
Particular attention should be paid to as yet unknown risks	x	x	x
Complexity of the approach itself	x	x	x
Risk of cancer and risk of death	x	x	x
Effect on the environment or third parties	x		x
Epigenetic influences open	x		x
Undesired immune reactions		x	x
Control of bodily processes		x	x
Quality of the materials and their origins		x	x
Prior exposure of patients		x	x
Biological materials		x	x
Spreading of manipulated stem cells and growth factors		x	x
Risks must be quantified and solution strategies must be developed		x	x
Ethical Aspects			
Ethics committees must be well balanced regarding members and provided with sufficient time; transparency must be guaranteed, and decisions must be checked	x	**x**	
Animal experimentation justifiable under certain conditions	x	**x**	x
Global ethical standards and regulations important	x	x	x
Ethical questions must be checked numerous times	x	x	x
GAMBA = reductionist human image	x		x
Adult stem cells are less critical compared with embryonic stem cells	x		
Enhancement must be discussed	x		x
Informed consent!		**x**	
Animals suffering from osteoarthritis		x	x
Patient data privacy!		x	
Other aspects			
Further research regarding the cause of primary osteoarthritis necessary	**x**	**x**	x
Negative results should also be published	**x**	x	x
Avoid hasty promises of cures	x	**x**	
Neutral presentation of the whole range of therapies	x	**x**	
Early dialogue important and desirable as a standard	x	**x**	
Sufficient funding and access to basic research in all areas and EU member states	x	x	x
Increased transparency and information exchange in research policies	x	x	x
Conflicts of interest must be made clear	x	x	x
Therapy should be effective, affordable and available for all	x	x	

x (bold) = both special panels, x (normal) = at least one special panel
***** Switzerland: mixed panel with 8 patients and 3 citizens

The first objective, which was to discover what laypersons are interested in with regards to GAMBA, and which recommendations they would make to researchers, scientists, politicians and society, was achieved in the opinion of the participating scientists and the dialogue project team. How the laypersons assessed the project can be found in chapter 4.2.

b) How do researchers profit from laypersons? Qualified science dialogue as an instrument of communication

The researchers in the GAMBA consortium, who were available as dialogue partners, assessed the dialogue with the laypersons as necessary and beneficial [46]:

- They could awaken interest in the research amongst the participants and were given conditional acceptance for their research[47].
- They were surprised at how capable the laypersons were at understanding and challenging the researchers and invited experts.
- They learned how important clear and open communication is, including the need to explain or avoid jargon.
- They discovered how important it is to embed the research in the societal surroundings: for example how important laypersons consider holistic, especially preventive (also complementary) therapies, or that laypersons attach great importance to considering potential risks and how interested they are in the question of who decides which risks are acceptable.
- They were encouraged to consider scientific values, for example that negative results are frequently not published, that conflicts of interest are sometimes not discussed and that funding criteria are often not transparent enough.
- They experienced that dialogue contributes to creating a mutual understanding and expressed a wish that dialogue becomes the norm in the future.

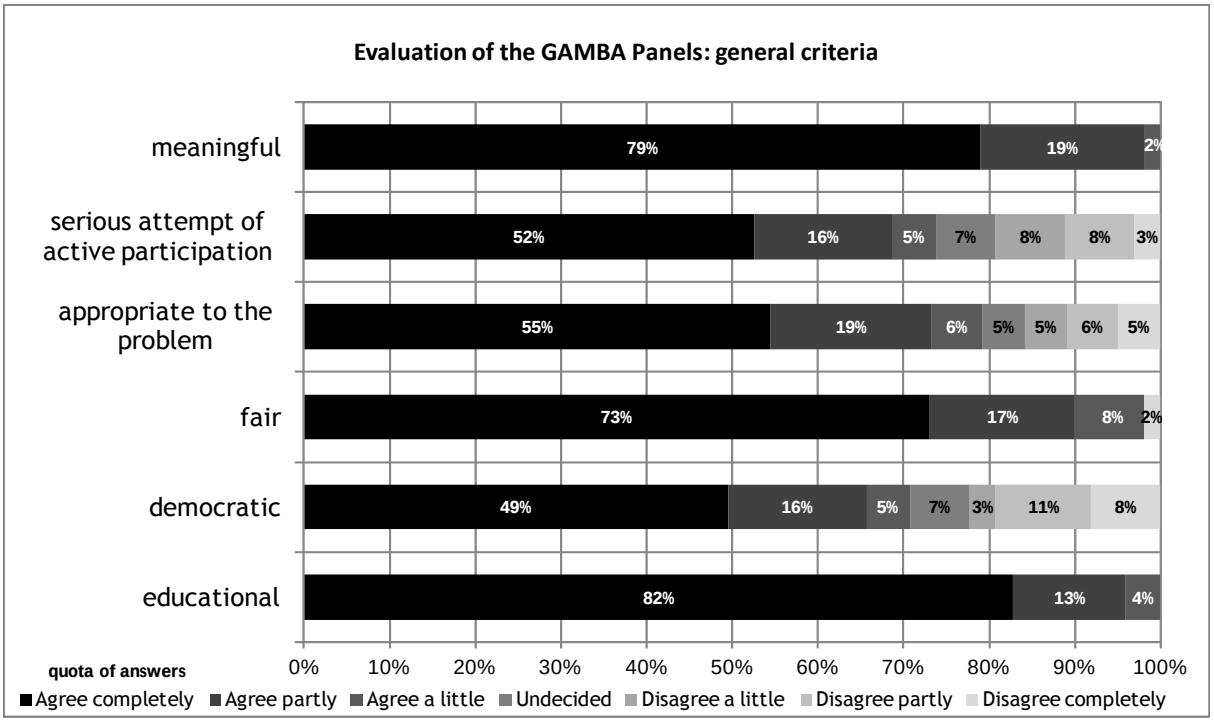
The researchers thus consider the goal of bringing basic research closer to laypersons in a balanced and clearly understandable way, and gaining feedback from them, as successfully achieved. The feedback in the format of the lay recommendations also includes recommendations to the scientific community and for research politics.

4.2 How did the laypersons assess the participation project?

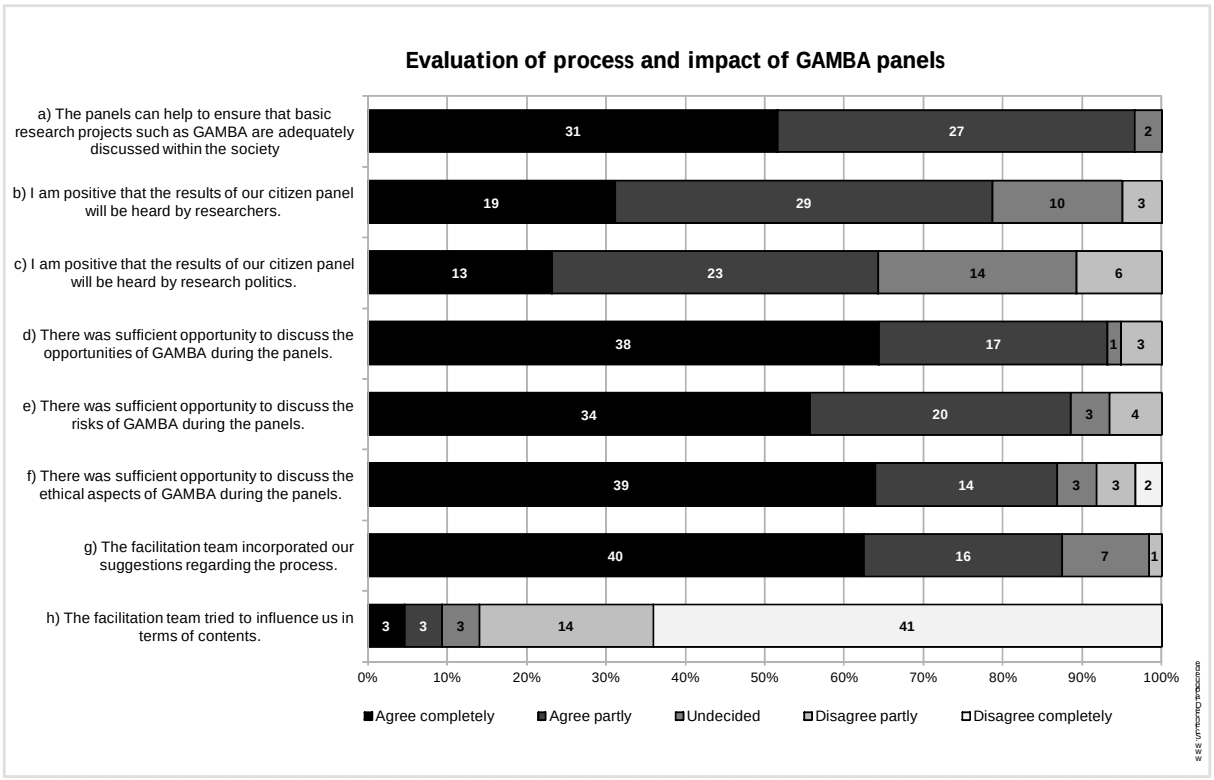
The participants in all five GAMBA panels were especially in agreement on one question: without exception all laypersons rated the panel as meaningful (see graph next page). They also experienced the panels as fair and educational, which was an important prerequisite for a credible, high-quality dialogue. The overwhelming majority of 70% experienced the dialogue as democratic; although a good 20% marked the opposite extreme „authoritarian“. Several times the critical point „time pressure“ was mentioned in this regard. In order to keep within the time schedule, for example, several presentations had to be interrupted after going well over schedule. In the German patient panel the request of the facilitators for the participants to take over the lead at the hearing was criticized[48]. That the sincerity of true participation in decision-making was doubted by 19% of the laypersons, can be ascribed to the weak mandate of the lay reports as opposed to decision-makers in politics and research. One participant bemoaned a lack of influence, which can also be seen in skepticism regarding the reception of the lay report

[46] The perspective of the researchers is taken from the detailed response to the recommendations of the laypersons (see the conclusion, as well as chapters 1.3, 2.3 and 3.2).
[47] For the conditions, see the conclusion of the lay report and the individual panels' assessments.
[48] This was intended to make the group more autonomous and reduce the likelihood of manipulation. The participants in the German patient panel felt overly challenged in taking over the lead, while all other panels took over the task of interviewing and facilitating the hearings themselves.

by research policy-makers: with around 60% the agreement is at its lowest here (see graph further down).



