3. 諸外国の状況

進捗状況のポイントは2点である。地域ベースで全症例を把握できるか、という点と、資金調達ができるか、という点である。前者に関しては、英国やオーストラリア、部分的にインドもクリアできている。また、カバーする人口が小さい国や地域も前者はクリアしやすい。しかしながら、小さい国やインドの場合、後者の資金調達が障害となっているようだった。今後、米国や国際機関へ、研究グループ全体として研究費の申請をする方向に向かっていた。

D. 考察

日本では発生頻度が低いと考えられているWilms 腫瘍と神経芽細胞腫は、欧米では比較的発生頻度が高く、重視されている。今回、遺伝子レベルでの解明や環境曝露の測定も視野に入れた国際的な共同研究プロジェクトが立ち上げられている。

日本の参加は前任者によって表明されているが、実際には何も着手されていなかった。今回、プロトコールを入手し、あらためて参加可能性を検討してみた。

まず、結果の3で述べた地域ベースでの症例把握については、大阪等のごく限られた地域では可能性があるものの日本の現状では不可能である。

次に、結果の2で述べた検体の採取や性・年齢・居住地をマッチさせた健常コントロールを得ることについては、日本の研究に対する一般認識や研究基盤の整備状況を考慮すると非常に困難と思われる。

E. 結論

小児がん研究に関する本邦の現状を考えると、ISET への参加は非常に困難と思われる。

F. 健康危険情報

なし

G. 研究発表

なし

H. 知的財産権の出願・登録状況

なし

International Study of Non-CNS Embryonal Tumors (ISET)

Pilot Study on Wilms and Neuroblastoma

Study Protocol

International Agency for Research on Cancer, Lyon, France

and

ISET Protocol Working Group

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Table of Contents

Appendices

1. BACKGROUND

Although childhood cancers are rare, research on childhood cancer could have major impact on public health particularly on the potential gain of years or quality of life. However, there is a lack of large-scale etiological studies in all types of childhood cancers and there are very limited data on causes and mechanisms. Previous studies of childhood cancers other than leukaemia and brain tumours, have been small and lacking in power. In addition, a number of important gaps can be identified in the current literature, including (i) the role of exposure to suspected risk factors at different key periods (preconceptional, prenatal or postnatal) are not elucidated, thus reducing the scope for intervention; (ii) limited studies have been conducted on genetic susceptibility factors and gene-environmental interactions; (iii) novel molecular markers (e.g., methylation and DNA repair capacity) have not been integrated in studies aimed to elucidate aetiology and eventually prevent and control these neoplasms.

To address these gaps in knowledge and provide new tools for their prevention and control, IARC has initiated a multicenter study, which aims to include large sample sizes to address the problems of lack of power and chance findings, to incorporate biomarkers of exposure and mechanism (e.g. DNA methylation and repair capacity), and to conduct comprehensive investigations on gene-environment interactions. To achieve these research goals, the study will be conducted in collaboration with clinical networks such as SIOP and COG.

The study will be focused on non-CNS embryonal tumors which have been severely under-studied due to their rarity. Non-CNS embryonal tumors are a group of specialized tumors seen in very young children, with microscopic appearance resembling the structures seen in developing tissues of the embryo and fetus. The study will include retinoblastoma, Wilms tumor, rhabdomyosarcoma, neuroblastoma and hepatoblastoma. The pilot study will be focused on Wilms tumor and neuroblastoma.

2. OBJECTIVES OF THE STUDY

The objectives of the full-scale study are to understand the etiology of embryonal tumors focusing on genetic susceptibility, prenatal factors and neonatal exposures as well as aspects of molecular epidemiology including epigenetic profiles, DNA repair capacity and mutation patterns. The following hypothesis will be addressed:

1) Factors associated with prenatal growth and development are important in determining risk
2) There are particularly vulnerable periods during histogenesis and organ development which may vary for different tumors
3) Maternal factors during the periconceptional period and pregnancy, including exogenous agents (e.g. viruses, diet, tobacco smoke) may influence risk
4) Paternal lifestyle and occupational exposures during the periconceptional period and the mother's pregnancy may influence risk
5) Exposure of the child during the neonatal period and infancy to potentially mutagenic agents may play a role. Premature and other infants experiencing neonatal intensive care may be particularly at risk.
6) Parents and child's genetic susceptibility will influence the risk of embyronal tumors.
7) Risk may be modified by the genotype of the child (or the parents) with respect to polymorphic variants of genes involved in metabolism, growth and development, as well as DNA repair and cell cycle.
8) DNA repair capacity and epigenetic profiles of the parents and / or the index child may influence risk.
9) A proportion of cases will occur in children with predisposing congenital anomalies/syndromes and/or mutations to high penetrance cancer-associated genes. These may be due to new germline mutations (see iii and iv above)

