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Health-e-Child Consortium

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- 03 I.R.C.C.S. Giannina Gaslini (IGG)
- 04 University College London – Great Ormond Street Children's Hospital (UCL)
- 05 Assistance Publique Hopitaux de Paris – Necker (APHP)
- 06 European Organisation for Nuclear Research (CERN)
- 09 University of the West of England (UWE)
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- 12 The French National Institute for Research on Computer Science and Control (INRIA)
- 13 European Genetics Foundation (EGF)
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1. Summary

The major objective of the Health-e-Child project is to gain a comprehensive view of a child's health by vertically integrating biomedical data, information, and knowledge that spans the entire spectrum from genetic to clinical to epidemiological aspects.

The proposal is very complex and raises an array of ethical issues that need accurate management and that we can gather into the following ethically-sensitive areas:

- Research on human beings, specifically children.
- The safe extraction, storage, and usage of human biological samples.
- The collection of personal data and its potential distribution, especially genetic information. All data collected, after a rigorous process to make them anonymous, will be shared among all clinical and IT partners involved in the project.

For all the previously mentioned topics a standing Ethical and Legal Review Committee was instituted to ensure that all tasks and activities planned during the work-plan adhere to the project ethical framework and National and European legislations.

The work of this Ethical committee during these two years was to face and solve any ethical issues emerged during the preparation of the protocol and informed consent form, or raised by the different Local Ethical Committee.

Different protocols were prepared for rheumatologic, cardiologic and brain tumour studies taking into account the guidelines already defined in the description of work of Health-e Child project. Moreover dedicated informed consent forms for the three different discipline were prepared in each Centre taking part in the project, according to different local law and regulation. Strict adherence was requested to all National and European regulations, as well as to the Ethical principles applied within each of the clinical institutions participating in HeC.

The study received favourable opinions from the relevant Ethical Committees and the regulatory approvals of the competent national or local authority(ies) in the countries in which the research is being carried out.

A copy of the official approval from the relevant national or local Ethics Committees was provided to the European Commission.

It will be necessary to comply with these legal and ethical frameworks for the entire lifecycle of the project. The Ethical and Legal Review Committee is now being enlarged, as suggested by the European Commission, to some independent experts in ethical issues in order to enhance its autonomy in dealing with any possible upcoming ethical or legal implication. The aim is also that of putting into being an ethical framework capable of taking into account also issues which can be more complex than just current personal data, biological samples or genetic testing, if new issues happen to come up in the course of the project.

Dr Joan Dzenowagis, Project Manager, e-Health, World Health Organization, was contacted by our Ethical and Legal Review Committee and has declared her acceptance of becoming a member of the Committee.

2. Future plans

As the complexity of the project increases and the various work packages reach critical stages in the development of their work, it is necessary to bring together the various ethical strands that run through the project and to paint a more comprehensive picture of the current state of affairs. In particular, as technical partners begin to integrate aspects of the project working towards a set of inter-related services, it will also be necessary to bring their work also within the purview of the Ethics Committee.

A further issue which is now urgently calling for attention is that of bio-samples. Ethical approval at each centre must be scrutinised for clear evidence that it is equally well prepared for the handling of samples as well as paper and electronic records.

2.1. Ethics Committee

The Ethics Committee, working through the various Work Package leaders, has overall responsibility for managing the impact of ethics and law on the project and for tracking social and organizational issues, broadly conceived, as they may affect the project. At the top level, the issue is one of *governance*: the high level principles that the project adopts and the mechanisms by means of which the collaboration will ensure that these principles are adhered to. Among the latter will be:

- a commitment to the ethical processing of bio-samples and data from the patients in the project;
- observance of all national and EU-wide legislation as it concerns all aspects of the project; and
- an undertaking to explore a broad spectrum of social implications of the project and its impact on clinicians' work, on patients' welfare and on the economics of health.

Governance encapsulates these principles through *roles, rights, responsibilities* and *rules* (4R). Each role (always meaning, each individual performing that role) has certain rights and responsibilities by virtue of that role, rather than because of who they are; these are expressed in policies, incorporated in processes and are capable of transparent audit by being translated into rules to be observed by the project as a whole and by each role.