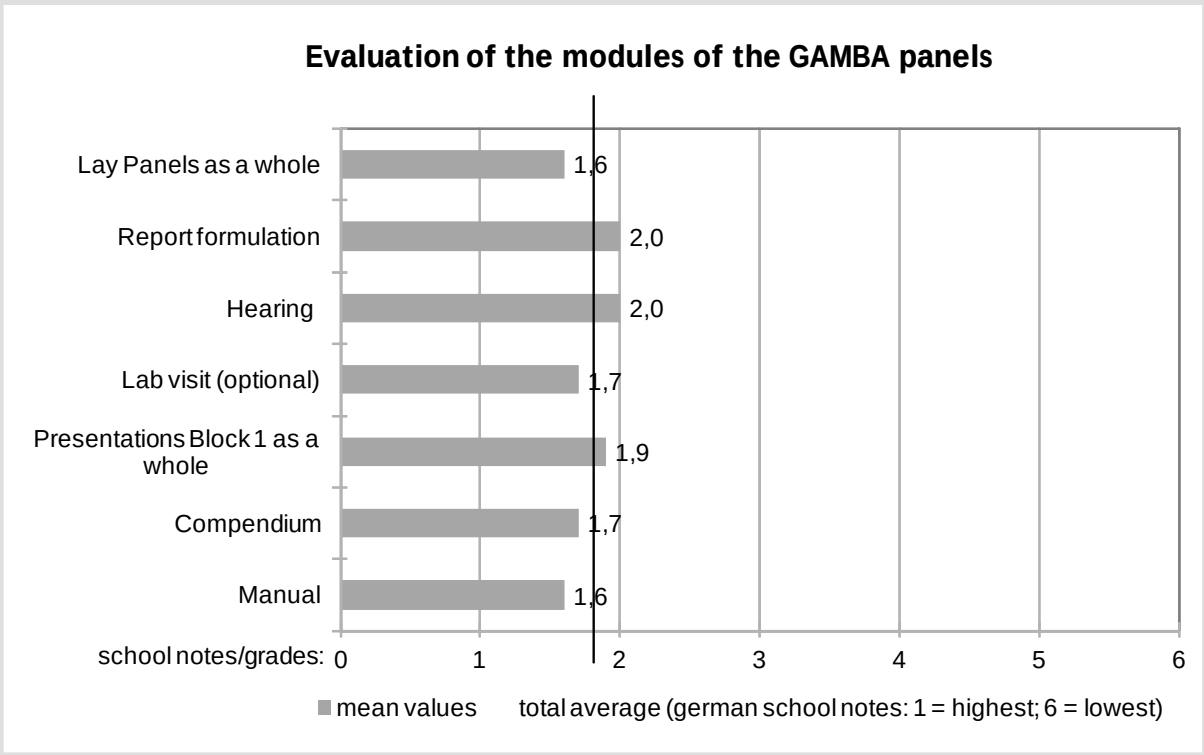
In contrast, more than three quarters of the laypersons believe that their recommendations will "certainly be heard" by researchers. And especially positive is the fact that all panellists were convinced that the panels “can help ensure that basic research projects such as GAMBA are adequately discussed within the society”.



Over 80% of the lay panelists considered the panel concept in general to be appropriate. This can also be seen in the personal remarks made by participants. The question was "What did you especially like about the GAMBA panels?" Here is an extract from the answers:

- The presence of the researchers
- The patient and informative researchers
- The comprehensive, competent information provided by experts and researchers
- The wide range of information, also because of the great number of different presenters
- The opportunity to ask questions to the experts, which were competently answered
- The mixed groups
- The open discussions
- The dialogue between doctors, researchers and laypersons.

This positive feedback rests on the core tasks of the panels - to discuss the opportunities, risks and ethical aspects of GAMBA. Almost 90% of the participants agreed completely or partly that ”there was sufficient opportunity to discuss the various aspects”. This comprehensive assessment of the procedure was based on the individual building blocks of the panels. The lay panels were given an overall score of 1.6 (see graph below). The Manual and Compendium, as well as the lab site visit received above average scores of 1.6 and 1.7 respectively. Only slightly lower were the presentations with 1.9, as well as the hearings and the creation of the lay report which scored 2.0. If one bears in mind that the last-mentioned building block was carried out on the final day of the dialogue, that the content was the sole responsibility of the participants and that the discussion process which led to the compilation of common statements and recommendations was a huge effort requiring tremendous concentration, this rating is also very positive.



Another indicator of the high level of satisfaction is that more than 90% of the laypersons would participate in a comparable science dialogue again - 23 participants of 71 probably and 40 certainly.

4.3 Assessment of the dialogues based on normative quality criteria

A high-quality dialogue, which is credible and does not instrumentalize the participants, must be compatible with following quality criteria (cf. Renn et al.1999 and Zöller 2005):

Quality criteria	Application in the GAMBA lay panels
Clear mandate: From the start it is clearly defined what will be done with the results and who the intended audience is comprised of. These addressees should commit to making a qualified public statement.	The lay panels formed a part of the GAMBA research project: researchers were present as dialogue partners and took a position on the lay recommendations both in the lay report and at the final events. At the final event in Germany the chairpersons of the national gene therapy and stem cell Associations were present.
Qualified input of information: This must be ensured by a qualified information base (brochures and other sources of information) which is balanced and understandable for laypersons, by expert presentations from various perspectives, as well as influence on the choice of experts and possibilities for own research.	The Manual and Compendium give a comprehensive and understandable overview of the GAMBA topics from various perspectives. In the panels laypersons heard presentations about opportunities, risks and ethical aspects. They also chose the experts for the hearings. Making their own presentations and the so-called topic ambassadorships enabled the participants to do their own research and to bring their own discoveries to bear in the panels.
Methodical empowerment of participants: This is supported by an inclusive, experienced and appropriate method of facilitation, which is committed to upholding the quality criteria. The facilitators empower the assessment skills and self-confidence of the participants, allowing a discussion between laypersons and experts at eye level.	The team of facilitators in all three countries consisted of experienced dialogue experts with many years of experience, who were committed to the principle of neutrality. They supported participants in discussions with the experts and in forming their own opinions. 86% of the panellists disagree with the statement that „the facilitation team tried to influence us in terms of content"; 88% state that "the facilitation team incorporated our suggestions regarding the process" (see graph above). These answers show the overall satisfaction with the facilitators.
Transparency: It is important to provide information about objectives including creative leeways and limits. Furthermore, a continuous visualization and documentation of the process supports the processing of information and the achievement of results.	The team of facilitators explained the goals and procedures of the dialogue at the start. Additionally, common rules for dialogue were agreed upon. The facilitators highlighted that the key objective was to advise the researchers themselves and their research communities. The entire process was continually documented on pinboards and flipcharts. Following the workshops the participants received photographic documentation of what had been visualized.
Outcome openness and impartiality: Participants can influence the information process through the selection of thematic aspects and experts as well as their own research; outcomes are generated as the sole responsibility of the participants.	Within the scope of the topics participants were able to set their own emphasis, for example at the hearings or the topic ambassadorships. The building blocks of the expert report - only the major topics opportunities, risks, ethical aspects, and other aspects of GAMBA were given - were created in alternating working groups, compiled into a text by the team of facilitators and passed on to the participants for agreement.

Challenges in conducting qualified science dialogue

Despite the panels being equally successful with both researchers and laypersons, as members of the dialogue project team we were faced with several challenges:

Recruiting the participants: Recruiting as diverse a group of laypersons as possible is essential for the credibility of the process.

It was not easy to find participants for the GAMBA dialogue. For the citizen panel we randomly contacted laypersons from the citizens register by mail in order to reach a wide range of potential participants. In Germany letters were personally addressed to 4000 residents living in the neighborhood of the clinic, and Switzerland to 3300 persons from the community living around the venue near to Zurich[49]. In Germany we initially had 49 interested persons, from whom we chose a group of 30 participants according to demographic criteria. Two of these participants dropped out before the panel began, meaning that before the first weekend 28 persons were registered. In Switzerland we had only 15 registrations, although in addition to the personal invitations we had also begun several other campaigns (see chapter II/1.4). Likewise, it was difficult to recruit participants for the patient panels. Writing to local orthopedists and requesting that they display our flyers (both in Germany and in Switzerland[50]) did not result in a single registration. Our press releases calling for participants were not taken up by the larger newspapers. They did however appear in two local newspapers, through which we gained several registrations.

We suspect that a combination of work effort, complexity of the topic, removal from everyday life and lack of knowledge about the processes of the GAMBA panels made gaining participants more difficult. The higher response rate in Germany can surely be traced back to the fact that MRI is a well-known and renowned neighbor to the residents who were targeted in the recruitment drive. The ARI is a specialized research Institute in Davos and is not as well known amongst the public in the region of Zurich. In the recruitment of laypersons the reputation of the institutes involved in the project seems to be an important component for the credibility of and trust in the offer to participate.

The participants who finally joined the project showed a great deal of interest and engagement, despite the unfamiliarity and complexity of the topic as well as the high amount of effort required.

Media interest: To publicize a high-value participation project and it's results the media is an important player. Gene and stem cell therapy are currently not on the political and media agenda, although large amounts of public funding are provided for this research.

As media reports are mainly oriented according to a political agenda (cf. Lehmkuhl 2011), the media has shown comparatively little interest in these topics. Despite scandals such as the death of the 18-year-old gene therapy trial participant Jesse Gelsinger (Stollorz 1999) or deaths and adverse events during stem cell transplantations (Kuhrt 2012) due to loopholes and gaps in the regulations the reporting of life science topics remains positive on the whole (cf. Ruhrmann et al 2011). In addition, the orientation towards constructive discourse and consensus which are typical of high-quality dialogue do not fit in with the main publication criteria of the media. The major triggers for publication are the number of affected persons, the novelty as well as surprising aspects of an event and failures or controversies (cf. Ruhrmann/Göbbel 2007). For an effective media and public relations campaign of discourse projects - for example using famous personalities or public events of the controversial nature -, significantly more financial resources would be required.

Recruitment of experts for specific themes: For certain GAMBA topics it was difficult to find suitable experts for the presentations and hearings. On the one hand there is almost

[49] In Ireland, a functioning citizens' register does not exist, so we had to undertake other activities to recruit participants, see chapter II/1.4..
[50] In Ireland, we did not trace where participants got the information about the panels from.

no independent risk research regarding gene and stem cell therapy. Most experts in these fields research the opportunities of therapies. Some researchers also include research of risks, in order to have data available for a future regulatory process which requires a risk benefit analysis. Also in the field of complementary medicine it was not easy to find appropriate experts. In Ireland, for example, complementary medicine is hardly known. Furthermore, the recruitment of regulatory and legal experts was difficult due to the fact that gene therapy is not yet permitted in Germany.