<u>The main objectives of the pilot study are</u>:

1) To test the various methods of case and control recruitment (the primary objective)
2) To assess the clarity and effectiveness of the questionnaire
3) To estimate the proportion of cases recruited, compared to the cancer registries
4) To estimate the exposure frequencies in our study population for power calculation of the full-scale study
5) To test the feasibility and mechanism of biological sample collection
6) To harmonise the study across participating countries

Participating centers will aim to achieve following items during the pilot phase

1) Obtain agreement to case recruitment in major treating hospitals in their region
2) Identify the best mechanisms of recruiting unrelated controls, and establish collaboration with the clinics or institutes accordingly.
3) Clarify the feasibility of obtaining biological samples, including tumor tissues in collaboration with the clinical trial group

Participating centers will start the subject recruitment, interview and biological sample collection with the most desirable mechanisms specified in each section. When the most desirable mechanism is proven not feasible, the center may proceed with the second option. A summary matrix will be prepared at the end of the pilot study to illustrate the feasible mechanisms in each center. This will help the protocol WG to come up with a set of criteria and a harmonized protocol for the full study.

The data collected prospectively in the pilot study will be included in the full-scale study. The biological samples collected in the pilot study will be analyzed for quality assessment, and the laboratory results obtained from the pilot samples will also be included in the full scale study when the quality is proven to be adequate.

3. SUMMARY OF THE STUDY DESIGN

Summary points

1. Multicenter study
2. Recruit cases of Wilms tumor and neuroblastoma
3. Trio design. Every center will recruit parents of the index cases
4. Unrelated controls are optional. Centers will test the feasibility of recruiting population-based controls in the pilot phase.
5. Structured lifestyle questionnaire and interview for parental and index child exposures
6. Obtain DNA sources from all subjects (trios and unrelated controls)
7. Obtain tumour tissue samples when possible

The pilot study will be conducted in eight countries in Europe (UK, France, the Netherlands, Italy, Switzerland, Czech Republic, Slovenia and Serbia), four centres in America (California USA, Ontario Canada, Sao Paulo, and Rio de Janeiro), and three countries in Asia / Oceania (India, Japan and Australia)

Each center will recruit at least one-year's worth of cases and will conduct a detailed personal interview with the parents of the index child during which they will provide information on lifestyle habits including, tobacco and alcohol consumption, medical and family history, and other environmental exposures. The primary care taker of the index child (can be either mother or father) will also provide information on neonatal and infancy history of the index child.

The unrelated control group will be recruited from subjects identified through a population list such as lists from local general practitioners, lists for child welfare clinics, or birth registries. Controls will be frequency matched to cases on age, sex and geographical region, and recruited during the same period of time.

A fresh blood sample will also be collected from the trios (parents 20ml, and index child 5-20ml if the blood sample need to be drawn for other medical reasons) and unrelated controls for analysis of genetic susceptibility and phenotypic assays such as DNA repair capacity. When blood samples are not available from any study subjects, saliva will be collected as the alternative DNA source, which is likely to be the case for the index child and unrelated controls. Tumour samples (frozen or paraffin embedded) will also be collected from the cases whenever possible in collaboration with clinical trials groups.

4. CASE RECRUITMENT

Summary points
1.Cases include children with Wilms tumor and neuroblastoma.
2.Cases may be identified and recruited based on initial diagnosis. Histological confirmation of diagnosis will follow.
3.Cases are aged less than 15
4. Parents of the index cases will be recruited for the trio design.

4.1 Case definition and eligibility

Cases will be eligible for the study if they (i) diagnosed before 15th birthday; (ii) have microscopically-confirmed diagnosis; (iii) diagnosed one year prior the start of the study to one year after; (iv) do not have a history of cancer prior to the current diagnosis; (v) parents are residents in the catchment area for at least one year. See Appendix 1 for the definition of catchment area in different centres. The eligibility of the cases will be screened with the Eligibility Assessment Form, and an informed consent should be obtained before proceeding to interview.