Therefore, WP3 must serve to ensure that all activity in the project complies with appropriate regulatory frameworks. In the course of doing so, it will collect and collate information on legislation, "common law" and regulatory requirements in Member States and overarching directives from the European Union. With a view to possible collaborations outside the EU, it will also consider the implications of legislation elsewhere, such as HIPAA in the USA and PIPEDA in Canada, and influential reports from major studies and completed research projects.

From the inception of the project, all clinical partners have sought and gained approval of their share of the work from local ethics boards. With major progress in the project, certain additional issues must be addressed:

- movement of data (and possibly bio-samples) between Member States;
- processing of data at academic centres and technical/industrial sites;
- incorporation of controls and audit of such activities in the fabric of the project; and

- management of governance issues through the active engagement of the Ethics Committee.

Work of permanent value, whose applicability extends beyond the confines of the project, will include:

- provision of exemplary documentary standards for governance and audit;
- provision of test-case scenarios to track from requirements through to execution;
- an outline design for a formally compliant data architecture for grids.

Thus, as the project approaches its conclusion, not only will its own requirements have been satisfied, but some tools of further usefulness and potential value to others will also have been provided.

2.2. Governance

The UK Department of Health summarised the principal features of a governance framework as follows: *Research Governance* is a framework which

- Sets out principles, requirements and standards
- Defines mechanisms to deliver them
- Describes monitoring and assessment arrangements
- Improves research and safeguards the public by:
 - enhancing ethical awareness and scientific quality
 - promoting good practice
 - reducing adverse incidents and ensuring lessons are learned
 - forestalling poor performance and misconduct
- Is for all those who:
 - design research studies
 - participate in research
 - host research in their organisation
 - fund research proposals or infrastructure
 - manage research
 - undertake research

Finally, its last two aspects are addressed almost entirely to stressing the inclusive nature of the legislation:

- Is for managers and staff, in all professional groups, no matter how senior or junior
- Is for those working in all health and social care research environments, including:
 - primary care
 - secondary care
 - tertiary care
 - social care
 - public health

From the point of view of the project, and with guidance from Dr Joan Dzenowagis, External Member of the Ethics Board, the Board has posed the governance issue to the consortium in these terms:

Do participants have policies, processes and audit capabilities to ensure they are abiding by local requirements?

Do participants have policies, processes and audit capabilities to ensure they are abiding by cross-border requirements especially if more stringent or vastly different?

Who will be responsible for finding out what those policies are and ensuring they are part of the documentation, and that project policies overall and of each new member reflect these or are in conformance?

What are the means for verifying (documenting, reporting and assuring) compliance on an ongoing basis?

Are there any examples that can be used to test whether policies hold up?

Given what the project hopes to do, what kind of planning and policies should be put in place now or in the near future so there are no surprises down the road?

Could this project develop a checklist/process that could be evaluated and published, and that would be a model for other, similar projects to follow?

The Ethics Committee, through its chair, is currently seeking the means to implement agreed processes and to report at the end of the project on deliverables of wider value.

3. IGG report

3.1. Inflammatory diseases (Juvenile Idiopathic Arthritis)

Responsible Prof. Alberto Martini

Gaslini's Local Ethical Board approved the JIA study on the 16th May 2006. No particular problems have emerged during the preparation of the protocol and the informed consent forms. The consent of the child, is required when the child's age and maturity make it necessary. For this reason three different informed consent forms were prepared: one for parent(s) or legal guardian, one suitable for the child and one to be used for patients older than 18 years old and/or to utilize if during the course of the study the enrolled patient will become legally able to consent.

Even if this project is a *non interventional study*, parents consent forms should be signed by both parents, whenever it is possible. In our experience we obtained the consent forms signed by both parents in about 70% of cases. It should be emphasised, however, that the consent forms have to be mandatory signed by both parents if divorced or if they have separate custody of the child.

In these informed consent forms, besides the design and purposes of the study it is clearly explained that participation is entirely voluntary and the child will receive the same level of care regardless of whether he or she is enrolled in the project. Moreover parents and children may decide at any stage to retract their consent to the project. In this case all information regarding the clinical status of the patient will be removed from our computer records and any residual biological samples will be eliminated.