Influence on decision-making processes: The lay recommendations should have an effect on decisions made within each of the topic fields. At GAMBA the audience is on the one hand the researchers themselves and on the other the research community within the stem cell and gene therapy field, as well as research policy makers. The researchers were reached as they were the direct dialogue partners. They took a detailed position on each of the recommendations (see summary). The other parties concerned were communicated with via the lay report. If these results are not taken into consideration, it should not be seen as a failure of the participation process, but rather as an expression of growing and largely accepted power and decision-making structures.

Even scientific expert reports are not always taken into consideration by decision-makers. For future EU participation projects a higher level of commitment and occupation with the results of the project should be demanded on a political and administrative level, and this involvement should be planned as a step in the process. Ideally decision-makers such as the EU research commissioner, heads of DG Research, the "Industry, Research and Energy" Committee of the European Parliament or the concerned European expert societies should declare their commitment in advance of the project to taking a public stance on the lay recommendations.

Recommendations for the communication of scientists with laypersons

In the communication between laypersons and experts several different attitudes and expectations come up against each other. In order to overcome factual misunderstandings and distrust from both sides, we have included and discussed below some objections to a stronger participation of laypersons in the scientific sphere:

1. **“Laypersons are not able to comprehend such complex research”.**

   Even complex contents can be explained in such a way that laypersons can understand them. The researchers participating in the GAMBA project were initially skeptical regarding whether this could be achieved, but by the end of the process they declared themselves positively surprised (see point 1b). It is essential that comprehension is facilitated by understandable presentations, repetition and reinforcement of complex contents within a range of contexts and from various perspectives, as well as the provision of phases to reflect, discuss, internalize, ask questions and gain background knowledge.

2. **“If I explain things in a clear enough way, laypersons will accept my research”.**

   Explanations which are understandable to laypersons are very important in the dialogue, however explanations in themselves do not suffice. Only within a joint exchange of argumentation and value scales is it possible to change or encourage the development of new convictions. In order to assess information, laypersons also require contextual knowledge: in high-quality dialogue the aim is to explain and make the underlying features of scientific activity transparent. The assessment criteria of laypersons and experts can diverge greatly. The discussion requires the willingness of both sides to accept and learn from the perspective of the other. This can engender credibility and trust, which can possibly lead to acceptance.

3. **"The effort required for dialogue is (far) too much: in a 2-hour information event one can reach a much larger audience."**

   Gaining trust takes a lot of time – for all participants. Experts need to invest some time to carry out presentations which are comprehensible for laypersons and demonstrate that they well consider the questions and reservations of non-experts. Laypersons require a lot of time to process complex contents, structures or the range of various expert opinions, as well as to develop their own positions and evaluations. Without discoursive elements or goal-orientation agreement cannot be achieved and the exchanges remain an unproductive, if sometimes entertaining, exchange of blows. Professional facilitation can contribute to the effective preparation of experts and laypersons for the dialogue; the intention is to save time for the experts and laypersons and thereby increase the efficiency of the dialogue. The dialogue can also take on a range of forms and formats according to the objectives and issues. However, trust is hardly developed in the course of one evening.

4. **"Most importantly, I must highlight the opportunities provided by my research".**

   Laypersons must be allowed to develop their own opinions. Participants tend to become skeptical if only the opportunities are shown. For this reason, promises of future cures should not be made, while risks and opposing arguments should be mentioned and discussed. Only a differentiated discussion about opportunities AND risks creates credibility.

5. **"Ethical questions should mainly be discussed in ethics committees".**

   The consideration of ethical questions cannot be delegated by researchers. In order to maintain credibility, they have to think about and take positions on ethical matters. This is not only about complying with regulations, such as dealing with donor material or animal testing, but also about the legitimacy of research in society.

Conclusion

The starting point for the GAMBA lay panels was an underlying conflict which exists across the whole field of medical research; despite stringent regulations applied to clinical studies and the preceding preclinical research (e.g. in animal testing) scandals still occur regularly, creating a high level of uncertainty in the public. Examples of this are fatalities during pharmaceutical studies (cf. Viciano 2006) or the fact that the outcomes of pharmaceutical studies conducted by the pharmaceutical industry are regularly more positive than those conducted by independent scientists (cf. SWR 2011). In contrast, researchers complain about the high hurdles set by regulatory procedures, as they put a brake on innovation.

One opportunity to raise the level of trust in research is high-quality scientific dialogue (in compliance with the quality criteria outlined above), in which small groups of laypersons assess arguments for and against the research very intensively, and make statements regarding those aspects they perceive to be significant. The participants are then in the position to develop a well-founded opinion, based on the carefully prepared and well-balanced information available and the range of opinions presented in the discourse process. The aim to compile a lay panel report raises the relevance of the dialogue and challenges each participant to take a stance and present his/her convictions.

Time-intensive forums such as the lay panels are not intended to be representative of the participants, but rather to harvest as wide as possible a spectrum of comprehensible arguments. The lay panels provide a foundation on which other dialogue formats can build by presenting the results to a wider circle of interested parties, where they can be discussed and expanded (this could also be done online).

At the GAMBA lay panels it became clear that laypersons are able to comprehend and take a qualified position on the underlying principles of complicated basic research projects – a differentiated assessment of opportunities and risks could be achieved.

Despite commonly expressed fears to the contrary, laypersons were prepared to support the use of research opportunities even if risks were required to achieve scientific progress. However, they expect these risks to be researched with as much care (and necessary resources) as the opportunities, and that clear lines of responsibility should be defined. In addition, they would like researchers to engage with societal and ethical aspects related to their areas of study of their own accord and not delegate this responsibility (e.g. to ethics committees) (cf. Zöller 2013).

Trust cannot be achieved quickly. Thus it will also be necessary in the future to employ further dialogue formats, which allow for a well-grounded discussion: not only regarding the research topics, but also how these are assessed in a societal context. Some scientific protagonists will initially perhaps be put off by the additional cost[51], but these could be seen over the long-term as a sound investment in the credibility of science, resulting in a better acceptance of science and scientific research.

References chapter 4:

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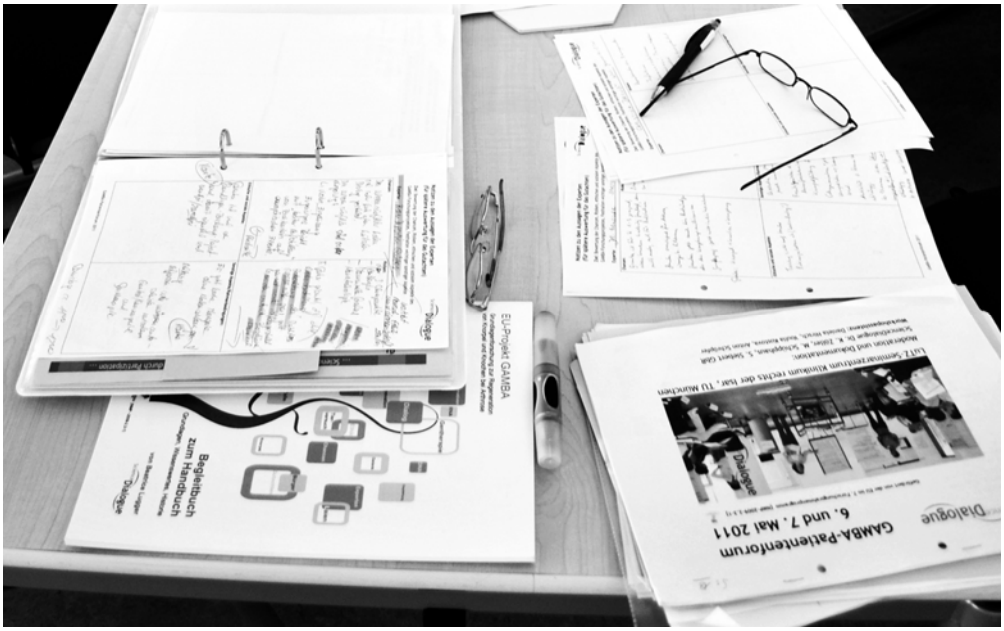
Zöller, K. (2013): Laien diskutieren und bewerten Wissenschaft: Partizipation bei Wissenschaftsthemen. Erfahrungen und Qualitätsanforderungen. In: UMID 2/2013

[51] The cost of qualified scientific dialogue is actually far lower advertising campaign, which are much less successful at increasing credibility. A full-page advert in the Saturday edition of the FAZ costs approx. €65,000. Each of the 5 lay panels, including all preparation and conclusion work, research, expert and staff costs only amounted to approx. €50,000.

Part III: Documentation



Ground Rules of the Lay Panels

The GAMBA patient and citizen panels are an exchange between lay persons and experts:

- Panels enable a structured and fair debate without a pre-defined result (open-ended dialogue process).
- All participants of the dialogue have equal status.
- In the panels, facts are explained and open questions solved as completely as possible by taking into account diverse vantage points and interests and by delivering rational and comprehensible arguments.

The participants of the GAMBA panels

- will draw up common lay recommendations on the opportunities, risks and ethical aspects of the GAMBA topics. They decide on recommendations for the researchers, for research politics, for decision makers and the general public
- will participate on an ongoing basis, are actively involved and share opinions, reservations as well as topics and suggestions.
- will treat each other fairly, respectfully and openly, this includes
    - listening
    - not interrupting others
    - acknowledging other opinions and a willingness to learn from the arguments and ideas of others and a willingness, if need be, to reconsider one's own position
    - refraining from making moralizing judgements on positions ("who-ever suggests such measures is ignorant") and
    - Introducing criticism at an early stage.
- aspire to achieve a consensus in the most important decisions of substance, if need be with abstentions (tolerated consensus). If this is not possible, a majority of two-thirds should be the goal.
- enjoy protection of confidentiality during the non-public phases of the discourse (the view of other participants may not be shared with a third party without prior arrangement).

The members of the facilitation team …

- will act and moderate the discussions impartially
- will support participants in their contribution and cooperation in the discourse
- suggest the agenda and methods and document the discussion visibly by noting down key points
- ensure that the ground rules and the programme are adhered to.

Press and publicity

- The GAMBA panels will be accompanied by continuous media work. Representatives of the media will be admitted, unless there are objections.
- Statements made to a third party (journalists and public) are the responsibility of each participant.
- Observers may be admitted in limited numbers.
- The public relations work of the project which Dr. Katharina Zöller takes responsibility for, includes:
    - the websites www.gamba-project.eu and www.ScienceDialogue.de (German)
    - a public concluding event where the lay recommendations will be presented to the project coordinator and the public
    - Manual and Compendium
    - ongoing press releases.