Patients with the following diagnoses will be included as two separate series of cases--

(i) Wilms tumors/nephroblastoma, (M8960/3, M8959/1)

(ii) Neuroblastoma (M9500/3) and Ganglioneuroblastoma (M9490/3)

4.2 Case ascertainment

An effort will be made to identify all cases in the catchment area. The completeness of the case ascertainment will be checked against cancer registry records.

To shorten the pilot phase, centers will recruit cases both retrospectively and prospectively.

4.2.1 Prospective recruitment

Cases should be identified from the participating hospitals as soon as possible after the clinical diagnosis is made, with an aim of identifying all cases within two weeks of diagnosis. Histological confirmation will follow for case eligibility. In particular all renal tumors of childhood should be recruited to avoid missing Wilms tumor cases. In this instance, a case should be interviewed and biological samples taken before the final reviewed microscopic diagnosis is established, pending subsequent confirmation.

Early identification is possible only through active searches with the following mechanisms --
(i) periodical visits to the hospital departments where cases are diagnosed or treated (i.e., pediatric oncology unit, pediatric department in the hospitals, etc). The frequency of the visits (daily, weekly etc.) will depend on the cancer burden of each department, and the organization of the hospital.
(ii) Collaborate with the SIOP/COG trials and periodical checks of the recruitment records for new patients registered into the trials.

Once the cases are identified, the local coordinator will obtain the consent of the referring physician to contact case parents. Upon the agreement of the parents, the interview team will proceed with the approach to parents, consent, interview and biological sample collection.

4.2.2 Retrospective recruitment

Retrospective cases will be identified at the start of the pilot study through the following means: (i) hospital records (ii) cancer registry (iii) SIOP/COG records. Only cases diagnosed within one year before the start of the study are eligible for the pilot study. Once the cases are identified, the local coordinator will obtain the consent of the referring physician to contact case parents. Upon the consent of the parents, the interview team will proceed with the interview and biological sample collection.

4.3 Trio design

Both parents of the index cases will be recruited into the study. They will be interviewed with questionnaires specifically for mothers or fathers and biological samples will be taken. Non-biological parents will still be interviewed if he or she has been living with the index child for at least 2 years. However, they will only be interviewed for their lifestyle risk factors in the neonatal periods of the index child. Biological samples will not be collected from the non-biological parents.

If the affected index child is one of the twins, an additional interview will be conducted for the unaffected sibling with the neonatal questionnaire. If the affected index child is one of the triplets or more, an additional interview will be conducted for the unaffected sibling in the next birth order (unless if the affected index child was born last, then the additional interview will be conducted for the unaffected sibling born right before the index child).

4.5. Non participants

For both prospective and retrospective recruitment, the interview team will keep a logsheet of all the subjects who they attempt to approach. In instances when the interview did not take place, the interview team should indicate the reason for lack of interview or material collection (e.g. refusal, etc). This information will be recorded in the logsheet of non-participants. Recruitment rates in relation to age, sex, stage etc and in relation to timing of approach relative to diagnosis will be assessed. These may vary by centre. Results will be valuable for the final study design.

5. CONTROL RECRUITMENT

Summary points
1. The first choice of unrelated controls is population-based controls. Centres will aim to recruit population-based controls in the pilot study.
2. Unrelated controls will be frequency matched with case on age, sex and geographical regions
3. Interviews and blood/saliva sample collection will proceed as for cases.

Unrelated controls will be recruited in each centre during the same period of time, frequency matched to cases for age (+/- 1 year), sex, ethnicity and geographical region. The geographical region is the catchment area defined in the Appendix 1. All unrelated controls should be less than 15 years old at the time of recruitment.

5.1 Population-based controls

Population-based controls should have no neoplasm at the time of recruitment. Centers will aim to recruit population-based controls in the pilot study with one of the following mechanisms.

5.1.1. Birth registry:

(i) The recruitment team will select controls randomly from the birth registry of the catchment area that match age, sex, ethnicity and residence area of the cases.

(ii) The recruitment team will obtain the contact information of controls' parents, and approach them and inform them of the study objectives. An informed consent should be obtained before proceeding to interview.

(iii) If the first-choice controls could not be contacted or refuse to participate, then the next randomly selected control is pursued. This process is repeated until an eligible control is successfully interviewed.