The objective of the project is to increase the knowledge of disease features and predictors of outcomes in children with JIA by integrating the data of imaging techniques (Conventional

radiography, Magnetic Resonance Image and Musculoskeletal Ultrasound) with those obtained with different techniques and approaches (clinical data, laboratory test, genetic investigations and proteomic data on biological fluids).

Because of this, biological samples (blood and, if there is a clinical indication to make an arthrocentesis, synovial fluid) will be collected and stored in a bio bank for rheumatologic diseases located in Gaslini Institute to perform immunologic, genetic and proteomic investigations. In this regard appropriate informed consent has been prepared and approved by the Gaslini Ethical Board, in which the detailed studies we are going to perform and the modalities to guarantee the patients privacy are fully explained.

Recent advances in genetic research, focalised on Juvenile Idiopathic Arthritis, have enabled us to verify how individual variation of genetic code might influence the disease process or the progression and outcome of the disease after its onset.

It should be pointed out that for JIA no susceptibility genes will be investigated in the context of this study and in all cases the project will ensure the highest coherence to existing regulation on the testing of minors.

We are going to test genes potentially involved in the conditioning of the disease course (disease modifying genes). In particular we are interested in studying the polymorphisms of some genes involved in the process of bone remodelling in order to verify their possible role in the establishment and the progression of structural bone damage. In order to perform the analysis of these polymorphisms we should have also DNA of parents, if they willing; in the informed consent form for genetic investigations there is in fact a part for collecting the consent to obtain and store for the genetic analysis parents blood sample. It is specified in the project outline and in the informed consent that the blood sample from the parents it is not mandatory in order to enrol the patients in the study.

In this study the results from genetic analysis, will be integrated with radiological, clinical and immunological evaluations to provide a better knowledge on the role of genetic factors in JIA.

So only at the end of this study, through the vertical integration with all other data collected we will improve our knowledge about the significance of the investigated genetic factors.

Patients and parents are informed, moreover, that the results of the genetic tests we perform during the study can not immediately be used in clinical practices to predict the disease evolution or support therapeutic decision making.

Genetic data distinguish the identity of individuals, and for this reason, all of the concerns and proactive measures to protect the privacy of the patients involved in this study will be assured in accordance with National and Local Regulation.

Samples will be anonymised in order to allow sample and information sharing for research purpose using standardized anonymisation techniques, and demographic and clinical data attached to anonymised samples will be coded with international nomenclature.

Biological samples will be retained in secure locations for the duration of the project and afterward, following the standard practice of the hospital in which they were gathered. In the informed consent forms we ask directly the parents and children (when applicable for age) if they would want us to eliminate any residual biological samples and the relative information after the termination of the project or if they would want us to store the residual biological samples in the biologic biobank located in our Institute, which acts according to all local regulation and recommendations of the European Society of Human Genetics.

In addition, we asked them to express their written consent for the storage and the utilization of any residual sample only for research purposes dealing with children's diseases or within other research projects which had been approved by an independent ethical committee.

The collection of the data for this study does not require procedures (e.g arthrocentesis, sedation etc) that are not part of the standard care of children with the only exception of the withdrawing of a small amount of extra-blood for immunological, genetic and proteomic analysis at the time of routine venipuncture.

Magnetic Resonance Imaging (MRI) and Musculoskeletal Ultrasonography of the wrist and/or hip will be performed at study entry, and then after one year and, when possible, a two years follow-up. These imaging techniques have been shown to be superior to clinical and radiographic examination in the diagnosis and localization of joint effusion, inflammation and bone damage. Moreover these examinations are also capable of detecting the involvement of the soft tissues surrounding the joint (tendon, ligament etc) which are not investigated with conventional radiography.

The wrist and the hip, are the sites most vulnerable to changes seen on radiographs in patients with JIA. Furthermore, wrist disease has been associated with a more severe course of arthritis and a poorer functional outcome. Hip involvement is another poor prognostic indicator. In patients with hip involvement, hip MRI is a standard routine practice in order to assess the damage of the hip, which is functionally an extremely important joint. Sedation will be performed only for the execution of hip MRIs in patients who are not able to remain motionless during the scans. This procedure is to be considered as a part of the essential medical diagnostic investigations in a patients affected by JIA and clinical hip involvement.