Information Material

In order to enable lay participants to enjoy as comprehensive an introduction as possible to the subject matter, involving both favourable and critical perspectives, a considerable amount of literature was compiled in the run-up period. Starting with the publications of the research consortium, relevant internet sources (blogs) as well as newspaper and magazine articles from the years 2006 to 2010 (in some cases even earlier) were researched and fed into a so-called research database (the complete list is available on the Internet[52]). The following publications we reviewed:

Magazines

- Spiegel
- Stern
- Focus
- PM
- Idw
- Zeit Wissen
- Geo Wissen
- SZ Wissen (ehemalige)
- Bild der Wissenschaft
- Spektrum der Wissenschaft
- Technology Review
- Das Parlament
- InnovationsReport

Regional broachcast stations (BR, SWR, RBB, NDR, HR, RBB, arte, MDR, RB, SR, WDR)

- Deutschlandfunk/-Radio
- Apotheken-Umschau
- Deutsches Ärzteblatt
- Doccheck.com
- Ärztliche Praxis
- Ärztezeitung
- Naturamed
- Fortschritte in der Medizin
- Kosmos/Natur
- Rheumamedizin
- Eurekalert
- Alphagalileo
- PLoS
- Ars Technica
- Slate

Newspapers

- FAZ
- Taz
- FR
- Financial Times D
- NZZ
- SZ
- Die Zeit

Blogs

- Research Blogging
- Science Blogs

[52] http://www.wissenschaftsdialog.de/index.php/projekte/30-community/20-dokumentation

Information Material: Overviews (distributed to all participants)[53]:

- Lugger, Beatrice: EU Project GAMBA: New hope for osteoarthritis patients (short version)
- Lugger, Beatrice: EU Project GAMBA: A Manual for patient and citizen panels regarding ethical, legal and social aspects of innovative therapies with adult stem cells, gene therapy and nanoparticles
- Lugger, Beatrice: EU Project GAMBA: Compendium to the Manual: Basics, Need-to-know, History

Ambassadorships

Information material (press articles) was provided for the topics mentioned below (see next page) and available on the website: www.wissenschaftsdialog.de/index.php/die-community.

Ambassadorship Task (topics see next page):

1. Please take over the role of "ambassadors" for one of the topics and read the indicated material from the Manual and Compendium. Please pay particular attention to opportunities and risks of your subject area and the ethical, social, possibly also legal issues that are important to you for the lay opinion.

2. Identify 2-3 important aspects (e.g. a statement, a recommendation) which you would like to have included in the patient opinion, possibly with a brief justification. Please bring your suggestions into the breakout group in order to discuss it with the other suggestions from your 'ambassadorship' theme.

3. In the group, find out what your shared aspects are and write them on a WHITE card. Frame opportunities in green, risks in red and ethical/social aspects in blue (all others stay without frame). The group output will be discussed later in the plenary.

If there are questions for the experts who will be invited to the hearing on our second weekend please write them on a yellow card so that we can capture them on the 'open questions' pin board.

Participants reviewing statements of the experts - rightmost Swiss facilitator Thomas Bänninger

[53] English and German versions are available on the following website: http://www.wissenschaftsdialog.de/index.php/download

	Topics for Ambassadorships	Sources M = Manual; C = Compendium Specification with chapter no. and page no.
A	**Cure by gene therapy: brilliant or dangerous?** Ethical arguments for and against; history so far including successes and casualties	C 4.3 (p 28-29) C 4.7 (pp 35-39) M Fig 11 (p36) {if time: C 7.9.1 Ethical arguments (p 57)}
B	**The human body's stem cells: Salvation Army, or ticking time bombs?** Adult stem cell therapies: Operation, application fields, clinical trials, safety/risks	C 3 Stem Cells (p 17-21) M 4.2.3 Stem cell risks (pp 39-40)
C	**Guidelines for the use of innovative therapies: can ethics and law provide an adequate basis for sound decisions**? Principles of biomedical ethics; a model for gradual ethical assessment of gene and cell therapy; regulation	M 5.1 + 5.2 principles (p 42-43) C 6 regulation (pp 42-50) C 7.8 gradual model (p 56)
D	**Reaching for the genes: what are we allowed to do?** What makes us human? Role of the genome, epigenetics, human images	M 5.3 + 5.4 (pp 43-45) C 2.2 Epigenetics (p14-16) C 7.9.1 Pros/Cons gene therapy (p 57)
E	**Diligent researchers and empowered patients - who takes responsibility?** In the tension between care and self-responsibility: ethics committees, clinical trials, Informed consent	C 7.1 Ethics committees (p 51) M 5.5 Informed consent (p 45-46)
F	**Ethical considerations: superfluous or essential?** Are these ethical aspects important? Problems of unrealistic promises of salvation("hype"), conflicts of interest, human enhancement, animal testing, research policy, patents on life	C 7.2 -7.8 diverse ethical aspects (pp52-56)

Experts at the GAMBA Lay Panels

Expert presentations Germany

	Patient Panel	Citizen Panel
Introduction Osteoarthritis	PD Dr. med. Tobias Renkawitz, Orthopaedic Clinic of the University of Regensburg, Asklepios Clinic Bad Abbach	PD Dr. Stephan Vogt, Orthopaedic Surgeon, Klinikum rechts der Isar, Technical University of Munich
Ethical Aspects	Prof. Dr. Christoph Rehmann-Sutter, Institute for Medical History and und Science Research, University of Lübeck	PD Dr. Arne Manzeschke, Institute Technique-Theology-Natural Sciences, University of Munich
Risks	Dr. med. vet. Dr. med. Thomas Brill, Centre for Preclinical Research at Klinikum rechts der Isar, Technical University of Munich	Prof. Dr. Boris Fehse, Cell- und Gene Therapy, Clinic for stem cell transplantation, University Hospital Hamburg-Eppendorf

Expert presentations Ireland

	Patient Panel	Citizen Panel
Introduction Osteoarthritis	Fintan J. Shannon, Consultant Orthopaedic Surgeon, Galway University Hospitals	Bill Curtin, M.Ch., F.R.C.S.I., Orthopaedic Surgeon, Galway University Hospitals
Ethical Aspects	Sorcha Ui Chonnachtaigh, PhD, Centre for Professional Ethics, Keele University, UK	Heike Felzmann, PhD, Centre of Bioethical Research and Analysis, National University of Ireland Galway
Risks	Timothy O'Brien, MD, PhD, Director REMEDI, National University of Ireland Galway	Mark Tangney, PhD, Cork Cancer Research Centre, University College Cork

Expert presentations Switzerland

	Lay Panel
Introduction Osteoarthritis	Dr. med. Stefan Mariacher-Gehler, Reha Clinic Zollikerberg
Ethical Aspects	Dr. Jean-Daniel Strub, executive director National Ethics Commission in Human Medicine (NEK-CNE), Bern
Risks	Andreas Marti, Institute for Cell Biology, University of Bern

Expert Hearings

In addition to the four introductory presentations on osteoarthritis, GAMBA, risks and ethics organised by the facilitation team, participants should get the chance to clarify and discuss open questions with additional experts in a hearing which participants could arrange for themselves.

For this hearing panellists could choose experts from a list. The objective of the facilitation team was to organise a wide spectrum of specialist perspectives and opinions as well as positioning on the GAMBA project. This resulted in the list of around 10 experts per panel (see below.)[54]. The selection of participating experts was made after discussions on important selection criteria using the experts' profiles. So, after the first weekend, the experts learned whether they had been selected and were given the questions posed by the panellists in advance. Most of the experts made their services available without remuneration, only claiming travel expenses; only those experts who had a very long journey, are freelancers or come from a non-profit organisation received an expense allowance.

Experts Germany	**Patient Panel**	**Citizen Panel**
Dr. Christina Berndt, Science Journalist, Süddeutsche Zeitung Munich		
Dr. med. Tobias Cantz, Max-Planck-Institute for Molecular Biomedicine, Münster		----------
Dr. med. Axel Eustachi, Competence Center for Complementary Medicine, Klinikum rechts der Isar, Munich	----------	
Dr. Michael Fuchs, Institute for Science and Ethics, University Bonn		
Dr. Katrin Grüber, Institute Men, Ethics and Science, Berlin		
Prof. Dr. Albrecht Müller, Institute for Cell Research, University of Würzburg	On the phone	
Govinda Georg Nebel, Healer („Heilpraktiker") and Yoga teacher, Munich		
Dr. Benno Rattel, Vice President Non clinical Development Micromet, Munich		
Dr. Peter Spork, Science Writer (Epigenetics)		
PD Dr. Stephan Vogt, Klinikum rechts der Isar, Sports Orthopaedics, Munich	Replaced by Dr. Brucker	
PD Dr. Peter Brucker, Klinikum rechts der Isar, Sports Orthopaedics, Munich		
Dr. Miriam Voß, Science Museum (Deutsches Museum) M.		
Prof. Dr. Heike Walles, Fraunhofer Institute IGB, Stuttgart; Micromet AG		ill
Prof. Dr. med. Peter Wehling, Orthopaedic Doctor, Orthogen company, Düsseldorf		
Dr. Michael Zichy, Institute Technique-Theology-Natural Sciences, University of Munich		
Bettina Ziegele, Paul-Ehrlich-Institute (regulator), Langen		ill

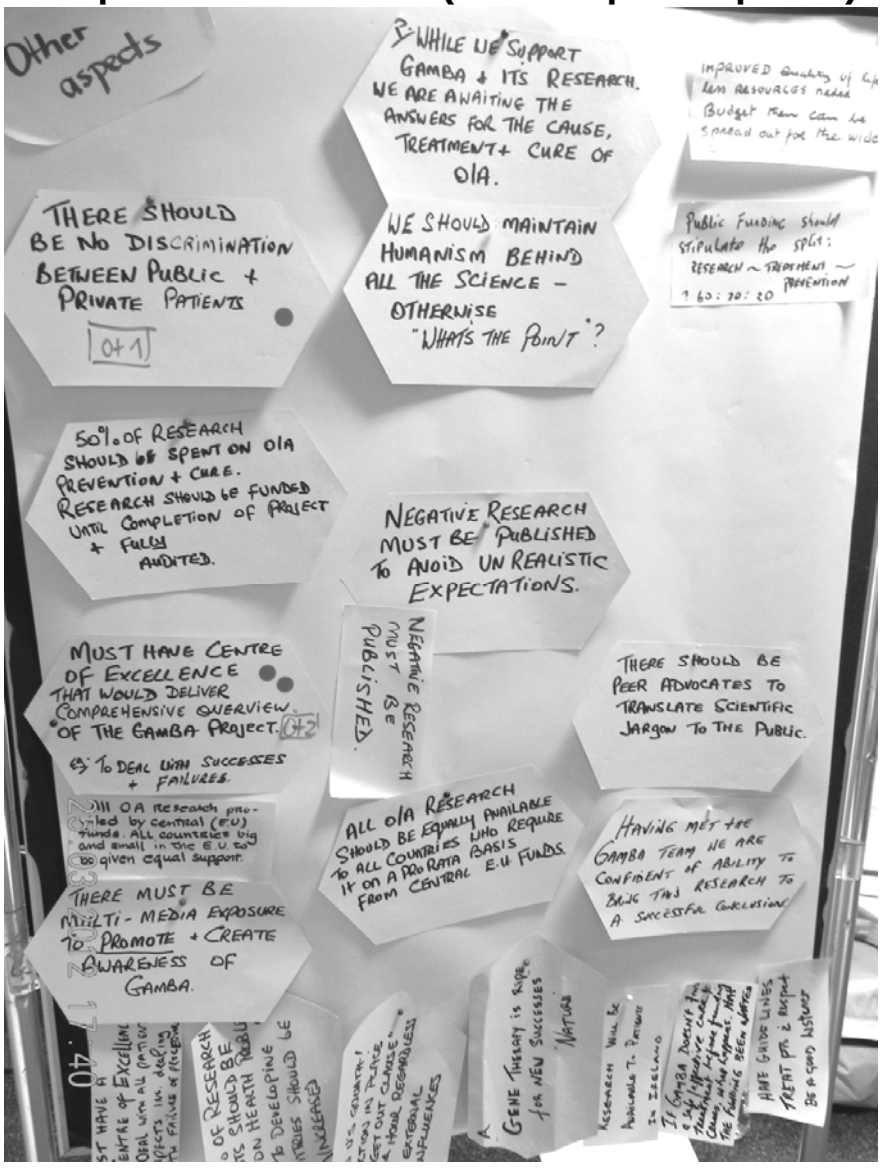
Explanation: Selected | Not selected | --- Not available