(iv) A log of non-participants and reasons for non-participation should be kept.

5.1.2.General practitioners or child welfare clinics:

(i) The recruitment team will contact a representative group of GPs throughout their catchment area. If the list of GPs in the catchment area is not available, parents of the index child will be asked for the name and the address of their general practitioner, along with signed authorization to contact the child's GP for the purpose of the study

(ii) The GP will be contacted and the background to the study will be explained, including the interview procedure for cases and controls.

(iii) Subsequently, the recruitment team will work with the GPs who are willing to participate and select potential controls who are of similar age (+/- 1 years), same sex and ethnicity to the index child, from GP's list of patients who will be coming in for either vaccination or healthy check-up.

(iv) To avoid selection bias, it is essential that the recruitment team, not the GP, decides which control to contact. A protocol that ensures random control selection will be developed at centres using GPs as the source of controls. These protocols will take account of local circumstances and will be drawn up with the IARC core group. The recruitment team will approach the potential controls until a group of controls with similar distribution of sex, age, ethnicity are successfully recruited.

(v) GP will contact the parents of the selected controls and inform them of the study. If the parents of the potential controls agree to participate, then they will be interviewed by a trained interviewer at the time when they are scheduled to come in to GP's office, and a blood sample will

be collected from the controls by the GP or the nurse. If the parents of the controls do not wish blood sample to be taken, a saliva sample will be collected instead.

(vi) An administration fee will be provided to the GP should they choose to participate.

5.2 hospital-based controls

For centers that are unable to recruit population-based controls from any of the mechanisms mentioned above can recruit hospital-based controls as an alternative source of unrelated controls.

5.2.1. Eligibility

The hospital controls will be identified in the pediatric department of the hospitals in the same catchment area of the index cases, frequency matched on age (+/- 1 years) and sex, ethnicity and area of residence. The hospital controls need to fulfill all of following criteria to be eligible for the study.

a, Parents have lived in the same geographical area as the index cases' parents for at least one year.
b. not admitted to the recruiting hospital for any neoplasm
c. not admitted to the recruiting hospital for any renal or neurological disorder
d. not admitted to the recruiting hospital for any congenital anomalies

5.2.2. Recruitment process

(i) The recruitment team will work with the hospital staff and conduct active search in the hospital records to look for potential controls.

(ii) To avoid selection bias, it is essential that the recruitment team makes the final selection of the potential controls. A protocol that ensures random control selection will be developed at centres using hospital controls. These protocols will take account of local circumstances and will be drawn up with the IARC core group. The recruitment team will approach the potential controls until the eligible parents of an eligible control are successfully interviewed.

(iii) The hospital staff will contact the parents of the selected controls and inform them of the study. If the parents of the potential controls agree to participate, then they will be interviewed by a trained interviewer at the time when they are scheduled to attend hospital and a blood sample will be collected from the controls by the doctor or nurse. If the parents of the controls do not wish blood samples to be taken, a saliva sample will be collected instead.

Based on the results of the pilot study, the protocol of the final study will include an Appendix specifying the mechanism of control recruitment in each centre.

6. INTERVIEW PROCEDURE

1. The first choice interview procedure is face-to-face. When face-to-face interview is not possible, the interview can be conducted via telephone.
2. Mother and Father of the index cases and unrelated controls will be interviewed with separate questionnaires.
3. Neonatal history will be answered by the main care taker of the child
4. Same set of questionnaires will be used for all tumor types
5. Non-respondents will be recorded in the logsheet.

A trained interviewer will conduct a structured interview with questionnaire, either face-to-face (preferable choice) or by telephone when face-to-face interview is not possible. A list of questionnaire topics will be sent in advance to help the participants better prepared for the interview. The interview will be conducted separately for mothers and for fathers with different questionnaire, and neonatal history will be answered by the main care taker of the child. Same set of questionnaires will be used for all tumor types and unrelated controls. (under development- will be attached as Appendix when ready)

Information on the basis for the diagnosis and clinical stage will be obtained for each case using a standard form (attached at the end of the questionnaire). A copy of histological report should be attached to the questionnaire.