For longer examinations, the potential need for sedation and intravenous administration of contrast material have limited the widespread use of MRI as a standard imaging modality for assessing arthritis in the paediatric population. Nevertheless, since more specific therapies have been developed for treating JIA recently, imaging scales targeted to the identification of early abnormalities are clearly needed.

In children there is still little experience with wrist MRI, a technique that has been extensively studied in adults affected by rheumatoid arthritis, and represents one of the most promising approach for the early detection of damage and for the sensitive assessment of its progression. The sedation to perform wrist MRI could not be considered a standard routine practice in JIA and so we decided that wrist MRI will only be performed on cooperating patients who do not require general anaesthesia.

Gaslini's Local Ethical Board approved the JIA study on the 16th May 2006. Patient enrolment started on June 2006. All parents and children to which the study was proposed accepted willingly and so far no ethical question raised after the illustration of the study. Most of the parents, furthermore, accepted willing to give a blood sample for the genetic analysis.

3.2. Paediatric heart diseases

Responsible: Dr. Giacomo Pongiglione

Gaslini's Local Ethical Board approved cardiologic study on the 29th September 2006. From October 2006 till the end of June 2008, 103 patients have been enrolled. Almost all parents and children to which the study was proposed accepted willingly and up to now (January 2009) no ethical questions were raised after the illustration of the study. Only one patient has

revoked the consent for enrolment in the project for personal reasons and has consequently been withdrawn.

As agreed, neither X-rays nor the use of sedation was additionally performed for research purposes. As stated in the study protocol and in the informed consent form the collection of data for this research project does not require procedures that are not part of the standard care of the child both at diagnostic and therapeutic levels for this specific type of heart disease. Therefore, the use of sedation will be taken in consideration in younger or non collaborative patients only in case that the diagnostic or therapeutic procedure is considered fundamental for the routine management of the patient. In conclusion no test, investigation (magnetic resonance imaging, cardiac catheterization...), nor procedures (e.g. sedation) were performed unless it is part of the essential diagnostic approach or medical treatment of the patient.

Reference is made to the informed consent form in which it has been stated that differently collected data and samples may continue to be conserved in the biobank for a prolonged period only after obtaining the patient's or legal guardian's authorization to do so.

Finally project updates have been periodically provided to the IGG Ethical Committee. An amendment to the study protocol has recently been submitted to the Local Ethical Committee: a request for a further year of patients enrolment was forwarded and approved. Moreover, the introduction of OPBG as a fourth clinical partner for the project was reported to the Committee.

3.3. Brain tumours (Gliomas) [December 2008]

Responsible Dr. Maria Luisa Garrè

Imaging studies (MRI, CT) of the 49 eligible cases studied up to now for gene expression profile, were available for review when cases were retrospective; in all new cases (12 patients) admitted, since the study began, MRI, Spectroscopy-MRI and CT scan were performed according to the routine protocol adopted for all brain tumours, and informed consent was obtained for anaesthesia, if required, and for gadolinium injection; no one of the new cases refused to perform the diagnostic test which was fundamental for surgery or tumour treatment.

All the new 12 cases were informed of the biological study and the written consent was obtained, at the moment of surgery, for tumour removal or biopsy. None of them refused to participate in the study. The retrospective cases (the cases whose tumours were available in the tumour bank) were contacted to obtain the informed consent. The families were informed by phone, by the PI (MLG), and subsequently the informed consent was collected at the follow-up visit. In some cases the informed consent was collected by mail, after one or more phone conversations and after letters containing the basic information concerning the study had been received by the signatories. Generally the compliance to the study was very high and parents cooperative. Even when parents could not come in person, they wrote letters to IGG, underlining their satisfaction regarding the initiative of the study.

Since the approval of the study by the local Ethical Committee (15th of November 2006), no ethical question was raised. The only problems were represented by the few cases of patients who died, when it was not possible to get easily in touch with the family.