[54] Enquiries were sent to 3-4 times as many experts but not everyone had the time or interest to participate.

Experts Ireland	Patient Panel	Citizen Panel
Fergal O'Brien, Dept.of Anatomy, Royal College of Surgeons Ireland	---	■
Veronica Campbell, PhD, Professor for Physiology, Centre for Bioengineering, Trinity College Dublin	---	
Padraig Corkery, Ref Dr, St Patrick's College, Maynooth (theologist)	■	---
Stephen Elliman, PhD, Procure Labs (enterprise)	---	
Heike Felzmann, PhD, Centre for Bioethical Research and Analysis, National University of Galway		---
Siobhan Guiry, President Chiropractor Association Ireland	---	
Senator Fidelma Healy Eames, PhD, Seanad Eireann (Irish Senate)		---
Thomas Ritter, REMEDI, National University of Ireland	■	■
Cormac Sheridan, freelance scientific journalist	■	■
Sean Small, NUI Galway graduate (law)	---	
Explanation: ■ Selected	Not selected	--- Not available

Experts Switzerland	Lay Panel
Dr. theol. Ruth Baumann-Hölzle, Dialog Ethik, Zurich (criticalbioethics)	
Dr. med. Simon Feldhaus, Medical Services Ambulatorium Paramed, Baar (general practitioner und specialist in complementary medicine)	■
Gabriele Gadola, Rheumaliga Zurich (patient organisation)	
Dr. med. Sabine Goldhahn, Goldhahn Science and News GmbH, Wallbach (scientific journalist and scientist)	■
Prof. Dr. Hans Jörg Häuselmann, centre for rheumatology and bone illnesses, Klinik Im Park, Zurich	■
PhD Katharina Maniura, Empa St. Gallen (researcher biomaterials and stem cells)	
Prof. Dr. Frank Mathwig, Schweizerischer Evangelischer Kirchenbund (federation of protestant churches in Switzerland)	
Prof. Dr. Marcy Zenobi-Wong, cartilage technologies and regeneration, University of Zurich (ETH)	■
Explanation: ■ Selected	Not selected

Example of Visualisation (work on panel opinion)



Information on ScienceDialogue and biographical details of the project participants

ScienceDialogue stands for a new form of intensive two-way dialogue between scientists and lay people. Founded in 2010, ScienceDialogue Dr K. Zoeller, M. Schüpphaus, S. Siebert GbR is a small company comprising three experienced social scientists, who share the aim of enabling qualified lay participation in scientific projects (for dialogue quality criteria see part II, 1.2).

Researching and shaping the future is not a task for experts alone – in democratic societies this is the collective mandate of the population as a whole. This requires the willingness to get into dialogue and to cooperate with others. Therefore, providing suitable methods for implementing such practices are needed. Qualified expert input and an open exchange of arguments, experiences and personal ideas in combination with healthy common sense is the basis for every development in a modern civil society. In reality, decisions regarding a new technology, far-reaching regional planning measures or an innovative therapy are generally made by closed bodies of experts or political bodies, often under time pressure. Enlightened laypersons or mature citizens are rarely given a voice.

How do we work at ScienceDialogue? We would like to create a level playing field for the intensive exchange of dialogue between scientists and the general public. For us dialogue means more than experts making information available and members of the general public receiving information and being allowed to ask a few questions. Within the lay panels we support participants as far as necessary but leave a large number of procedures up to them, as in the case of the autonomous performance of a hearing with experts of their own selection, for example. After the input phase, lay panellists debate with each other in rotating breakout groups on opportunities, risks and ethical/social aspects of the subject area concerned. As a result they assess and evaluate the subject area from their own particular perspective as patients or interested lay persons. They draft recommendations to scientists and other sectors of society such as business and politics.

Through dialogue of this kind both “parties”, scientists and laypersons, learn from each other. In addition, decision-makers from the sectors of politics, administration, business and others profit from the ideas and evaluations of participants since their views and associations are early indicators for the acceptance of the new technologies under discussion. Although we only reach a limited number of lay persons with these intense dialogues, the idea behind is that a small group of 10-25 people intensely discusses and assesses the subject area so that everyone else interested can later reconstruct the issues and arguments. Lay panels therefore prepare a qualified debate for larger stakes of society.

The ScienceDialogue project team

Dr rer.nat. Katharina Zoeller: Project Leader

Born in 1964, Dipl.-Wirtschaftsgeographin (economic geography graduate), doctoral thesis “Stakeholder-Dialoge zur Sicherung des neuen Standortfaktors <Akzeptanz> bei deutschen und amerikanischen Chemieunternehmen” (stakeholder dialogues as a safeguard to the new location factor <Acceptance> in German and American chemical corporations). Since 2000, self-employed consultant and facilitator (www.DialogZ.de), in addition, since 2010, associate of ScienceDialogue. 1995-2000, research associate and project manager, “Akademie für Technikfolgenabschätzung” (Centre of Technology Assessment) in Baden-Württemberg (Stuttgart) with Prof. Ortwin Renn. 1992-1995, assignments in the public relations sector. Numerous discourse projects, including “Diskurs Bioethik” (discourse on bioethics) (Federal Ministry of Education and Research, BMBF,2012-2013); “Jugendforen Nanomedizin” (youth juries on nanomedicine) (Federal Ministry of Education and Research,

BMBF, 2008-2009); round table “Seeuferplanung Thalwil/Switzerland” (lakeshore planning, Schweizer Stiftung Science et Cité, 2001-2004); round table “Ernährung und Nachhaltigkeit” (nutrition and sustainability) (Federal Ministry of Education and Research, BMBF, 1997-1998); lay panels “Zukunftsverträgliche Energieversorgung” (future-compatible energy supply, 1996); “Bürgerbeteiligung an der Abfallplanung für die Region Nordschwarzwald” (citizens’ involvement in planning of waste disposal services for the northern Black Forest) with citizen panels (1995-1996) (the final three projects at the Centre of Technology Assessment in Baden-Württemberg). Teaching assignments on topics including participation, facilitation techniques and risk communication at universities and universities of applied science, lectures and publications on participation.

Maren Schuepphaus, dialogimpulse: Facilitation and Project Management Switzerland

Born in 1967.Dipl.-Volkswirtin (economics graduate). Since 1995: consultant, mediator and facilitator. Until 2004: director of hammerbacher, Osnabrück. Since 2005: director of dialog:impulse (www.dialogimpulse.de), Munich, and in addition, since 2010: associate of ScienceDialogue (www.sciencedialogue.de), Weilheim. Wide project experience with discourse and dialogue processes in the public and in the business sector as well as in change management and strategic communications consulting. Core areas in biotechnology and gene technology and ethics discourse respectively: Nano-Jugend-Dialog (youth juries on nanomedicine, Federal Ministry of Education and Research (BMBF), Berlin, 2007-2008), lay discourse “Streitfall Therapeutisches Klonen" (the therapeutic cloning dispute), German Reference Centre for Ethics in the Life Sciences (DRZE), Bonn/BMBF, Berlin, 2005-06); “Diskurs Grüne Gentechnik” (discourse on green gene technology), Federal Ministry of Consumer Protection, Food and Agriculture (BMVEL), Berlin, 2002). Additional project experience in the areas environment, nature conservation, sustainable development, education, culture, planning and civic participation – for example: neighbourhood dialogues of business enterprises, trainings and workshops on team-building and strategy, facilitation of large-scale groups and congresses.

Sven Siebert, konzept: gruen GmbH: Organisation and co-facilitation Germany

Born in 1961, Dipl.-Sozialgeograph (social geography graduate), director of the “konzept: grün GmbH” consultancy bureau (www.konzept-gruen.de). In addition, since 2010, associate of ScienceDialogue GbR, Weilheim. For the past 15 years consultant and facilitator of manifold projects on change processes in business enterprises and local communities, such as: “Lernen vor Ort” (‘learning on location’ (City of Munich, 2009-2012), youth participation in “Module 7” (ExWoSt, Federal Institute of Building Research, Town and Country Planning, 2009), guidelines on education (City of Munich, 2008-2009), youth juries on nanomedicine (Federal Ministry of Education and Research,BMBF, 2008-2009), resident participation programmeme „Na klar!“ (City of Munich, 2004-2007), specialist forum on heat insulation in residential buildings (City of Munich, 2000-2006), “Bürger- and Nutzerbeteiligung MessestadtRiem: Dialog” (dialogue, Riem exhibition centre citizen and user involvement, MRG, 2000-2003), advisory programme “ÖKOPROFIT” (ECOPROFIT, administrative district of Fürstenfeldbruck, Geretsried & Wolfratshausen, 1998-2001). Prior to this, research projects for MAN Nutzfahrzeuge AG (life cycle assessment), Deutsche Forschungsgemeinschaft (German Research Association, technological change) and others, as well as lectures at LMU Munich (environmental economics) and FH Landshut (environmental compatibility and appraisal of technological consequences).