If the interviews were not completed, the interviewer will maintain a record in the logsheet and specify the reason for lack of interview or incomplete interview (refusal, not eligible, etc)

Interview Guidelines

6.1. The Start

6.1.1.At the start of the interview the interviewer should present him/herself to the subject and also present the study. A general introduction is contained in page 2 of the questionnaire. The interviewer should explain that the interview may last about one hour and that the participant may stop the interview at any moment. It should also be explained that participation is voluntary and that all of the data will be completely anonymous at the point of analysis. A written consent will be obtained at this moment. All interviews should be conducted privately.

6.1.2. Subject refusal

When someone refuses to participate in the interview the interviewer should ask why he/she refuses to participate and record the answer on the log sheet for non-participating cases and controls. If the subject is unwilling to give a reason for refusal, the interviewer should accept this without further questioning. If feasible the interviewer should propose to reschedule. If the participant does not wish to reschedule, then the interviewer should ask if it is possible to obtain at least the basic information in the demographic section. If the subject is an unrelated control then the interviewer should attempt to identify an alternative control. Subjects who refuse to participate still receive an identification number and their details are noted on the appropriate logsheets.

6.1.3. Subject unable to complete the interview

If the parents of the cases feel unable to go through the whole questionnaire, the interviewer should propose to have a break in the interview or to come back / call back at another time. Even if the information from a case trio is not complete they are still considered a participating case trio. If the interview has started but did not go beyond demographic section, then these subjects are considered non-responder.

This questionnaire is structured and so there should not be any missing data. There are some general guidelines for minimizing the extent of missing data on page 1 of the questionnaire.

7. COLLECTION, STORAGE AND PROCESSING OF BIOLOGICAL SPECIMENS

1. 20ml of blood samples will be collected from the parents of the index child
2. Blood samples will be collected from the index child and unrelated controls when they have been obtained for other medical reasons.
3. When blood samples are not available, saliva will be collected as alternative
4. The fresh whole blood will be separated into plasma, white and red blood cells, and viable lymphocyte will be prepared when 2nd tube of blood sample is provided
5. Fresh tumour samples will be collected whenever possible.
6. In the absence of fresh tissue samples, paraffin embedded blocks will be requested.
7. The collection of tumor tissues will be conducted in collaboration with SIOP/COG trials.

7.1 Objectives of biological sample collection

As stated in Section 2, we are interested in the role of genetic susceptibility, epigenetic profile and DNA repair capacities of the index child and the parents on the risk of embryonal tumors. Genomic DNA from the trios will be required for the analysis of genetic susceptibility and epigenetic profiles. Viable lymphocytes will are required for the phenotypic assays, and tumor DNA is needed for epigenetic alterations and better classification of molecular subtypes.

In particular, we plan to conduct genome-wide association studies to identify the susceptibility genes of embryonal tumors. Genome-wide association (GWA) studies aim to cover the majority of genetic variation by genotyping up to 1,000,000 tagSNPs, and do not require prior knowledge of the functional significance of the variants studied. The power of this approach for identifying new susceptibility genes has become apparent for a number of chronic diseases including diabetes (type 1 and 2), Parkinson disease, Alzheimer's disease, and autoimmune diseases such as rheumatoid arthritis. In the field of cancer research, the US National Cancer Institute is leading a large multipartner initiative focusing on breast, prostate and pancreatic cancer. These studies include multiple phases and thousands of subjects and are due to report their combined findings in 2008. GWA studies have also identified several common variants on human chromosome 8q24 which are independently associated with prostate cancer risk.

Despite the rapid development of GWA studies in adult cancer, there has been no genome-wide scan conducted on embryonal tumors so far. We aim to collect sufficient sample size for such undertaking in the full study. Therefore it is important to pilot the feasibility of obtaining biological samples including blood samples, saliva samples (when blood samples are not available) and tumor tissues at this pilot study.

7.2 Blood samples

A sample of 20 ml of blood will be collected from the parents of the index child using two 10ml Vacutainer tubes, one with EDTA coding and one with ACD coding. If blood sample of less than 20ml but more than 5ml are collected from children, the sample should be equally divided into EDTA and ACD tube but if 5ml are collected, the whole sample should be placed in EDTA. Collected blood sample will be separated into plasma, leucocytes and red blood cells, and processed for viable lymphocytes. Details for conducting this separation can be found in Appendix. If participating centers are unable to process their own samples, then these should be sent to their nearest receiving laboratory

No biological samples will be collected from the non-biological parents.

Blood samples will be collected from the index child and unrelated controls only when they have been obtained for other medical reasons (for example, the GPs are taking the blood samples for routine clinical purposes).