4. UCL report

4.1. Inflammatory diseases (Juvenile Idiopathic Arthritis)

Professor Patricia Woo

The Research Ethics Committee for the Institute of Child Health/Great Ormond Street Hospital approved the study on December 22nd 2006 (approval no. 06/Q0508/111) In compliance with their approval we also registered the study with the Research and Development office at UCL. In line with this a clinical risk assessment was carried out and approved on the 14th June 2006. On the 25th January 2008 we provided an annual report of our work in order to re-registered the study and ensure up-to-date approval from the R&D department at UCL.

Since enrolment began on the 30/07/07, we have enrolled 80 patients to date and as of now, no patients have refused to participate on ethical grounds. 4 participants have withdrawn from the study post-baseline due to time issues. Aside from this, there have been no ethical issues raised by participants/ guardians.

Since our previous report last year we have upheld ethical practice:

Appropriate informed consent in which the detailed studies we are carrying out and the modalities to guarantee the patients privacy are fully explained, are signed by all participants/guardians (as age appropriate under Consent Laws). Informed consent is obtained on the day of the recruit's first visit with the parent/guardian. A time period in excess of 24 hours is maintained from the initial introduction of the project to the subject, to the actual signing of consent.

Consent forms are kept in patient research folders and a copy is kept in the patient medical records. These files are kept in a security code protected room in the hospital grounds. All electronic data is stored on the hospital's internal firewalled system. All files are password protected and encrypted.

Biological samples are retained in secure locations for the duration of the project. In the informed consent form we ask consent from parents and children (when applicable for age) directly that the samples are gifted to the researcher at GOSH. One Guardian did refuse to provide their child's DNA data owing to concern about confidentiality despite reassurances. As indicated in the consent form signed prior to taking part, the participant's right to withdraw was respected and no DNA data has been included from this participant. All other patients thus far have expressed their written consent to the storage and the utilization of any residual sample for research purposes dealing with children's disease and within other research projects that have been approved by an independent ethical committee.

Patients and parents are informed that the results of genetic test we perform during the study could not immediately be used in clinical practice to predict the disease evolution and support therapeutic decision. Furthermore, the UK data protection laws are applied to the data collected. Samples are anonymised in order to allow sample and information sharing between the centres for research purpose using standardized anonymisation techniques, and demographic and clinical data attached to anonymised samples is coded with international nomenclature. This year we changed the coding system from an initial-based code to a random numerical/letter code so that the HeC patient numbers no longer contain any personal information.

With regards to MRIs carried out for the purpose of the study, sedation is performed only for the execution of hip MRI in patients who are not able to remain motionless during the scans.

This procedure is to be considered as a part of the essential medical diagnostic investigations in a patients affected by JIA and clinical hip involvement. The sedation to perform wrist MRI could not be considered a standard routine practice in JIA and so we only perform Wrist MRI on cooperating patients who do not require general anesthesia. In our experience sedation is not required to perform wrist or hip conventional radiography and musculoskeletal ultrasound.

4.2. Paediatric Heart disease

The Research Ethics Committee for the Institute of Child Health/Great Ormond Street Hospital approved the study on December 22nd 2006 (approval no. 06/Q0508/111) In compliance with their approval we also registered the study with the Research and Development office at UCL. In line with this a clinical risk assessment was carried out and approved on the 14th June 2006. On the 25th January 2008 we provided an annual report of our work in order to re-registered the study and ensure up-to-date approval from the R&D department at UCL.

Data collection protocols for Paediatric Heart Diseases was discussed between Clinicians of the three Hospitals at the start of the study, and established with regard to cardiovascular MR, echocardiography, exercise-testing, familial and para-clinical investigations (e.g. basic haematological tests, specific laboratory tests etc.).

There have been 200 patients recruited to the study at UCL in total. In accordance with their ethical and legal rights to refuse participation, 2 patients chose not to participate in the study and this was respected. Aside from this there have been no ethical issues raised by participants/ guardians to date.

Since the study received ethical approval in 2006 we have upheld ethical practice:

The Information and consent forms for this study which were approved by the ethics committee, fully explain the research we are carrying out and the modalities to guarantee the patients privacy. All participants/guardians read and signed the consent forms before taking-part. One parent/guardian has been required to consent on behalf of the child, in line with standard practice/ guidance of the Ethics Committee.