Beatrice Lugger, science journalist: Popular representation of scientific content matter for lay panel usage, Manual and Compendium

Born in 1967, Dipl.-Chemikerin (chemistry graduate), science journalist and blogger. Since 2008, social media consultant to the Lindau Nobel Laureate Meetings. Previously managing editor of ScienceBlogs.de. Writes for WIRED, FOCUS, Süddeutsche Zeitung, Technology Review, netdoktor.de among numerous others; DGE Prize for Journalism, 2001. Currently: Deputy Science Director of the National Institute of Science Communications, NaWik, in Karlsruhe, Germany.

Team Germany

The German team was composed of the German ScienceDialogue team. Responsible for the scientific parts (2 presentations on GAMBA) were the researchers of the Technical University of Munich, Klinkum rechts der Isar, Dr Martina Anton and Prof Christian Plank (also coordinators of GAMBA) who were present most of the time as dialogue partners. Organisational support during the panels came from the research associates and (PhD) students Mehrije Fehrizi, Daniela Hirsch, Youlia Kostova, Dr Ulrike Schilling und Anton Schröpfer.

Team Ireland

The Irish team was made up of facilitator Paula Weir (www.lighthouseconsulting.ie) and the on-site organiser, Christine Ritter. It was coordinated by Dr Katharina Zoeller of ScienceDialogue (project leader lay dialogues and co-facilitator for Ireland). Organisational support (in finding experts, for example) was provided by the scientists Prof Mary Murphy and Dr Eric Farrell of the National University of Ireland, Galway (members of the GAMBA consortium). The PhD student Niamh Fahy supported the Patient Panel in her role as presentor and conference assistant during the panel sessions. All three scientists gave the lectures on GAMBA during the panels and were available as dialogue partners most of the time.

Team Switzerland

The Swiss team was made up of facilitator Thomas Baenninger (www.kons-ens.ch), the scientist Dr Sibylle Grad (member of the consortium) and the scientific research assistant Dr Ursula Menzel (also conference assistant during the panel sessions) of the AO Foundation in Davos. It was coordinated by Maren Schuepphaus of ScienceDialogue (facilitator for Germany and project manager/co-facilitator for Switzerland).

Marketing

Poster: Search for Participants Citizen Panel

Research in the critical eye of citizens

Gene and stem cell therapy could one day provide cures for illnesses such as cancer, cardiac and bone/joint diseases (i.e. osteoarthritis).

Although some successes have been *achieved, there are nevertheless some* risks as adverse side effects have been observed. Who weighs up whether taxpayers' money should be invested in this research - maybe you? This project is looking for your input: What demands are there on research, what should researchers be allowed to do and what not? Should there be limits? What are the needs of patients? What do interested citizens want?

For the patient panel of an EU research project we are looking for **interested citizens from Galway and the surrounding areas,** who are willing to discuss their ideas and concerns with researchers and other experts. With the support of an experienced team of facilitators you will be able to evaluate the chances and risks, as well as the ethical and social aspects of the project and will help to draw up a "citizen opinion".

No drug trial, no medical treatment!

Info: Christine Ritter, phone: 091 494276 or www.gamba-project.eu/panels

Application deadline: May 1st 2012

Dates Patient Panel Galway:

Saturday/Sunday May 19th/20th, June 9th/10th 10 A.M.- 6 P.M.

Location: National University of Galway

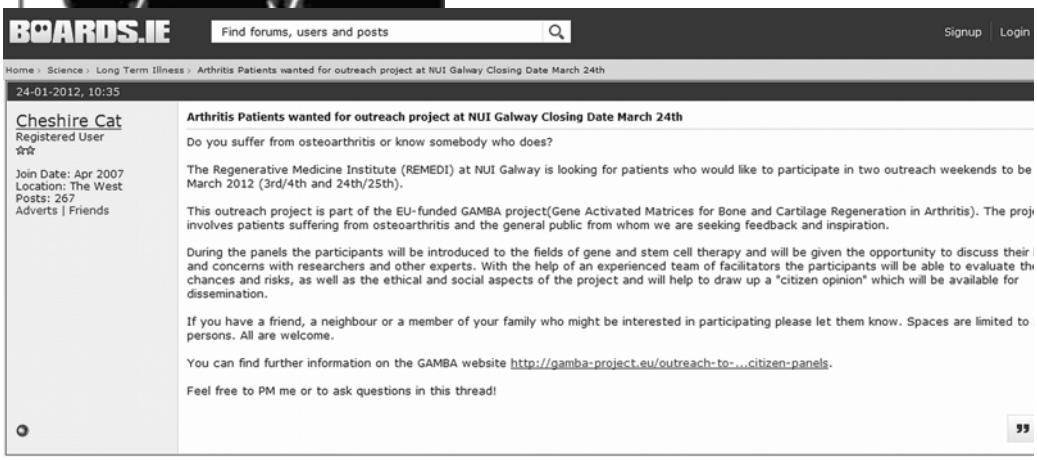
You will receive a gratuity of EUR 50,-.Meals/soft drinks are free.

Posters und Flyers were distributed in local shops, libraries, public places (details see part II chapter 1.4).

Small ads and online marketing[55]

Ireland

Facebook posted 2012-1-17



Boards.ie posted 2012-1-24

Galway Independent posted 2012-1-23 (text see next page)

[55] In Germany, similar Marketing/PR activities took place, see German Lay Report at www.sciencedialogue.de


Galway INDEPENDENT

Tuesday 25th September 2012

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SETLIST

It's been a busy summer for The

Examining arthritis

Health & Beauty Posted on 01/02/2012 by Lorraine O'Hanlon @galwayindo

Tweet 0 Empfehlen 0 +1 0

Osteoarthritis researchers at NUI Galway are part of a new European project which is looking to incorporate the views of patients and the general public at the earliest stages of research

EPAPER

Galway INDEPENDENT

300 new tech jobs

As part of the EU-funded GAMBA project, NUI Galway is looking for osteoarthritis patients who would like to learn about new therapy approaches and are willing to evaluate these approaches from a patient's point of view. The patients should be resident in Galway, be at least 18 years old, and be available for four days in March 2012. The views of the general public will be sought in early summer.

Osteoarthritis is a very common joint disease, which can impact quite severely on the quality of life of patients. At the age of 65 most people are affected, and women are more commonly affected than men.

Symptoms such as restricted mobility and pain can be alleviated and the progression of the disease can be slowed, but up to now it is not possible to heal the disease.

For the consultation project, based at the Institute for Regenerative Medicine (REMEDI) at NUI Galway, the participants will be introduced to the topics of innovative basic research into osteoarthritis and – depending on interest – further background information on gene therapy, stem cell research and nanomedicine.

"We are really planning to engage with the people who arguably know most about arthritis, the sufferers. What is it that patients need and want? Will it be possible to regrow bones, to generate cartilage in the body and to stop joint inflammation effectively in 20 years time? What risks and ethical aspects are associated with such visions? These are just some of the questions we want to discuss," said Dr Mary Murphy, REMEDI, NUI Galway.

Dr Murphy added that until now, the evaluation of the risks associated with new health technologies are normally left to the experts.

"New therapy approaches usually don't come to the attention of patients and society until they are tested in clinical trials or once the products are launched on the market. However, NUI Galway is actively inviting those suffering from osteoarthritis and the general public to contact them, so share their own insights with scientific experts."

All the sessions will be supported by a experienced team of moderators, who will ensure that the information supplied is comprehensible.

As part of the GAMBA project (Gene Activated Matrices for Bone and Cartilage Regeneration in Arthritis) researchers at REMEDI are involved in developing new methods for the treatment of osteoarthritis.

In collaboration with nine partner institutions from Germany, France, Ireland, Italy, the Netherlands and Switzerland, researchers in REMEDI hope it might be possible to heal diseased joints in ten to 20 years. This would be done by introducing a combination of biomaterials, stem cells harvested from the patient, gene vectors and nanoparticles directly into the diseased tissue.

"The hope is that these enriched biomaterials could make a regeneration of the joints possible," explains Dr Murphy.

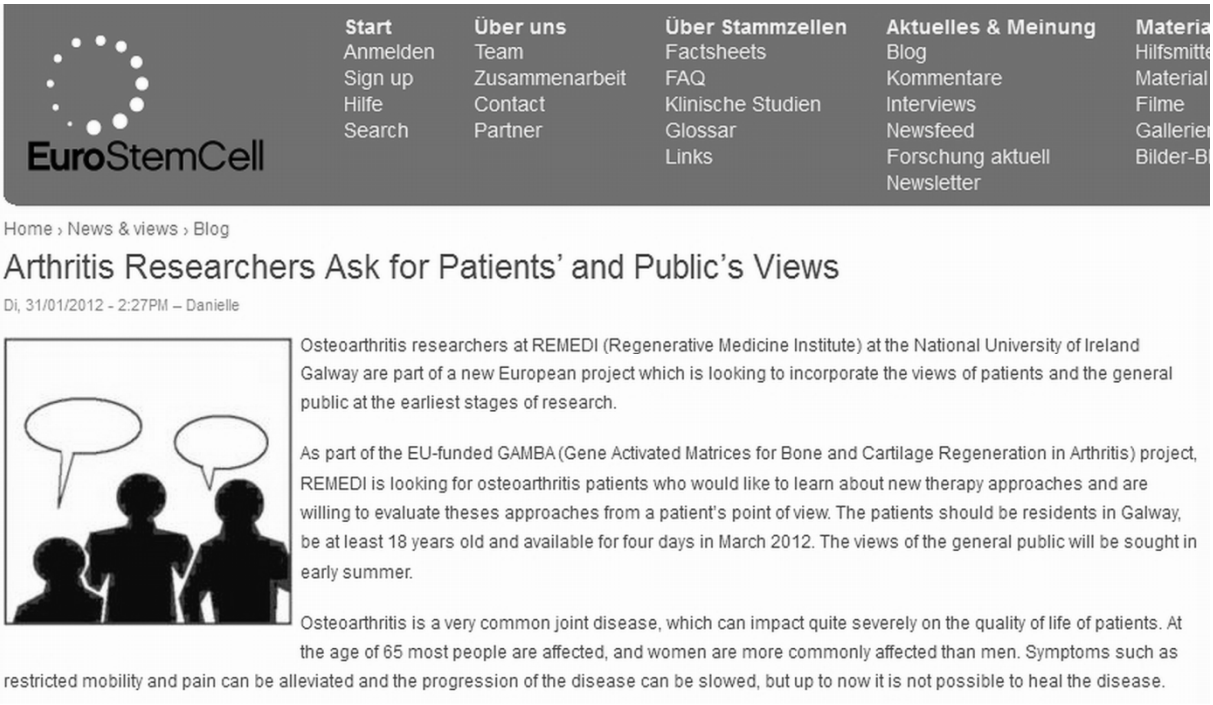
The application form and further information are available online http://www.gamba-project.eu/panels or can be requested on 091-494276. The main website for the project is http://gamba-project.eu.