7.3 Saliva samples

Whenever blood samples are not available from the study subjects, the recruitment team will present the saliva collection kits to the study subjects as alternative. The details of how to collect the saliva from adults and children can be found in the Appendix.

7.4 Fresh tumour tissues

When possible a tumour biopsy sample should be obtained from each case. If the case is operated, the material is obtained at the time of staging or surgery, in collaboration with the local pathologist.

Whenever fresh tissue is collected it is essential that the specimen should not be put in formalin or any other preserving medium. The study specimen should be frozen as soon as possible to minimize degradation of the DNA using liquid nitrogen or by placing it in a freezer at -70°C. If it is not possible to freeze the tissue immediately, it will be kept on ice or in a standard refrigerator at +4°C until it can be frozen. A time lapse of maximum four hours at +4°C between collection and freezing of the sample is acceptable. Each specimen will be kept in a Nunc tube or equivalent, labeled with a pre-printed label and stored at -70°C.

Adequate arrangements have to be made at each centre to have rapid access to the freezer and procedures to cover potential problems, such as of an electrical failure.

In case the collection of a frozen biopsy is not possible, it is still recommended to obtain the paraffin embedded blocks of any biopsy available (see below).

7.5 Sections from paraffin embedded blocks

For the cases without a sample of fresh biopsy (see 4.6.3), 10-15 μ thick sections from the paraffin embedded block should be obtained, for analysis of genetic alterations. These sections will not be returned to the laboratory of origin. Alternatively, the block can be provided and sections will be made centrally. The remaining block will be returned to the laboratory of origin.

7.6 Procedures for dealing with sample collection/storage failure

In case of problems with the sample collection (inadequate) or storage, researchers should contact the subject to obtain a new sample.

7.7 Samples storage and transport

Shipment

The International Air Transport Organization (IATA) (http://www.iata.org) and the International Civil Aviation Organization (ICAO) (http://www.icao.int) govern the transport of biologic materials and there are specific regulations regarding the packaging, labeling and documentation of shipped material according its classification.

Storage

The samples will be split into two parts: one part will be kept at IARC and the other at the responsible center.

7.8 Future use of samples

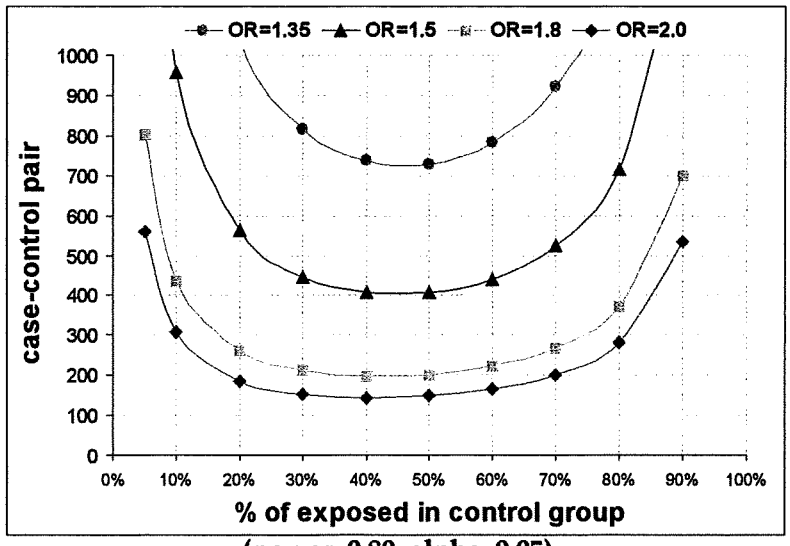
During the course of the study, additional requests to use blood, DNA or other biological materials or associated data collected during the study shall be presented to the study Steering Committee. The Steering Committee will determine whether such additional use is appropriate, and will evaluate such requests upon consideration of the scientific merit of the proposal and the conflict

or burden such request would place upon the primary study (if any).
For biological proposals that are approved by the study Steering Committee, the transfer or provision of biological materials to the collaborators shall be via Material Transfer Agreement ("MTA") between IARC and the institution representing the proposed collaborator(s).