No genetic data has been acquired at UCL as this is not performed as routine analysis and the ability for genetic data assessment outside the UK is not possible, thus storage of these samples is not an issue.

As stipulated in the participant consent forms, the UK data protection laws are applied to the data collected; data is anonymised in order to allow information sharing between the centres for research purposes whilst upholding the participants' anonymity. This is done using standardized anonymisation techniques, and demographic and clinical data attached to anonymised samples is coded with international nomenclature. All electronic copies of HeC participant details are stored on the internal firewalled hospital system and all files password protected and encrypted.

As stated in the study protocol and assured to patients in the participant consent forms, the collection of data for this research project does not require procedures that are not part of the standard care of the child both at diagnostic and therapeutic levels, for the specific type of heart disease. Sedation is only used in younger or non-cooperative patients for diagnostic or therapeutic procedure that are considered fundamental for the routine management of each patient. In conclusion, no test, investigation (e.g. magnetic resonance imaging, cardiac

catheterization etc.), nor procedures (e.g. sedation) are performed unless it is part of the essential diagnostic approach or medical treatment of the patient.

5. APHP report

5.1. Inflammatory diseases (Juvenile Idiopathic Arthritis) [2008]

Responsible Pierre Quartier

The CPP (Committee for the Protection of Patients) approved the Juvenile Idiopathic Arthritis (JIA) part of HeC study in September 2006. The CNIL (National Ethical Committee) received the same month the information about the trial and in the absence of any comments from this committee within 2 months it is considered that there is no disagreement. The official confirmation from CNIL was received in June 2007. The patient's enrolment started on October 2006 and until the end of December 2007, 52 patients had been enrolled. Seven of them have had a one-year follow-up visit. All parents and children to whom the study was proposed accepted it without problems and up to now no ethical question was raised after the illustration of the study. Clinical data are available for all patients. All of them had undergone all imaging (including one-year control group) and, for each patient, blood samples had been collected and stored in biobank to perform genetic studies. In almost all cases, blood sample collection was done for both parents as well. The question about how to transfer blood samples abroad for genetic analyses to be performed at IGG is ongoing (some specific authorizations are required), and it is still to be seen how the samples can be sent.

5.2. Paediatric Heart disease [2008]

Responsible: Dr. Younes Boudjemline

The study has been considered an observatory, thus informed consent was not required. Patients are informed that medical data will be used and anonymised before being input into the network, and they can refuse to participate in the study without compromising their follow up. The export of informative data is now authorised, since CNIL's approval on May 15th, 2007. One patient refused to participate in the study. As expected, 33 patients for cardiomyopathy were enrolled since September 2006. Clinical data were collected for all of them, and 2D/3D echocardiography and 24 hours Holter EKG. None had MRI as it is not Necker's current medical practise. All had metabolic exams at diagnosis. Some patients refused to have biological testing. 21 had BNP, all had DNA storage. 67 patients were enrolled for dilated right ventricle since the end of November 2006; all had a 2D echocardiography, 55 had MRI (5 pace makers and 7 refusals of MRI), 55 had exercise testing, 56 had BNP and 59 had 24 hour Holter EKG. Medical data were recorded on paper forms (identical to the informative forms). Echocardiographic exams were stored on a hard drive in raw data. Systematic X-rays were not performed if it was of no utility for the patients. In very rare cases, management of some patients required sedation, especially for blood sample collection. Applying HeC's protocol, no additional use of sedative medication had to be taken. Genetic investigations were carried out in the way in which they are usually performed according to the various pathologies. Since the study was considered as an observatory, no specific consent was obtained for genetic testing. For cardiomyopathies, DNA was stored for all patients but no specific analysis was carried out. If it were decided to

analyze the DNA, specific authorization (mentioning the gene to be searched) should be obtained from Ethical Committee and from the parents. For Tetralogy of Fallot, all patients had standard caryotype and a FISH to look for 22q11 deletion. No patient was asked to have further genetic studies.