Galway Independent posted 2012-2-1

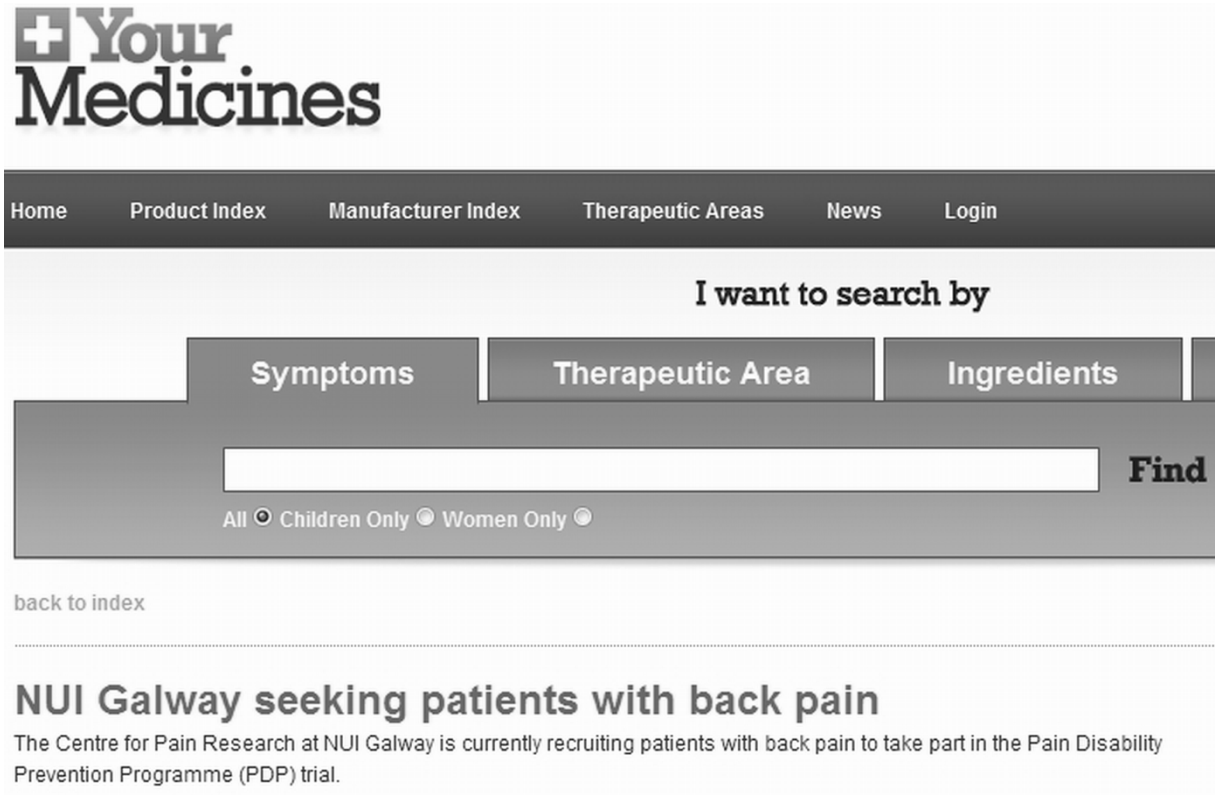
Arthritisireland.ie posted 2012-1-13

nuigalway.ie posted 2012-1-23 (text see previous page)

Irishealth.com posted 2012-1-25 (text see previous page)



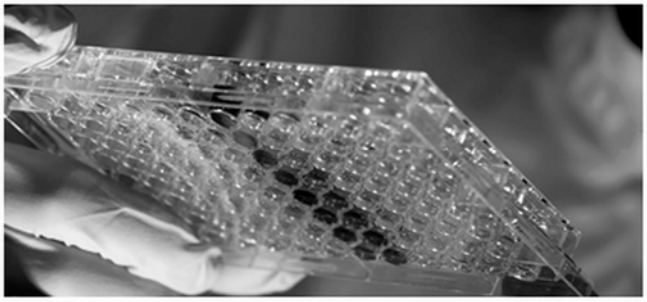
Eurostemcell.org posted 2012-1-23



Yourmedicines.ie posted in January 2012

Scientists Informed by General Public Regarding Gene and Stem Cell Therapy

Tuesday, 30 October 2012



Report to be published on 2 November

A cure for osteoarthritis would be a sensation. Many international research teams are working towards this goal, but few, if any, of these groups have asked the 'target group' of their research, patients and interested lay people, for their opinion.

Researchers at the Science Foundation Ireland funded Regenerative Medicine Institute (REMEDI) at NUI Galway have led the Irish effort to hear the views of the ordinary patient member of the general public. The speakers of the patient and citizen panels will officially present their report to Marian Harkin, MEP at 5pm this Friday, 2 November in the Orbsen Building at NUI Galway. Members of the general public, political and scientific communities and the media are expected to attend.

The research was run by a project called GAMBA (Gene Activated Matrices for Bone and Cartilage Regeneration in Arthritis), which asked osteoarthritis patients and citizens to participate in an intensive dialogue and to evaluate their EU-funded research. A series of discussion panels took place in Germany, Switzerland and in Galway and surprisingly, the opinions generated by the five panels involved are quite similar, despite different professional and cultural backgrounds.

Involving end users at the early stages of research is a novel and exciting approach which could lead to better understanding and acceptance by the public and also gives valuable insights to the researchers themselves.

Researchers at REMEDI in NUI Galway were joined by 17 patients and 10 interested citizens, aged between 19 and 78. Over the course of four days the volunteers were given comprehensive information. Researchers, journalists, ethicists, surgeons and health professionals from NUI Galway, and elsewhere in Ireland and the UK, joined them to discuss the opportunities, risks and the ethical aspects of adult stem cell and gene therapies and nanomedicine.

The resulting report emphasises the need for more research in osteoarthritis, allied with a responsibility for researchers not to raise false hopes in patients. Panels expressed concerns about the ability of ethics committees to assess complex topics under time pressure with the Irish citizen panel called for a peer review system.

All panel groups were adamant that good communication between research teams and between researchers and the public was of utmost importance and stressed that successes and failures in research needed to be published. All panels also thought it was important not to neglect research into the causes of osteoarthritis and to also explore alternative and complementary medicine. Overall, the Irish participants were the most positive in the evaluation of the process with the final outcome a tentative endorsement of the GAMBA approach.

"Our experience with the Galway panels was very positive and rewarding. The dialogue challenged us as researchers to be more thoughtful about research questions and ethical standards, to place the patients centre stage and engage with the public in general as we develop novel therapies for the medicines of the future," says Dr Mary Murphy, the GAMBA leader at REMEDI.

-ends-

Keywords: *Press.*

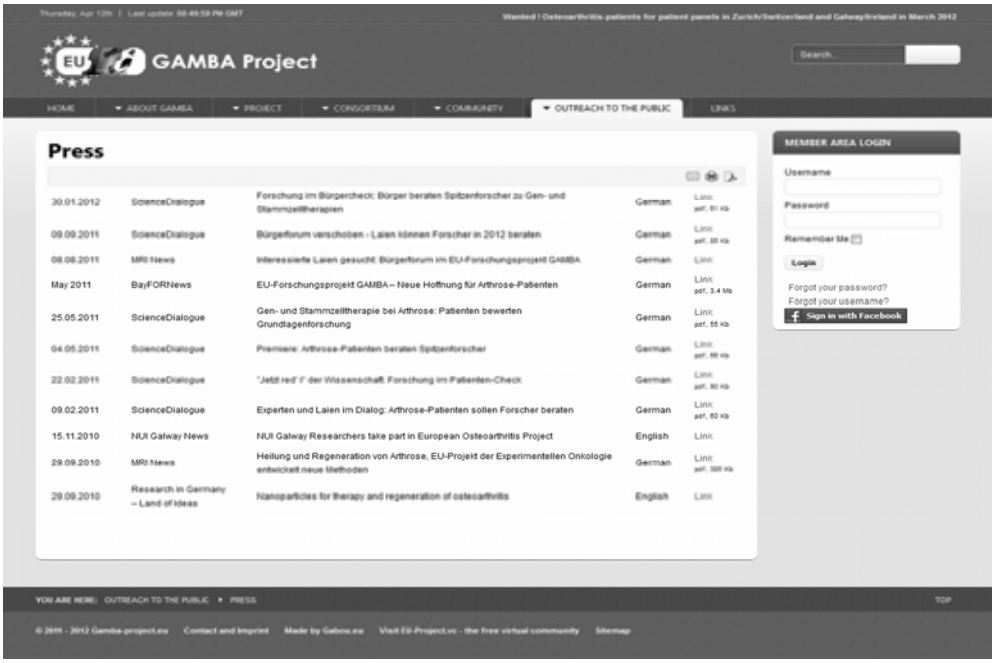
Author: Marketing and Communications Office, NUI Galway

« Back

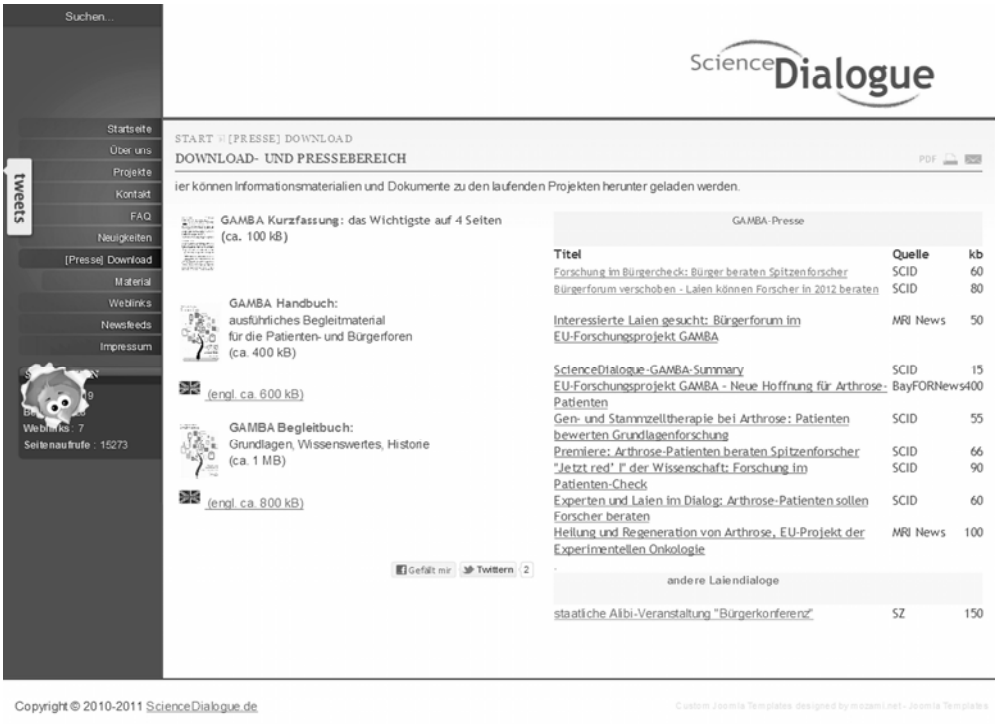
NUI Press posted 2012-10-30

Press releases

Press Releases on the homepages



www.gamba-project.eu (in English)



www.sciencedialogue.de (in German)

Press articles Ireland

Galway osteoarthritis researchers seek help of sufferers

OSTEOARTHRITIS researchers at NUI Galway are part of a new European project which is looking to incorporate the views of patients and the general public at the earliest stages of research.