8. SAMPLE SIZE AND POWER

Each centre will aim to recruit at least one-year's worth of cases and corresponding controls, based on the incidence data from the cancer registries (see Appendix 1). Larger centres (e.g. France and Brazil) will aim to recruit 50-100 cases of each tumor type. The sample size for unrelated controls will be 1:1 ratio. In total, we anticipate to have 382 Wilms' tumor case-control pairs with trios and 411 neuroblastoma case-control pairs with trios.

The main objective of this pilot study is not to conduct detailed statistical analysis but to establish the infrastructure of the large international multicenter case-control study. Nevertheless, the total number from all participating centers will allow us to detect the minimum OR of 2.0 when the prevalence of exposures in the control group is at least 10%.



(power=0.80, alpha=0.05)

We aim to reach at least 1000 case-control pairs with trios for both Wilms and neuroblastoma in the full study, which will have sufficient power to detect very moderate increased risk (OR=1.35) for exposures or risk allele with prevalence higher than 20% in the general population, or OR of 1.8 or more for relatively uncommon exposures or risk alleles (prevalence =5%), assuming an 80% power and a 5% significance level (Figure 1).

9. ORGANIZATION OF THE STUDY AND ETHICAL ISSUES

In each centre the principal investigator will be responsible for obtaining funding, the supervision of the field activities including identification of suitable cases and controls, supervision of interviewers, checking of the questionnaires to ensure that all questions have been properly answered and coded, supervision of the collection, and storage of specimens.

Each centre retains the ownership of its own data. The ownership of the overall dataset and biological specimens remains with the Study Group, which comprises the principal investigator from each centre and from each laboratory and scientists from IARC. The biological specimens will be used for laboratory analyses to test hypotheses. Any material remaining after completion of the main study may be used in other studies of childhood cancer aetiology and biology at the discretion of the Study Group. Any members who leave the Study Group should be replaced by their participating centre/laboratory to maintain the balance of the Study Group. The Study Group takes decisions on all aspects of the study, including laboratory and statistical analysis and publications. Although consensus is always sought, the Study Group can decide according to majority.

Each centre will obtain the clearance of the local ethical committee. In order to participate in the study, cases and controls will sign an informed consent form. Copy of the clearance and of the consent form will be provided to IARC.

The Genetic Epidemiology group in IARC will be responsible for the overall coordination of this study. Periodical visits will be paid to the participating centers to assist in the planning and implementation of the study and in particular to ensure adherence to the protocol.

10. PUBLICATION OF RESULTS

The results based on the overall dataset will be published by the Study Group. The results of the data from each centre can be published independently; however, they should not be published before the

results based on the overall dataset are available. Efforts should be made to coordinate centre-specific and overall publications. Timelines will be set for the publications. A detailed authorship policy will be established by the group at the end of the pilot phase, before the start of the full scale study.

11. TIME TABLE

May 2007	All study document finalized
May to Sep 2007	Center to translate the questionnaires and relevant study documents Center to prepare ethical approval Center to locate local funding IARC to prepare ACCESS database and consumables
Late Sep, early Oct	***ISET kick-off meeting***
Jan 2009 Dec 2009	**Launch ISET pilot study** Complete ISET pilot study

12. CONTACT INFORMATION OF COLLABORATORS

A. Recruitment centers

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Appendix 1 Catchment area and target number in each center

Country	Center PIs	Catchment area	Target number (no. cases / year)	
			Wilms	Neuroblastoma
UK	Birch / McKinney/Murphy/Pritchard-Jones	4 regions (i) North West England, (ii) North East England (iii) South West and South Central England (iv) London and South East coast of England	35	38
the Netherlands	Roeleveld / Hooiveld	Nation-wide	19	10
Italy	Magnani / Cuttini / Bisogno	Piedmont (NW Italy), Lazio region, Rome, Veneto region	15	25
France	Menegaux / Clavel	France metropolitan *(have conducted neuroblastoma study)*	95	140
Switzerland	Kuehni	Nation-wide	9	11
Czech Republic	Bencko	Bohemian part of the Czech Republic including Prague,	9	13
USA	Buffler	38 counties in N/C/S CA	30	-
Brazil	de Camargo, Ribeiro, Pombo-de-Oliveira	Sao Paulo, Rio de Janeiro, Bahia	105	89
India	Kurkure / Laskar	Mumabi , INDIA	30	30
Japon	Saito	Kanto district, Japan	5	17
Thailand	Nuchprayoon	Thailand, all regions	24	51
Australia	Milne	Nation-wide	30	38
		TOTAL	382	411