6. OPBG report

6.1. Inflammatory diseases (Juvenile Idiopathic Arthritis)

Responsible Prof. Alberto G. Ugazio, Dott.ssa Claudia Bracaglia

Bambino Gesù's Local Ethical Board approved the JIA study of the Health-e-Child project on the 18th March 2008 and the patient enrolment started on April 2008. Until now 29 patients have been enrolled. All parents and children to which the study was proposed accepted it gladly and up to now (January 2009) no ethical question raised after the illustration of the study.

No particular problems have emerged during the preparation of the protocol and informed consent forms. The consent of the child, as well as that of the parent(s) or legal guardian, is required when the child's age and maturity make this doable.

For this reason three different informed consent forms were prepared: one for parent(s) or legal guardian, one suitable for the child and one for teenage patients.

In these informed consent, in addition to the design and purpose of the study, it is clearly explained that the participation is completely voluntary and that the child will receive the same level of care regardless of whether he/she is enrolled or not in the project. Moreover parents and children may decide at any stage to decline further participation in the study. In this case all information regarding the clinical status of the patient will be removed from our computer records.

The objective of the project is to increase the knowledge on disease features and on predictors of outcome in children with JIA by integrating the data of imaging techniques (X-rays, Magnetic Resonance Image and Musculoskeletal Ultrasound) with those obtained with different techniques and approaches (clinical data and laboratory test).

We did not collect biologic samples for the genetic study because the OPBG did not participate to the genetic investigations in JIA of the HeC project.

In this study clinical evaluations will be integrated with radiological and laboratory data to provide a better knowledge of the JIA. So only at the end of this study, through the vertical integration of different data may we improve the significance of the investigated factors. The collection of the data for this study does not require procedures (e.g. arthrocentesis, sedation etc) that are not part of the standard care of children.

Magnetic Resonance Imaging (MRI) and Musculoskeletal Ultrasonography of the wrist and/or hip will be performed at study entry, and then after one year and, when possible, a two years follow-up. These imaging techniques have been shown to be superior to clinical and radiographic examination in the diagnosis and localization of joint effusion, inflammation and bone damage.

The wrist and the hip, are the sites most vulnerable to changes seen on radiographs in patients with JIA. Furthermore, wrist disease has been associated with a more severe course of arthritis and a poorer functional outcome. Hip involvement is another poor prognostic indicator. In patients with hip involvement, hip MRI is standard routine practice in

order to assess the damage of the hip, which is functionally an extremely important joint. Sedation will be performed only for the execution of hip MRI in patients who are not able to remain motionless during the scans and who needs to be studied very accurately and in those patients who MRI is considered essential regardless of study.

In children there is a poor experience with wrist MRI, a technique that has been extensively studied in adults affected by rheumatoid arthritis, and represents one of the most promising approaches for the detection of early damage and for the sensitive assessment of its progression. The sedation to perform wrist MRI can not be considered a standard routine practice in JIA, so we decided that wrist MRI will be usually performed in cooperating patients. This study will not include those patients who need sedation to perform wrist MRI.

In our experience general anaesthesia or sedation is not required to perform wrist or hip conventional radiography and musculoskeletal ultrasound.

6.2. Paediatric Heart disease – OPBG report

Responsible: Dr. Stephen P. Sanders.

The ethical committee approved the study in May 2008 but due to organizing issues we could not start to enrol patients until the 1st July. We worked at the Day Hospital Department. As stated in the study protocol and in the informed consent form, the collection of data for this research project does not require procedures that are not part of the standard care of the child both at diagnostic and therapeutic levels, for the specific type of heart disease. Sedation will be used only in younger or non-cooperative patients for diagnostic or therapeutic procedure that are considered fundamental for the routine management of each patient. We do not change our current medical practice. We enrolled 50 patients for Tetralogy of Fallot. No patient or family who was approached about the project refused to take part once the concepts had been illustrated to them. Although some of them refused to have the genetic tests, in all cases it was because they (or their parents) were afraid of having blood drawn.

Currently we are recording medical data in an excel database which is contained in the Hospital system. Echocardiographic exams are stored in videotapes as is the usual procedure in the Ecocardiographic laboratory. We have not performed X-rays investigations to date as they have of no utility to the specific patients in question.