As part of the EU-funded GAMBA project, the University is looking for osteoarthritis patients who would like to learn about new therapy approaches and are willing to evaluate theses approaches from a patient's point of view. The patients should be resident in Galway, be at least 18 years old, and be available for four days in March 2012.

The views of the general public will be sought in early summer.

Osteoarthritis is a very common joint disease, which can impact quite severely on the quality of life of patients. By the age of 65 most people are affected, and women are more commonly affected than men. Symptoms such as restricted mobility and pain can be alleviated and the progression of the disease can be slowed, but up to now it is not possible to heal the disease.

For the consultation project, based at the Institute for Regenerative Medicine (REMEDI) at NUI Galway, the participants will be introduced to the topics of innovative basic research into osteoarthritis and – depending on interest – further background information on gene therapy, stem cell research and nanomedicine.

"We are really planning to engage with the people who arguably know most about arthritis, the sufferers. What is it that patients need and want? Will it be possible to regrow bones, to generate cartilage in the body and to stop joint inflammation effectively in 20 years time? What risks and ethical aspects are associated with such visions? These are just some of the questions we want to discuss," said Dr Mary Murphy, REMEDI, NUI Galway.

Dr Murphy added: "Until now, the evaluation of the risks associated with new health technologies are normally left to the experts. New therapy approaches usually don't come to the attention of patients and society until they are tested in clinical trials or once the products are launched on the market. However, NUI Galway is actively inviting those suffering from osteoarthritis and the general public to contact them, so share their own insights with scientific experts."

All the sessions will be supported by a experienced team of moderators, who will ensure that the information supplied is comprehensible.

The application form and further information are available online http://www.gamba-project.eu/panels or can be requested on 091 49 4276. The main website for the project is http://gamba-project.eu.

Galway City Tribune 2012-1-27

Osteoarthritis study in Galway

A European research project into the experiences of people with osteoarthritis is due to get underway in Galway this month.

Researchers at NUI Galway are involved in a new EU-funded project on the condition, which aims to include the views of patients and the general public.

The GAMBA Project has been recruiting people with osteoarthritis living in Galway who would like to learn about new approaches to therapy and are then willing to evaluate these approaches.

"We are really planning to engage with the people who arguably know most about arthritis – the sufferers. What is it that patients need and want? Will it be possible to regrow bones, to generate cartilage in the body and to stop joint inflammation effectively in 20 years time? What risks and ethical aspects are associated with such visions? These are just some of the questions we want to discuss," explained Dr Mary Murphy of NUI Galway.

She pointed out that until now, the evaluation of risks linked with new health technologies were 'normally left to the experts'.

"New therapy approaches usually don't come to the attention of patients and society until they are tested in clinical trials or once the products are launched on the market. However, NUI Galway is actively inviting those suffering from osteoarthritis and the general public to contact them, to share their own insights with scientific experts."

Further information is available online at **www.gamba-project.eu**

Nursing in the Community 2012-2-16

{4} 13–08 GALWAY NEWS {sin} 30–01

New Research seeks Patients' and Publics' Views on Arthritis

By Martina Gannon

Osteoarthritis researchers at NUI Galway are involved in a new European project seeking to engage the views of patients and the general public at the earliest stages of their research.

As part of the EU-funded GAMBA project, the researchers are appealing for osteoarthritis patients who would be interested in learning about new therapy approaches and who are willing to evaluate theses approaches from a patient's perspective. The patients should be resident in Galway, be at least eighteen years old and be available for four days in March 2012. The views of the general public will be sought at the beginning of summer this year.

Participants will be introduced to the topics of innovative basic research into osteoarthritis during the consultation project, which is based at the Institute for Regenerative Medicine (REMEDI) at NUI Galway. Further information on gene therapy, stem cell research and nanomedicine will also be provided based on participants' interest.

Osteoarthritis is a common joint disease, which can have severe impacts on patients' quality of life. Most patients are affected at age sixty-five, with women more commonly affected than men. Symptoms such as restricted mobility and pain can be alleviated and the progression of the disease can be slowed, but up until now it has not been possible to cure the disease.

Dr Mary Murphy from REMEDI at NUI Galway claimed: "We are really planning to engage with the people who arguably know most about arthritis; the sufferers. What is it that patients need and want? Will it be possible to re-grow bones, to generate cartilage in the body and to stop joint inflammation effectively in 20 years time? What risks and ethical aspects are associated with such visions? These are just some of the questions we want to discuss".

Dr Murphy added: "Until now, the evaluation of the risks associated with new health technologies are normally left to the experts. New therapy approaches usually don't come to the attention of patients and society until they are tested in clinical trials or once the products are launched on the market. However, NUI Galway is actively inviting those suffering from osteoarthritis and the general public to contact them, so share their own insights with scientific experts."

Each of these interactive sessions will be supervised by experienced moderators who will ensure all aspects of the research are clearly and comprehensively explained to the patients.

Researchers at REMEDI in NUI Galway are involved in developing new methods for the treatment of osteoarthritis as part of the GAMBA project.

"The hope is", Dr Murphy concludes is "that these enriched biomaterials could make a regeneration of the joints possible."

Teresa Gannon, Vice Chairperson of Arthritis Ireland (Mayo) commented on the research initiative: "this research sounds very promising and it is encouraging to know that it is a European project as it should provide a wealth of new experience in the field of arthritis research. I look forward to their findings with great interest."

The application form for participation in this research and further information are available online http://www.gamba-project.eu/panels or can be obtained on 091 49 4276.

SIN 2012-1-30

Arthritis researchers looking for insights

Osteoarthritis researchers at NUI Galway are part of a new European project which is looking to incorporate the views of patients and the general public at the earliest stages of research.

As part of the EU-funded GAMBA project, NUI Galway is looking for osteoarthritis patients who would like to learn about new therapy approaches and are willing to evaluate theses approaches from a patient's point of view. The patients should be resident in Galway, be at least 18 years old, and be available for four days in March. The views of the general public will be sought in early summer.

Osteoarthritis is a very common joint disease, which can impact quite severely on the quality of life of patients. At the age of 65 most people are affected, and women are more commonly affected than men.

Symptoms such as restricted mobility and pain can be alleviated and the progression of the disease can be slowed, but up to now it is not possible to heal the disease.

For the consultation project, based at the Institute for Regenerative Medicine (REMEDI) at NUI Galway, the participants will be introduced to the topics of innovative basic research into osteoarthritis and – depending on interest – further background information on gene therapy, stem cell research and nanomedicine.

"We are really planning to engage with the people who arguably know most about arthritis, the sufferers. What is it that patients need and want? Will it be possible to regrow bones, to generate cartilage in the body and to stop joint inflammation effectively in 20 years time? What risks and ethical aspects are associated with such visions? These are just some of the questions we want to discuss," said Dr Mary Murphy, REMEDI, NUI Galway.

Dr Murphy added that until now, the evaluation of the risks associated with new health technologies are normally left to the experts.

"New therapy approaches usually don't come to the attention of patients and society until they are tested in clinical trials or once the products are launched on the market. However, NUI Galway is actively inviting those suffering from osteoarthritis and the general public to contact them, so share their own insights with scientific experts."

All the sessions will be supported by a experienced team of moderators, who will ensure that the information supplied is comprehensible.

As part of the GAMBA project (Gene Activated Matrices for Bone and Cartilage Regeneration in Arthritis) researchers at REMEDI are involved in developing new methods for the treatment of osteoarthritis.

In collaboration with nine partner institutions from Germany, France, Ireland, Italy, the Netherlands and Switzerland, researchers in REMEDI hope it might be possible to heal diseased joints in ten to 20 years. This would be done by introducing a combination of biomaterials, stem cells harvested from the patient, gene vectors and nanoparticles directly into the diseased tissue.

"The hope is that these enriched biomaterials could make a regeneration of the joints possible," explains Dr Murphy.

The application form and further information are available online http://www.gamba-project.eu/panels or can be requested on 091-494276. The main website for the project is http://gamba-project.eu.

Galway Independent 2012-2-01

REMEDI collaborate in major European osteoarthritis project

Dr Mary Murphy (NUIG) and Dr Thomas Ritter (NUIG)

Researchers at REMEDI became involved in an EU-funded col
2010 known as GAMBA which is short for 'Gene Activated M
Regeneration in Arthritis'. GAMBA which is coordinated by the
Iser at the Munich Technical University in Germany with additio
Netherlands and Switzerland, aims to use regenerative medicine
for osteoarthritis. REMEDI has received €382,000 in funding ov
total budget of €3.2 million.

Dr Mary Murphy of the orthobiologics group leads the GAMBA pr
the gene therapy group led by Dr Thomas Ritter to develop me
the osteoarthritic joint to prevent progression of osteoarthritis and
greater awareness and debate on the societal and ethical issu
affect patients and the public alike.

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MMI Annual Report 2010

Other Public Relations Work

Besides the distribution of press releases to all major German and local (Munich) media we delivered news to the GAMBA site (www.gamba-project.eu) and the ScienceDialogue.de site. The GAMBA website had the following hits (state August 2012):

- www.gamba-project.eu/outreach-to-the-public/panels: 2.556 Hits
- www.gamba-project.eu/outreach-to-the-public/press: 1.500 Hits
- www.gamba-project.eu/outreach-to-the-public/panels/patient-and-citizen-panels: 1.806 Hits

The sites www.ScienceDialogue.de or www.Wissenschaftsdialog.de had 3.250 hits (from November 2010 to August 2012).

At the Twitter account we published 150 tweets since August 2011. The Twitter site had about 500 followers (December 2012).

On March 5th 2012, the Bavarian broadcast station sent a one-hour broadcast with GAMBA researcher Prof Christian Plank, medical doctor Stephan Vogt as well as interviews with the speakers of the patient and citizen panels.